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Abstracts

HORMONE RESEARCH IN PÆDIATRICS

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Plenary Lectures

PL1
Oncofertility: From Bench to Bedside to Babies

Teresa Woodruff

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Facing a cancer diagnosis at any age is devastating. However, young cancer patients have the added burden that life-preserving cancer treatments, including surgery, chemotherapy, and radiotherapy, may compromise their future fertility. The possibility of reproductive dysfunction as a consequence of cancer treatment has a negative impact on the quality of life of cancer survivors. The field of oncofertility, which merges the clinical specialties of oncology and reproductive endocrinology, was developed to explore and expand fertility preservation options and to better manage the reproductive status of cancer patients. Fertility preservation for females has proved to be a particular challenge because mature female gametes are rare and difficult to acquire. The purpose of this presentation is to provide a comprehensive overview of how cancer treatments affect the female reproductive axis, delineate the diverse fertility preservation options that are currently available or being developed for young women, and describe current measures of ovarian reserve that can be used pre- and post-cancer treatment.

PL2
Oxytocin and the Healing Power of Love

Sue Carter

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This presentation will discuss the hormonal and neural mechanisms that support the beneficial and healing effects of loving relationships. Love is deeply biological and has profound effects on our mental and physical health, pervading every aspect of our lives. Without loving relationships or in isolation, humans fail to flourish, even if all of their other basic needs are met. Two neuropeptides, oxytocin and the related molecule, vasopressin, and their receptors, form an integrated system that is at the heart of the biology of love and attachment. These peptides also help to explain the consequences of positive or negative relationships. The evolution of oxytocin allowed human evolution. Embedded in this system are neuroendocrine processes that regulate a sense of fear or safety across the life cycle. These in turn permit social cognition, social bonding, social support, growth and restoration. Oxytocin and vasopressin interact to regulate the functions of the autonomic nervous system, with effects on vagal and sympathetic pathways. Oxytocin also has direct antioxidant and anti-inflammatory consequences for tissues throughout the body. The oxytocin system is influenced by early experience, and oxytocin can epigenetically alter the expression of its own receptors. The capacity of oxytocin to regulate these systems helps to explain the pervasive adaptive consequences of social experiences for emotional and physical health across the lifespan. Knowledge of the pathways through which oxytocin and vasopressin act offers a new perspective on the healing power of love.

PL3

Abstract not available

PL4

Abstract not available

PL5
Dynamic Control of Tissue Glucocorticoids – Lessons for Optimising Replacement Therapy

Brian Walker

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Although Endocrinologists have focused for decades on circulating concentrations of cortisol, arguably the important concentrations are those within tissues which are available at corticosteroid receptors. Tissue concentrations are influenced by plasma proteins binding cortisol, by physicochemical characteristics of the steroid, by active transport across cell membranes, and by steroid metabolism within target tissues. Many of these factors vary between individuals, and within individuals according to nutritional and inflammatory status. For example, common variants at the locus encoding corticosteroid binding globulin (CBG) make a genetic contribution to variations in plasma cortisol, affecting CBG stability and affinity for cortisol and thereby potentially altering the tissue delivery of cortisol. Moreover, cortisol metabolism within tissues varies substantially after feeding and during acute illness; indeed, tissue regeneration of cortisol by 11ß-HSD1

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has provided a target for therapeutic manipulation of tissue cortisol levels independently of circulating levels. These variations reinforce the unmet need for monitoring of glucocorticoid effects which extends beyond measurement of blood steroid concentrations.

Recently, we discovered differences between tissue-specific control of cortisol and corticosterone, the other endogenous glucocorticoid in humans. Using stable isotope tracers we found rapid exchange between free and bound cortisol pools in plasma, and between plasma and brain or liver cortisol pools, but very slow exchange between plasma and adipose tissue, consistent with substantial buffering of ultradian and circadian cortisol rhythms within adipose. We attributed this to tissue-specific expression of ABCB1, an ATP-binding cassette transporter, which exports cortisol from brain but not adipose tissue. However, in adipose we showed that an alternative transporter, ABCC1, exports corticosterone and not cortisol. Consistent with these findings, in Addison's disease we showed that ACTH suppression is relatively resistant to cortisol while adipose tissue transcript induction is relatively resistant to corticosterone. Development of corticosterone as a novel replacement therapy may therefore allow adequate suppression of ACTH, for example in congenital adrenal hyperplasia, without adverse effects that are mediated in adipose tissue such as obesity and metabolic dysfunction.

PL6

Personalizing Treatments Using Microbiome and Clinical Data

Eran Segal

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Accumulating evidence supports a causal role for the human gut microbiome in obesity, diabetes, metabolic disorders, cardiovascular disease, and numerous other conditions. I will present our research on the role of the human microbiome in health and disease, ultimately aimed at developing personalized medicine approaches that combine human genetics, microbiome, and nutrition.

In one project, we tackled the subject of personalization of human nutrition, using a cohort of over 1,000 people in which we measured blood glucose response to >50,000 meals, lifestyle, medical and food frequency questionnaires, blood tests, genetics, and gut microbiome. We showed that blood glucose responses to meals greatly vary between people even when consuming identical foods; devised the first algorithm for accurately predicting personalized glucose responses to food based on clinical and microbiome data; and showed that personalized diets based on our algorithm successfully balanced blood glucose levels in prediabetic individuals.

Using the same cohort, we also studied the relative contribution of host genetics and environmental factors in shaping human gut microbiome composition. Notably, although our cohort consists of individuals from several distinct ancestral origins who share a relatively common environment, we found no association between microbiome and genetic ancestry. In contrast, we show that over 20% of the gut microbiome variance can be explained by environmental factors related to diet, drugs and anthropometric measurements. We further show that 24-36% of the variance of several human traits and disease risk factors can be explained by the microbiome even after accounting for the contribution of human genetics. These results suggest that human microbiome composition is dominated by environmental factors rather than by host genetics.

Finally, I will present an algorithm that we devised for identifying variability in microbial sub-genomic regions. We find that such Sub-Genomic Variation (SGV) are prevalent in the microbiome across multiple microbial phyla, and that they are associated with bacterial fitness and their member genes are enriched for CRISPR-associated and antibiotic producing functions and depleted from housekeeping genes. We find over 100 novel associations between SGVs and host disease risk factors and uncover possible mechanistic links between the microbiome and its host, demonstrating that SGVs constitute a new layer of metagenomic information.

PL7

Abstract not available

PL8

Turner Syndrome: New Insights from Prenatal Genomics and Transcriptomics

Diana Bianchi

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Prior to the clinical and commercial introduction of noninvasive prenatal testing (NIPT) by sequencing of maternal plasma cell-free DNA in 2011, most fetuses with Turner syndrome were detected by sonographic findings related to lymphedema or incidentally. NIPT, however, has transformed prenatal genetic screening, and an estimated 4-6 million tests have been performed worldwide. In the maternal plasma sample there is both maternal and placental cell-free DNA. Following a screen positive NIPT result, it is universally recommended to confirm the screening test by a diagnostic procedure such as amniocentesis or CVS. While NIPT performance is excellent for trisomy 21 (positive predictive value [PPV] ~91%), it is less so for 45, X (PPV ~25%). The reasons for the relatively high number of false positive results include high rates of confined placental mosaicism, demise of a co-twin, and maternal incidental findings. The mother can have constitutional mosaicism for 45, X, or somatic mosaicism resulting from physiologic X-chromosome loss due to ageing. At present there is a significant knowledge gap as to how to clinically manage pregnant women ascertained through NIPT to have 45, X mosaicism. Transcriptomic analyses of cell-free RNA from living mid-trimester fetuses with 45, X demonstrate a consistent and unique pattern of gene expression. As expected, *XIST* is significantly down-regulated. Dysregulated genes of interest include *NFATC3, LDLR, and IGFBP5.* These genes are involved in perivascular tissue remodeling, hyperlipidemia, and growth and fertility, respectively. Using a dysregulated pathway approach, novel treatments could be developed that could be given antenatally to a pregnant woman carrying a fetus known to have 45, X. Prenatal screening for Turner syndrome creates ethical challenges for the fetus and mother, yet it also provides novel opportunities for treatments to prevent infertility and cardiovascular disease.

Symposia

Recent Developments in the Understanding of Hypothalamo-Pituitary Disorders

S1.1
Molecular Basis of Pituitary Hormone Deficiency: From Mouse to Man and Back

Sally Camper

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Hypopituitarism is genetically heterogeneous disorder that can affect solely the pituitary gland and its target organs, or it can present with craniofacial, brain, and/or neurosensory abnormalities. Mutations in over thirty genes are reported to cause hypopituitarism and growth insufficiency, yet most cases are unexplained. Mutations in the transcription factor PROP1 are the most common known cause of hypopituitarism in humans. Using *Prop1* mutant mice we discovered that PROP1 regulates the transition of pituitary stem cells to hormone producing cells in an epithelial to mesenchymal-like transition process. PROP1 is necessary to maintain stem cell proliferation, migration, and pituitary placode fate identity. To discover novel causes of hypopituitarism, we carried out exome sequencing on a cohort of 26 unrelated patients with hypopituitarism and identified mutations in known genes as well as novel candidate genes. To identify additional individuals with mutations in these novel genes and candidate genes from mouse studies, we developed an efficient, cost-effective method to capture the genomic DNA from 37 candidate genes and 30 known genes. We demonstrated that the method is sensitive and accurate in identifying genetic variants and applied it to over 100 patients and their families. We identified rare, likely deleterious variants in many genes, including *HESX1, POU1F1, TGIF1, SIX3,* and *GH1*. We are using cell culture and mouse models to assess the pathogenicity of variants of unknown significance. Our findings reinforce the idea that variants in multiple genes interact to influence the severity of clinical presentation.

S1.2
Stem Cells in the Pituitary: A Role for Regeneration?

Karine Rizzoti

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During morphogenesis, embryonic progenitors proliferate, differentiate and establish the shape of the future organs and tissues. In the mature organism, a certain degree of plasticity and potential for regeneration is retained as most organs maintain a population of adult stem cells sharing important similarities with embryonic progenitors; they are characterized by the ability to both self-renew and differentiate into the full range of the specialized cell types corresponding to the organ in which they reside. It is important to understand how these cells participate in organ cell turnover and regeneration, particularly because adult tissue stem cells can give rise to cancer stem cells. However, it is also relevant to regenerative medicine because stem cells can be transplanted once differentiated into the desired cell type or be manipulated *in Vivo* to restore missing cells.

In the last 12 years we and others have characterized a population of adult pituitary stem cells. While lineage tracing experiments have firmly established their adult stem cell properties, they have also shown that the cells are relatively quiescent in unchallenged animals. This is perhaps not surprising because the pituitary gland is an organ with a relatively low turn-over. In addition, endocrine cells can divide and this may be enough to maintain a functional pituitary. Therefore, the role of stem cells during homeostasis remains unclear. In contrast, when the gland is challenged, pituitary stem cells are mobilized. Endocrine cell ablation experiments show that stem cells react by actively proliferating and suggest that they also give rise to new endocrine cells, to replenish the depleted population. Moreover, pituitary target organ ablations, representing physiological challenges for the gland, have also been shown to stimulate both the proliferative and differentiation potential of the stem cells, demonstrating their regenerative potentialities. Characterization of the molecular mechanisms underlining mobilization of the stem cells is now required to be able to manipulate their fate.

S1.3
A Novel Role for Vasopressin in Parenting

Andres Bendesky

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The extent and quality of parental care that children receive greatly influences their development, impacting their physical and psychological growth, their educational and social achievement, and their disease risk as both children and adults. It is thus remarkable that around 25% of children are physically abused worldwide. Parenting is a complex behavior, and we still know little about the causes and mechanisms by which people differ in their parental behaviors.

To learn more about the mechanistic basis of parental care, I took an evolutionary-comparative approach. I set out to identify the genetic, molecular, and neuronal bases of the evolution of parental care in a pair of closely-related sister species of deer mice (genus *Peromyscus*) that have naturally evolved dramatically-different parental behaviors. Using quantitative-genetics techniques, I localized 13 genetic regions that contribute to interspecific differences in parental behavior. Remarkably, most of these regions differentially affect maternal and paternal behavior, implying that parental behavior evolves through different genetic routes in the two sexes. In one of these regions, I narrowed in on a specific gene, the neuropeptide vasopressin, and showed that it mediates interspecific differences in parental nest-building behavior. This gene is expressed at 3-fold higher levels in the hypothalamus of the less parental *Peromyscus* species. Finally, I confirmed the causal role of

this neuropeptide by demonstrating that an increase in vasopressin levels in the brains of the more parental Peromyscus species inhibits their parental care.

Together, an evolutionary-genetics approach led to the discovery that variation in parental behavior has a different genetic basis in males and females and to finding that the highly-conserved neuropeptide vasopressin modulates parental behavior.

Gonads/DSD

S2.1

The Biology of Germ Cell Tumors in Disorders of Sex Development

Leendert Looijenga

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Germ cell tumors (GCTs) comprise a heterogeneous group of neoplasms. The WHO classification 2016 recognizes three types of testicular GCTs, including the GCNIS-related (Germ Cell Neoplasia In Situ) GCTs, being the malignant seminomas and non-seminomas. They originate from a totipotent embryonic germ cell. GCNIS, seminoma and embryonal carcinoma, are characterized by the pluripotency marker OCT3/4 (POU5F1). Seminomas (and GCNIS) are positive for SOX17 and embryonal carcinomas for SOX2. Individuals with part of the Y chromosome (GBY) are at higher risk, likely related to TSPY. This directly relates to risk stratification of individual patients with various types of Disorders of Sex Development (DSD). Detection of KITLG (SCF) is informative for the earliest phase of GCNIS formation. A new level of risk stratification has been provided based on Genome Wide Association studies (GWAS) indicating that a selection of Single Nucleotide Polymorphisms (SNPs) are associated with testicular GCTs. These map to a limited number of genes related to relevant pathways, including gonadal development (DMRT1), embryonic germ cell proliferation and maintenance (KITLG, SPRY4, TERT, BAK1, etc). Data will be presented that this information is informative in a clinical context. A unifying model will be presented in which a delicate interaction between the genomic constitution and (gonadal) micro-environment (GENVIRONMENT) is the actual determinant for the risk of an individual to develop a malignant testicular GCT, including patients with DSD. Functional studies on the role of P53 identified that a selected set of embryonic-specific microRNAs, being the miRs 371-3 and 302/367 clusters are highly expressed in the various types of GCTs, including the precursor lesion GCNIS. The only exception is the fully differentiated element teratoma. These miR are informative as molecular serum markers to identify patients with a malignant GCT at the moment of diagnosis, as well as during clinical follow up. The current data based on a quantitative detection protocol will be presented, showing the outperformance of this test compared to the currently used standard biomarkers AFP and hCG.

S2.2

Disruption of Testicular Development and Function

Rod Mitchell

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Male reproductive disorders are common and there is evidence for increasing incidence over recent decades. These disorders may present at birth (hypospadias and cryptorchidism) or in adulthood (infertility, testicular cancer) and can arise as a result of underlying genetic abnormalities or following environmental (e.g. phthalates) and pharmaceutical (e.g. analgesics, chemotherapy) exposures that impact fetal, neonatal of prepubertal testicular development. Understanding the relevance of these perturbations on the testis and subsequent reproductive function in humans is often based on the findings of animal studies, however there are important differences between rodent and human in terms of fetal and postnatal testis development, in particular germ cell development. Therefore, reliable human experimental models that can demonstrate human and clinical relevance are required.

We have validated in-vitro and ex-vivo experimental models of human testis development. This includes a 'hanging drop' culture system and a human testis xenograft approach that can be utilised to investigate the development and function of the human testis during fetal, neonatal and prepubertal life. These model systems can recapitulate seminiferous cord formation, germ and somatic cell development and hormone production. Furthermore these model systems can be combined to investigate the long-term effects of genetic disruption to model the gonadal effects of Disorders of Sex Development and environmental exposures (e.g. industrial chemicals, pharmaceuticals and chemotherapeutics) on the testis.

We have utilised these models to mimic in-utero exposure to analgesics on human fetal testis development and function and the effects of therapeutic analgesic exposures on human fetal germ cell development and testosterone production will be described. The effect of knockdown, in the human fetal testis, of known and novel genes implicated in Testicular Dysgenesis Syndrome and Disorders of Sex Development will also be presented. The model systems have also been adapted for the investigation of human prepubertal testis development as part of a fertility preservation programme for boys treated for cancer. Studies investigating the effects of chemotherapy exposure on the prepubertal testis will be described, in addition to experimental approaches to preserving fertility in childhood cancer.

S2.3

Abstract not available

Recent Consensus Guidelines

S3.1

Diagnosis and Management of Silver–Russell Syndrome: First International Consensus Statement

Irene Netchine

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The first Consensus Statement on Silver Russell Syndrome has been held in 2015, on behalf of the COST Action BM1208 (European Network for Human Congenital Imprinting Disorders, http://www.imprinting-disorders.eu), ESPE, PES, APPES and SLEP with the participation of five representatives from a parent support group from different countries.

It has been published in 2016 (https://www.nature.com/articles/nrendo.2016.138). For dissimination, a patient « friendly » document has been generated and has been or will shortly be translated into seven languages.This consensus summarizes recommendations for clinical diagnosis, investigation and management of patients with Silver–Russell syndrome, an imprinting disorder that causes prenatal and postnatal growth retardation. Considerable overlap exists between the care of individuals born small for gestational age and those with SRS. However, many specific management issues exist and evidence from controlled trials remains limited. SRS is primarily a clinical diagnosis; however, molecular testing enables confirmation of the clinical diagnosis and defines the subtype. A 'normal' result from a molecular test does not exclude the diagnosis of SRS. The management of children with SRS requires an experienced, multidisciplinary approach. Specific issues include growth failure, severe feeding difficulties, gastrointestinal problems, hypoglycaemia, body asymmetry, scoliosis, motor and speech delay and psychosocial challenges. An early emphasis on adequate nutritional status is important, with awareness that rapid postnatal weight gain might lead to subsequent increased risk of metabolic disorders. The benefits of treating patients with SRS with growth hormone include improved body composition, motor development and appetite, reduced risk of hypoglycaemia and increased height. Clinicians should be aware of possible premature adrenarche, fairly early and rapid central puberty and insulin resistance. Treatment with gonadotropin-releasing hormone analogues can delay progression of central puberty and preserve adult height potential. Long-term follow up is essential to determine the natural history and optimal management in adulthood.

S3.2

Abstract not available

S3.3

Pediatric Obesity—Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline

Dennis Styne

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Pediatric obesity remains an ongoing serious international health concern affecting about 17% of children and adolescents in the United States while worldwide over 41 million children under 5 years are overweight or obese, threatening their adult health and longevity. Pediatric obesity has its basis in genetic susceptibilities influenced by a permissive environment starting in utero and extending through childhood and adolescence. Endocrine etiologies for obesity are rare and usually are accompanied by attenuated growth patterns. Comorbidities are common in obese children and adolescents, as are long-term health complications. Clinicians should screen for obesity comorbidities in a hierarchal, logical manner so as to detect them early and prevent more costly complications. Genetic screening for rare syndromes is indicated only in the presence of specific historical or physical features. The psychological toll of pediatric obesity on the individual and family necessitates screening for mental health issues and counseling if indicated. The prevention of pediatric obesity before onset, via physical activity and a healthful diet and environment, should be a primary goal; once obesity occurs, it is difficult to treat effectively with lifestyle modifications. Although some behavioral and pharmacotherapy studies have reported modest success in preventing and/or treating pediatric obesity, there remains a need for substantial research in these areas. Treating children or adolescents with weight loss medications should be restricted to clinical trials. Increasing evidence indicates that bariatric surgery is effective in the most seriously affected mature teenagers who have failed lifestyle modification; however, this requires experienced teams with resources for long-term follow-up. Despite a significant increase in research in recent years, we need more studies to better understand the genetic and biological factors that cause an obese individual to manifest one comorbidity versus another or to be free of comorbidities. Furthermore, we need continued investigation into the most effective methods of preventing and treating obesity and into methods for changing environmental and economic factors that will lead to worldwide cultural changes in diet and activity. We need to focus particular attention on finding ways to effect systemic changes in food environs and total daily mobility, as well as methods for sustaining healthy BMI changes.

S3.4

Prevention and Management of Rickets

Wolfgang Högler

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Calcium and phosphorus represent the main building material for bone and growth plate mineralization and bone stiffness. The supplier of these bone minerals is the hormone calcitriol, which originates from vitamin D, itself made by sunshine in human skin. Requirement for bone mineral supply is highest during phases of rapid growth, such as during pregnancy, infancy and puberty.

The body can be deprived of calcium either through low dietary calcium intake and/or low vitamin D. Such calcium deprivation can lead to serious health consequences throughout life, such as hypocalcaemic seizures, dilated cardiomyopathy, skeletal myopathy, 'nutritional' rickets and osteomalacia. These 5 conditions, often summarised as 'symptomatic vitamin D deficiency', are fully reversible but also fully preventable. Asymptomatic and undiagnosed morbidity from vitamin D or calcium deficiency is the subject of intensive research.

Calcium deprivation has reached epidemic proportions, not only in the third world, but also in high-income countries - specifically amongst dark-skinned and other at-risk populations. The increasing prevalence of rickets and osteomalacia, and infant deaths from hypocalcaemic cardiomyopathy, demand action from global health care providers. The global consensus for the prevention of management of rickets has provided evidence-based guidance on how such programs can be delivered and recommends vitamin D supplementation for risk groups (min 600IU/day), pregnant women (min 600 IU/day), and infants (min 400 IU/day). The success of prevention programs is intrinsically linked to policy implementation, including accountability of medical and parental responsibilities. Our work outlines substantial differences in supplementation policies and their efficacy in Europe and calls for better policy implementation strategies and also well-designed food fortification with vitamin D.

The quality of a nation's public health standards can be derived from how it treats and invests in its children and other vulnerable risk groups. The foetus and infant have the human right to be protected against harm. Prevention programs, including vitamin D supplementation and food fortification, should have the same public health priority as vaccinations.

Management of Lafe Effects of Cancer Therapy

S4.1

Abstract not available

S4.2

Hypogonadism in Girls After Cancer Therapy: Causes, Diagnosis, and Treatment

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Hypogonadism, both primary and secondary, are well documented following cancer therapy. Primary ovarian insufficiency (POI) has most often been associated with exposure to alkylating agents (dose response) and radiation (RT) that includes the ovary (dose response). Early onset POI occurs commonly in girls exposed to ovarian RT at doses >10 Gy and following high-dose alkylating agents as is given for stem cell transplant. Late onset POI (ie, premature menopause) may be seen following modest doses of alkylating agents, especially exposure to procarbazine and lower doses of ovarian RT (<10 Gy). Childhood cancer survivors treated with doses of RT > 30–40 Gy to the hypothalamic-pituitary axis are at risk for deficits of LH and FSH.

Elevated gonadotropins, especially FSH, are the hallmark of POI. It is important to note that levels can fluctuate over time; it is not uncommon for girls treated with chemotherapy alone to demonstrate normalization of gondatropins and spontaneous puberty/menses over time. As there are no long-term data correlating AMH levels in children and adolescents and subsequent ovarian function, measurement of AMH is not useful in making a diagnosis of POI.

Gonadotropin deficiency needs to be considered in survivors exposed to high-dose hypothalamic-pituitary radiation who demonstrate delayed or arrested puberty associated with low or normal gonadotropins and low levels of estradiol.

Treatment of hypogonadism in cancer survivors is, in general, similar to what is done in the non-cancer population. Special considerations are needed for those who have been exposed to chest RT and are at higher risk of developing breast cancer later in life.

S4.3

Diagnosis and Treatment of Hypogonadism in Male Survivors of Childhood Cancer

Wassim Chemaitilly

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Gonadal dysfunction is among the most commonly reported endocrine late effects in childhood cancer survivors (CCS). The main risk factors include the exposure of the hypothalamic-pituitary-gonadal axis to radiotherapy and treatment with gonadotoxic chemotherapy drugs such as alkylating agents. Individuals may experience gonadal dysfunction because of central (or hypogonadotropic) hypogonadism or as a result of primary gonadal injury. The testes have two distinct functional entities: a reproductive compartment that consists of germ cells and their supporting system (including the Sertoli cells) and a hormone producing compartment that consists of testosterone producing Leydig cells. These compartments vary in their vulnerability to cancer treatments that target the proliferative properties of cancer cells. The rapidly multiplying germ cells are more likely to be decimated by such treatments than the more quiescent Leydig cells. Therefore, a subset of male CCS exposed to gonadotoxic treatments may experience germ cell failure and infertility despite having spontaneously progressed through puberty and maintained normal testosterone secretion during adolescence and adulthood. This presentation seeks to provide medical care providers with guidance regarding the management and treatment of central or primary hypogonadism in male CCS with emphasis on issues and challenges that are specific to this vulnerable population.

ISPAD – ESPE Preventing Late Complications in Children with T1D

S5.1

Prognosis of Diabetic Children Today: Global Perspective

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Abstract not available.

S5.2

Re-defining Targets for Optimal T1D Control

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HbA1c reflects mean glucose levels over 2-3 months. ISPAD's and ADA's HbA1c target level is <7.5% (58 mmol/mol) in all pediatric age groups, but UK and Sweden have adopted ≤6.5% based on NICE Guidelines and DCCT results, provided that the person does not have hypoglycemia problems. NICE states: "Explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that an HbA1c target level of 48 mmol/mol (6.5%) or lower is ideal to minimize the risk of long-term complications."

Longitudinal data clearly show that it is very important to reach an HbA1c within target during the pediatric years. Improving HbA1c as a young adult is not enough to avoid complications. The current practice of tolerating some hyperglycemia to minimize the risk of hypoglycemia in young children with T1D may not be optimal for the developing brain.

Diabetes onset is a "window of opportunity" when the family is open for change. We used to say that diabetes is a difficult condition that you gradually need to adjust to, but in later years we are much stricter with intensive therapy right from the onset, teaching carbohydrate counting, insulin always given before meals and recording of mean glucose levels.. All are started on MDI; if< 10 years with an injection aid (i-port) to reduce injection pain, and if < 7 we start a pump and CGM within a few weeks. Older children get CGM (Libre) within a week to alleviate the pain of finger pricking.

We stress that these routines need to be continued throughout the remission phase with close follow-up and instructions to contact us if BG is > 8 mmol/l (145mg/dl) for 2 weeks in a row. At this time, the introduction of a target HbA1c of ≤ 6.5% is readily accepted by the family, and can be achieved by most, if not all families. The most critical period is actually when the child or teenager goes out of the remission phase and needs a quick increase in insulin doses. If you do not catch them in time, they will come back to clinic some months later with a high HbA1c, which will be difficult to bring down.

HbA1c during the first 2 years determines long-term levels both individually and on a clinic level. It is therefore vital to achieve and maintain optimal control already from the onset of diabetes.

S5.3

Abstract not available

Molecular Mechanisms of Tissue Sensitivity to Glucocorticoids: Potential Clinical Implications

S6.1

Cardiomyocyte Glucocorticoid and Mineralocorticoid Receptors Antagonistically Regulate Heart Disease

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Robert H. Oakley, Diana Cruz-Topete, Bo He, Julie F. Foley, Page H. Myers, Monte S. Willis, Celso E. Gomez-Sanchez, Pierre Chambon, and John A. Cidlowski

Stress is increasingly associated with cardiac disease. Glucocorticoids are primary stress hormones that regulate homeostasis through two nuclear receptors, the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR). Cardiomyocytes express both receptors but little is known concerning their specific and coordinated actions in heart physiology and pathology. To examine the *in Vivo* function of glucocorticoid signaling in the heart, we generated mice with cardiomyocyte-specific deletion of GR (cardioGRKO), MR (cardioMRKO), or both GR and MR (cardioGRMRdKO). The cardioGRKO mice spontaneously developed cardiac hypertrophy and left ventricular systolic dysfunction whereas the cardioMRKO mice exhibited normal heart function. Surprisingly, the cardioGRMRdKO mice were protected from cardiac disease. Gene expression profiling identified cardioprotective gene changes in the double knockout hearts that limit cardiac hypertrophy and promote cardiomyocyte survival. Re-installation of MR into the cardioGRMRdKO hearts reversed the cardioprotective gene changes and resulted in cardiac dysfunction. These findings demonstrate a deleterious role for cardiac MR signaling when unopposed by GR. Moreover, they reveal the target genes and cellular responses altered by MR that contribute to cardiac pathology. Therapies that shift the balance of cardiomyocyte glucocorticoid signaling to favor more GR and less MR activity may provide an improved approach for treating heart disease.

S6.2

Immune Regulation by Glucocorticoids

David Ray

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Glucocorticoids (cortisol in humans, corticosterone in rodents) are critical regulators of energy metabolism and immunity. Their secretion by the adrenal gland follows a circadian pattern, with serum concentrations peaking before the active phase (day in humans, night in rodents). Synthetic glucocorticoids are the most potent anti-inflammatory agents known, and are widely used therapeutically, with >1% of the UK population holding a prescription long-term. However, frequent therapeutic use is accompanied by development of severe side effects notably fat accumulation, hyperglycaemia, and hepatosteatosis.

Inactive GR is bound by ligand in the cytoplasm and undergoes nuclear translocation, where it binds glucocorticoid response elements (GREs) in the genome to either enhance, or repress gene transcription. Mechanisms to explain how the same molecule can drive gene activation or repression remain under investigation, but likely require an allosteric change induced by DNA target sequence, and/or co-binding with other transcription factors. For gene activation, homodimeric GR recruits co-activator molecules including steroid receptor co-activators (SRC1-3), and histone acetyltransferases (CBP/p300).

In contrast, gene repression in the context of anti-inflammation is more complex, with multiple mechanisms of action proposed. Publications report that activated GR binds to, and inhibits the transactivation function of proinflammatory transcription factors, notably the RelA component of the NFkB complex. This was suggested to require recruitment of a co-repressor protein, such as the SRC2 co-modulator. This tethering mechanism explains the lack of consensus GR binding sites in the regulatory regions of inflammatory genes, with the mode of action for GR being to bind to DNA-bound NFkB. However, an alternative mechanism of action has also been proposed, which does not require GR recruitment to the inflammatory genes at all. Here, GR is proposed to act in a conventional manner, to transactivate genes that themselves have anti-inflammatory actions. These include TNFAIP3, DUSP1, and IkB. The protein products of these genes are proposed to act directly on components of NFkB, thereby opposing recruitment to target genes, and thereby interrupting gene activation.

The translational implications of uncertainty likely underpin the difficulties in harnessing the anti-inflammatory power of glucocorticoids in the absence of metabolic off-target effects. While some selective glucocorticoid receptor agonists (SeGRMs) have been developed they are struggling in the clinic. However, an orally-active, and selective GR ligand would have potential to transform the management of chronic inflammatory diseases.

S6.3

Chemical Modification of the Glucocorticoid Receptor as a Determinant of Tissue Glucocorticoid Sensitivity: Implications to Circadian Rhythms, Stress Response and Treatment of Pediatric Leukemia

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Glucocorticoid hormones virtually influence all human functions both in a basal homeostatic condition and under stress. Thus, many other biological pathways adjust glucocorticoid actions in local tissues (tissue glucocorticoid sensitivity) by targeting the single receptor molecule glucocorticoid receptor (GR) as part of the regulatory loop coordinating complex human functions. Among them, chemical modification of GR, such as by acetylation and phosphorylation, is highlighted as one of the important molecular

mechanisms for changing local glucocorticoid actions. For example, the circadian transcription factor CLOCK acetylates GR, and participates in the reverse synchronization of local glucocorticoid sensitivity against circadian fluctuation of circulating cortisol. The cyclin-dependent kinase 5 (CDK5) phosphorylates several serine residues of the GR and modulates local glucocorticoid actions in the brain, and participates in the adaptive stress response and pathophysiology of mood disorders. Further, aberrantly activated v-akt murine thymoma viral oncogene homolog 1 (AKT1) develops glucocorticoid resistance in pediatric acute lymphoblastic leukemia by phosphorylating serine 134 of the GR and by inhibiting its cytoplasmic to nuclear translocation in cooperation with 14-3-3 proteins. I review recent progress in the research investigating chemical modification of GR as a determinant of tissue glucocorticoid sensitivity and discuss its physiologic or pathophysiologic implications.

Bone

S7.1
X-linked Hypophosphataemic Rickets: Disease and Treatment

Agnes Linglart

APHP, Paris, France

XLH is a dominant disorder with a prevalence of approximately 1.7/100,000 children to 4.8/100,000 persons. *PHEX*, the gene responsible for XLH was identified on chromosome Xp22. It codes for a cell surface-bound protein-cleaving enzyme expressed predominantly in bone and teeth. The altered function of *PHEX* causes both the mineralization defect and the renal phenotypic abnormalities of XLH. Clinical manifestations of XLH occur most often around the age of walking, despite an adequate vitamin D supplementation. In children the primary clinical symptoms are skeletal pain and deformity, abnormal gait, decreased growth velocity, dental abscesses and craniosynostosis. In adults, osteomalacia, bone pain, stiffness and enthesopathy are typical findings. Dizziness and deafness due to abnormalities of the inner ear may develop towards adulthood. Many patients may have partial synostosis of the sagittal sutures leading to a dolichocephalic shape of the head. This, however, is rarely accompanied by intracranial hypertension. XLH is characterized by elevated ALP, low serum phosphate, phosphate wasting and elevated levels of circulating FGF23. On radiographs, the metaphyseal signs are those of common rickets. In contrast, the bone has a mesh-like appearance with gross bone trabeculations and the cortices are thick. The current conventional treatment of XLH associates vitamin D analogues and repeated doses of phosphate supplements. Active vitamin D analogues are given to counter calcitriol deficiency, prevent secondary hyperparathyroidism, and increase phosphate absorption from the gut. The optimal dose of treatment varies from patient to patient. Higher doses are given during period of rapid growth and at initiation of treatment when the skeleton requires mineral accretion. Thereafter, doses need to be adjusted according to the efficacy, i.e. improvement of bone deformities, rickets on radiographs and ALP, and safety, i.e. prevention of nephrocalcinosis and hyperparathyroidism.

The human anti-FGF23 monoclonal antibody, burosumab, is now an alternative to the conventional therapy as it was approved by The FDA for adults and children and by the EMA in children, and is now available in some countries. We do not have enough evidence yet to compare both therapeutic strategies and we do not know if one has better short/mid/long term results than the other. The administration of growth hormone improves growth in prepubertal children with XLH but no clear indication exist to support systematic treatment of patients with XLH. Surgery is indicated for severe bowing or tibial torsion unlikely to improve with medical management alone.

S7.2
Hypophosphatasia: Disease and Treatment

Nick Bishop

University of Sheffield and Sheffield Children's Hospital, Sheffield, UK

Hypophosphatasia affects both hard and soft tissues. Its manifestations may become apparent at any time from fetal life to old age and the range of its severity and presentation varies perhaps more than any other metabolic bone disease. With the advent of enzyme replacement therapy, children who would have died not only survive, but can also thrive. As follow-up of treated children continues, we are beginning to understand the potential for complications of treatment and co-morbidities emerging from the disease, as well as being able to provide better prognostic information for families. Continued research in the field is providing new insights into the biology of mineralisation and the role of pyrophosphate and other mineralisation inhibitors both in bone and in other tissues. The emerging issues of musculoskeletal pain and fatigue raise questions about the relationship of muscle and bone in disease settings; these manifestations of HPP remain a target for treatment in those patients who are otherwise apparently mildly affected.

S7.3
Achondroplasia – New Hopes

Melita Irving

Guy's and St Thomas' NHS Trust, London, UK

Achondroplasia is the most common form of genetic disproportionate short stature or dwarfism with an incidence of 1 in 20 000. It is caused by a recurrent mutation (G380R) in *FGFR3*, which encodes the transmembrane protein fibroblast growth factor receptor type 3, activating the FGFR3 signalling pathway in the absence of its FGF ligand. This disrupts both endochondral and in-

tramembranous ossification, causing a number of bone modelling abnormalities with secondary complications. These include limb shortening with an impact upon the activities of daily living and functionality, macrocephaly with ventriculomegaly, stenosis of the foramen magnum, thoracolumbar kyphosis, lumbar spinal stenosis, chronic otitis media and obstructive sleep apnoea. Additional health considerations are of a propensity towards obesity, chronic pain and degenerative joint disease. Management has always been conservative and anticipatory, with a multidisciplinary input required to alleviate and prevent these complications.

Understanding of the underlying molecular mechanism has allowed exploitation of the FGFR3 pathway to develop potential medicinal treatments for achondroplasia. These treatments include long and short-acting C-natriuretic peptide and other therapies that modify the effects of the activated FGFR3 pathway, such as an FGFR3 decoy and an anti-FGFR3 antibody. Here these different strategies will be explored, along with the anticipated effect upon individuals with achondroplasia. The possible application of these strategies in managing other rare diseases will also be discussed.

Thyroid Disorders

S8.1
Thyroid Hormone Transporter Defects

W. Edward Visser

Erasmus MC, Rotterdam, Netherlands

Thyroid hormone is crucial for metabolism and development. Cellular thyroid hormone homeostasis requires adequate function of (1) thyroid hormone transporter proteins, (2) deiodinating enzymes and (3) nuclear receptors. Thyroid hormone transporters are crucial for cellular uptake of T3 and T4. Over the last years, a number of thyroid hormone transporters have been identified and their physiological relevance has been established. The most well-studied example is MCT8 deficiency, which is associated with severe neurocognitive impairments and peripheral thyrotoxicosis. The pathogenesis as well as therapy development for this disease will be discussed. In addition, recent discoveries illustrate the relevance of transporters for clinical practice.

S8.2
Central Hypothyroidism – An Update

Paul Van Trotsenburg

Amsterdam University Medical Centers, Amsterdam, Netherlands

Central hypothyroidism can be best defined as lower than desirable thyroid hormone production and secretion because of insufficient stimulation of a normal thyroid gland by a defective pituitary or hypothalamus, resulting in a too low plasma or serum (free) thyroxine (FT4) concentration accompanied by a more or less normal thyrotropin (TSH) concentration. Central hypothyroidism can occur isolated or as part of multiple pituitary hormone deficiency and can be a congenital or acquired condition. Because basal TSH is generally unusable as diagnostic test for central hypothyroidism, its diagnosis heavily relies on the height of the FT4 concentration, making especially isolated central hypothyroidism a challenging diagnosis. In the last six to seven years, three new genetic causes of isolated central hypothyroidism - mutations in the *IGSF1*, *TBL1X* and *IRS4* genes - have been added to the two well-known causes (mutations in *TRHR* and *TSHB*). This speaker will present an overview of the current knowledge about diagnosing, and the genetic causes of (isolated) central hypothyroidism.

S8.3
Paediatric Differentiated Thyroid Cancer: Outcome and Long Term Effects

Thera Links

University Medical Hospital Groningen, Groningen, Netherlands

Pediatric differentiated thyroid carcinoma (DTC), which includes papillary (PTC) and follicular thyroid carcinoma (FTC), has an excellent prognosis (15-year survival rates >95%). The initial treatment in children generally consists of a (near) total thyroidectomy, followed by ablation therapy with radioiodine (131-I), nowadays, the latter often depends on risk stratification. TSH suppressive therapy with thyroid hormone has for decades been administered during follow-up to diminish the risk of recurrent disease. However, data about long-term effects of 131-I treatment, long-term TSH suppressive therapy and quality of life in pediatric DTC patients are limited. In the Netherlands a nationwide study in patients with pediatric DTC has been performed regarding presentation, treatment-related complications and outcome of treated and long term effects. Overall survival of 170 patients was 99.4% after a median follow-up of 13.5 (range 0.3-44.7) years. Medical follow-up data were available from 105 patients (83.8% women). At last follow-up, 8.6% patients had persistent disease and 7.6% patients had recurrent disease. Permanent hypoparathyroidism was found in 23.8%, 12.4% patients had recurrent laryngeal nerve injury. Health-related quality of life (RAND 36), fatigue (MFI20), anxiety and depression (HADS) scores of survivors and age, sex, and socioeconomic status survivors and matched controls did not differ significantly. However, survivors had more physical problems ($P = 0.031$), role limitations due to physical problems ($P = 0.021$), and mental fatigue ($P = 0.016$) than controls. Evaluation of the achievement of psychosocial developmental milestones was evaluated by the course of life questionnaire (CoLQ) and showed similar development on social, autonomy, and psychosexual domains of survivors compared to controls. While systolic function is unaffected, diastolic dysfunction was present in 21.2% of the asymptomatic survivors, which may suggest early cardiac aging. In survivors clinically significant salivary gland dysfunction was found in 35.5%, related to the cumulative 131I activity.

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Novel Advances in Endocrine Imaging

S9.1

Abstract not available.

S9.2

Novel CNS Imaging Techniques

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Novel CNS imaging techniques is a fast advancing field with frequent new developments in scanner's hardware, protocols, clinical indications, and post-processing techniques. These techniques are designed to focus on the assessment of functional tissue characteristics, such as neuronal activity (functional MRI- fMRI), microstructural properties (diffusion tensor imaging-DTI) and tissue perfusion (DSC perfusion, ASL).

fMRI reveals brain activation during performance of behavioral tasks, based on the blood oxygen level dependent (BOLD) MRI signal, which is modulated by neural activity via a process of neurovascular coupling. Resting-state fMRI can be performed and correlates brain areas with similar spontaneous fluctuations in the BOLD signal — thereby enabling estimates of "functional connectivity". DTI evaluates brain microstructure and quantifies integrity through metrics such as apparent diffusion coefficient (ADC) and fractional anisotropy (FA). "Structural connectivity" is based on white matter tracts that can be depicted and assessed with tractography.

Perfusion MR imaging methods detect signal changes that accompany the passage of a tracer through the cerebrovascular system. A less invasive approach is arterial spin labeling (ASL) that uses arterial water as an endogenous tracer to measure CBF. MR perfusion is applied in the evaluation of brain tumors, neurological diseases and developmental disorders.

Clinical applications of novel CNS imaging techniques are expected to expand greatly in the future due to the increasing availability as well as the continuous advancements in the field of research.

S9.3

Novel Techniques in Diagnostics of Bone Strength

Nicola Crabtree

Birmingham Women's and Children's NHS Trust, Birmingham, UK

There are several different techniques for assessing bone strength and fracture susceptibility in children namely; dual-energy x-ray absorptiometry (DXA), quantitative computed tomography (QCT), plain radiography and magnetic resonance imaging (MRI). The most readily available technique and recommended by the International Society of Clinical Densitometry (ISCD) is DXA. The advantage of DXA is that it is widely available, affords the child a low radiation dose and can assess fracture prone areas of the body with fast scanning times. The main disadvantage of DXA is that it is a two-dimensional technique which measures the ratio of bone mineral content to projected bone area, such that areal bone density is highly dependent on bone size. As a result, reduced bone density in childhood is frequently a reflection of poor growth rather than a true measure of reduced bone strength.

Given the limitations of DXA it is not surprising that other imaging techniques are appealing for assessing reduced bone strength and fracture risk. Techniques such as QCT have the advantage of being able to separately measure cortical and trabecular bone densities. Dedicated peripheral QCT scanners can assess fracture prone long bones with minimal radiation exposure and high resolution QCT scanners now give almost in-vivo bone biopsy type outputs of parameters such as trabecular bone volume, trabecular separation etc. However, small measurement regions, long scanning times and a high susceptibility to movement, keep these techniques predominantly in the research arena rather than for routine clinical assessments.

The most recently developed technique is MRI. It can be applied to the peripheral or axial skeleton. The advantage of MRI is that it uses non-ionising radiation to assess bone architecture and muscle structure in multiple planes without repositioning. The disadvantages of MRI are that it is time consuming, expensive and has been used only in few research protocols. As with QCT its applicability in clinical practice has yet to be fully assessed.

Increasingly, old and new technologies are being combined to fully exploit currently available diagnostic procedures. The improved image resolution of modern DXA scanners has facilitated accurate assessment of osteoporotic vertebral fractures. At the same time, sophisticated intelligent computer software programs have enabled techniques such as textural analysis, shape modelling and finite element modelling to be genuine contenders for the assessment of bone strength in children. How well any of these novel diagnostic tools are incorporated into clinical practice remains to be seen.

Paediatric Obesity: Mechanisms and Novel Treatment

S10.1

Abstract not available.

S10.2

Functional Leptin Deficiency Disorders and Treatment

Martin Wabitsch

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Leptin is a type I cytokine and belongs to the long-chain helical cytokine subfamily just as GH, IL-6 and G-CSF. Leptin is produced mainly in white adipose tissue and thereby reflects body energy stores. Leptin serum concentrations are high in obese and low in underweight individuals or in those with low body fat e.g. in athletes and in patients with lipodystrophy.

The leptin/leptin receptor system is crucial for the regulation of body weight. Rare homozygous mutations in the leptin gene can lead to defects in synthesis and/or secretion of leptin resulting in congenital leptin deficiency with low or undetectable serum levels of leptin. Affected children show an insatiable appetite and food seeking behaviour, excessive weight gain and a multitude of metabolic and hormonal disturbances including hypogonadotropic hypogonadism. Patients can be effectively treated by substitution with recombinant human leptin (metreleptin).

Recently, we have described mutations in the leptin gene which result in secreted proteins which are however not able to activate the leptin receptor due to structural alterations in binding site II. Affected patients have high circulating leptin levels which appear to be appropriate for their fat mass. Their clinical presentation is similar to that of patients with classical leptin deficiency. As these patients can also be treated effectively with metreleptin we have developed an immunoassay which measures only the bioactive fraction of total serum leptin capable to bind to the receptor in order to facilitate early diagnosis.

In conclusion, patients have shown us the occurrence of functional leptin deficiency. Interestingly, mutagenesis studies suggest that other mutations in the leptin gene might occur resulting in diverse alterations in protein sequence, secretion, structure and receptor interaction. Theoretically, affected patients would need specific diagnostic workup and treatment regimes depending on the underlying molecular defect.

S10.3

MC4R Agonists in the Treatment of Monogenic Disorders of Obesity

Peter Kühnen

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The leptin melanocortin signaling pathway plays a pivotal role in body weight regulation within the hypothalamus. Gene mutations within this cascade are leading to early onset obesity and severe hyperphagia in rodents and humans. For the affected patients it is extremely difficult to stabilize body weight based on the persisting hunger feeling. Traditional treatment options (increased exercise, reduced caloric intake) are not effective in most cases. Therefore, there is a need to identify new treatment options because otherwise the long-term prognosis regarding health and life expectancy is serious for these patients. Until recently only leptin deficient patients could be treated successfully with metreleptin. This replacement therapy is leading to a normalization of hunger scores and body weight. However, leptin treatment is not successful in patients with *LEPR*or *POMC*mutations. In an investigator-initiated proof-of-concept trial, we have treated POMC and LEPR deficient patients with a MC4R agonist. This led to a significant reduction of hunger feeling and body weight. However, further studies are needed to gain insights into the impact of this pharmacological treatment option on body weight and to examine, whether further groups of patients might benefit from this pharmacological treatment option.

Special Symposia: Nutrition and Growth

SS1.1

It Is Not Just the Growth Hormone-IGF-I Axis

Ola Nilsson

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For decades, the dominant conceptual framework for understanding short and tall stature was centered on the GH-IGF-I axis. However, recent findings in basic molecular and cellular biology and in clinical genetics have uncovered a vast array of other regulatory systems that control skeletal growth and an accompanying vast array of genetic defects outside the GH-IGF-I axis that can cause disorders of linear growth. As a result, the traditional view of short or tall stature that is centered on the GH-IGF-I axis is now far too narrow to encompass the ever-growing number of defects that cause abnormal linear growth. A much broader conceptual framework can be based on the simple concept that linear growth disorders are necessarily due to dysfunction of the growth plate, the structure responsible for bone elongation and therefore overall body size. Consequently, short stature can more generally be conceptualized as a primary or secondary disorder of the growth

plate chondrocytes. The wide array of genetic defects, many newly-discovered, that affect growth plate chondrocyte function and thereby cause childhood growth disorders will be reviewed. A novel concept that has emerged from recent findings is that sequence variants in a single gene can produce a phenotypic spectrum that ranges from a severe skeletal dysplasia to disproportionate or proportionate short stature, to normal variation in height, to tall stature. The recent advances reviewed in this paper are steadily diminishing the number of children who receive the unhelpful diagnoses of severe idiopathic short stature or tall stature.

SS1.2

Fascinating Growth Phenomena: What Causes Individual Catch-Up Growth and Population Secular Change?

Jan M Wit

Leiden University Medical Center, Leiden, Netherlands

Catch-up growth (CUG) is characterized by a period of supranormal height velocity following a transient period of growth inhibition. The two classical hypotheses on the mechanism are the neuro-endocrine hypothesis (a central mechanism that would recognize the degree of mismatch between actual size and target size) and the growth plate hypothesis (local regulation of growth according to a preset cellular program of senescence, characterized by decreasing growth proliferation rate). Unilateral CUG in animal experiments argue against the neuro-endocrine hypothesis, and the fast growth in type A CUG argues against the growth plate hypothesis. Recent data indicate that various regulatory factors may be involved in CUG after malnutrition, including Hypoxia-Inducible Factor 1 (HIF1), mTOR, Sirtuins (class III histone deacetylases), microRNAs, the GH-IGF-1 axis, Ghrelin, Leptin and insulin.

Positive secular changes in body size and tempo of growth have occurred in most western countries since 1850, generally considered as an indicator of better nutrition, hygiene and health status. Secular increase is most prominent at 4-11 years of age. At the completion of the secular trend in various countries adult height has increased up to 20 cm and is reached >8 years earlier. However, attained mean adult heights are different, suggesting that besides environmental influences also genetic or geographic factors play a role, and possibly also culturally engrained nutritional habits. The magnitude of secular trend is relatively strong in individuals of low socio-economic background, reducing social class differences in height. Regarding the mechanism, epigenetic processes (in foetal life or early infancy) seem most plausible. The extensive time interval and magnitude of secular trend, the different stages of secular trend in high income and many low- and middle income countries, on top of the presumed effect of genetic and geographic variations, make it difficult to defend the concept of a "global growth standard".

SS1.3

Interaction between Nutrition, the Endocrine System and the Growth Plate

Moshe Phillip

Schneider Children's Medical Center Of Israel, Petah Tikva, Israel

Children's linear growth is a complex process determined by genetic and environmental factors. It is well known that nutrition influences linear growth, but the precise mechanisms by which nutrition interact with height gain was never fully elucidated. In the present lecture, the way by which nutrition affects linear growth will be discussed. Specifically, we will discuss the effect of nutrition on the GH- IGF-1 axis and its local effect on the chondrocytes of the epiphyseal growth plate of the long bone. Results from experimental animal studies will be presented including the epigenetic changes and the effect nutrition has on leptin and its effect on aromatase expression within the growth plate. Laboratory data and clinical data on the way by which leptin might determine the adult height will be presented.

Meet The Expert

MTE1.1

The Role of Radiology in the Diagnosis of Skeletal Dysplasias

Amaka C Offiah

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Skeletal dysplasias are conditions in which there is an abnormality of bone and/or cartilage growth, which may show phenotypic evolution throughout life. They are genetically and radiologically heterogeneous, with accurate diagnosis requiring careful correlation of clinical, genetic and radiological information. Presentation may be with unexplained short stature, and this, in the presence of disproportion is the most common indication for a skeletal survey within paediatric endocrinology. However, it is important that imaging is used with care and that only those patients who need it are selected for skeletal survey.

This session will demonstrate the utility of radiological assessment, and skeletal surveys in particular, in guiding laboratory and genetic tests and in differentiating causes of short stature in children. Important differential diagnoses will be discussed and key results of a systematic review of the applicability of the Greulich and Pyle bone age standard to children of different ethnicities will be highlighted. Given its increasing use, the session will also review the automated bone age software tool, BoneXpert, which not only assesses bone age according to both Greulich and Pyle and Tanner and Whitehouse standards, but also provides an assessment of bone health – the "bone health index".

By the end of the session, delegates should have an understanding of when to investigate for skeletal dysplasia, which images to request and be able to recognise salient features of some relatively common genetic conditions presenting to the paediatric endocrinologist with short stature.

MTE2.1

Endocrine Complications in Thalassaemia

Nicos Skordis

Paedi Medical Center for Specialized Pediatrics, Nicosia, Cyprus

Multiple transfusions in patients with Thalassaemia Major (TM) result in iron overload, which accumulates in tissues with high levels of transferrin-receptors such liver, heart and endocrine glands The nature and frequency of endocrinopathies differ between countries because of the different levels of treatment followed by centres across the world.

1. Short stature. The child with TM has a particular growth pattern, which is relatively normal until age 9-10 years; after this age a slowing down of growth velocity and a reduced or absent pubertal growth spurt are observed. The origin of growth failure is multifactorial. The origin of growth failure is multifactorial: chronic anemia, hypersplenism, chronic liver disease, skeletal dysplasia, Desferrioxamine toxicity, dysfunction of the GH – IGF 1 axis, hypothyroidism and delayed puberty. Therapeutic response with GH administration in cases with GH deficiency is often non satisfactory

2. Delayed puberty and hypogonadism. This represents the most common complication, where proper management is crucial not only for self-image but also for the prevention of bone loss. Therapeutic response to sex steroids is excellent.

3. Hypothyroidism. The subclinical type is the most commonly seen form that usually presents after age 10 years.

4. **Impaired glucose tolerance / diabetes mellitus.** Patients usually present with impaired glucose tolerance, mostly due to insulin resistance and subsequently develop insulin deficiency. Other contributing factors include: liver dysfunction, genetic loading and hormonal treatment.

5. Hypoparathyroidism. This rare complication presents after the age of 16 years equally in both sexes with mild hypocalcaemia and very rarely with tetany and cardiac failure.

6. Adrenal insufficiency. Biochemical adrenal insufficiency varies up to 45%, but clinical adrenal insufficiency is extremely rare.

7. Bone disease. Patients with TM display an unbalanced bone turnover with an increased resorption phase and decreased formation phase, resulting in severe bone loss

Therapeutic advances have significantly increased the average lifespan and improved the quality of life in patients with TM. Attainment of reproductive capacity and creation of a family has become a great task for both women and men. Early recognition and treatment of endocrinopathies is vital to prevent late complications and increase the chances of parenthood.

MTE3.1

Abstract not available

MTE4.1

The Use of Modern Technologies to Optimize Diabetes Care

Olga Kordonouri

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The gold standard for the treatment of Type 1 diabetes in children and adolescents is the intensified insulin therapy using either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) pump according to the basal-bolus-principle. Blood glucose measurement is the mainstay of diabetes management, guiding insulin dosing decisions and monitoring glycemic control.

New technological advances including subcutaneous continuous glucose monitoring (CGM), either from real-time use (rt-CGM) or intermittently viewed (iCGM) are of particular importance for children and adolescents due to the age-related metabolic

fluctuations. They provide more information about intra- and interday glycemic excursions that may lead to acute events (such as hypoglycemia) or postprandial hyperglycemia, which have been linked to both microvascular and macrovascular complications. Both rtCGM and iCGM facilitate monitoring of time spent in- and outside the target glucose range (glycated hemoglobin (HbA1c), which has been the traditional method for assessing glycemic control so far. Furthermore, the combination of CSII and rtCGM in form of a sensor-augmented pump (SaP) treatment allows semi-automated insulin dosing with the aim of reduction of hypo- and hyperglycemia in patients with Type 1 diabetes.

Current studies show that the implementation of modern technologies into diabetes treatment can help the optimization of metabolic control and also lead to improved quality of life both in patients with type 1 diabetes and in their families.

MTE5.1

Gonadal Function in Congenital Adrenal Hyperplasia (CAH)

Hedi Claahsen - Van Der Grinten

Radboud University NIjmegen Medical Centre, Nijmegen, Netherlands

Congenital adrenal hyperplasia (CAH) is a group of rare congenital disorders of the adrenal cortex due to a defect in one of the enzymes involved in steroid synthesis leading to cortisol deficiency and overproduction of adrenal androgens. In the most severe forms CAH is a life threatening disease due to the risk of Addisonian and salt wasting crisis. In the last 50 years diagnostics and treatment improved significantly. Patients are treated with lifelong replacement of glucocorticoids and, in aldosterone deficieny, also mineralocorticoids. Nowadays, most children reach puberty and adulthood without severe complications and a good quality of life. Therefore, long term complications of CAH become more important also for pediatric endocrinologist as some of these complications may have their origin already in childhood.

One of the most severe complications in adult male and female CAH patients is infertility due to primary (hypergonadotropic) or secondary (hypogonadotropic) gonadal dysfunction. The most important cause of infertility in male CAH patients is the presence of testicular adrenal rest tumours (TART) leading to obstruction of the seminiferous tubule and obstructive azoospermia. Longstanding TART can lead to irreversible damage of testicular tissue. This complication already occurs during childhood and puberty. Another important factor contributing to infertility is the suppression of the hypothalamic-pituitary-gonadal axis due to high circulating levels of androgens resulting in secondary gonadal failure.

In female CAH patients fertility can be impaired due to adrenal overproduction of androgens and progestins (17-hydroxyprogesterone and progesterone), ovarian hyperandrogenism (polycystic ovary syndrome), ovarian adrenal rest tumours, genital surgery, and psychological factors such as delayed psychosexual development and reduced sexual activity.

In this expert meeting we will discuss different causes of gonadal dysfunction in male and female CAH patients with a special focus on their occurrence during adolescence.

MTE6.1

Management of Hypo and Hypercalcaemia

Nick Shaw

Birmingham Children's Hospital, Birmingham, UK

The approach to the management of a child presenting with Hypo or Hypercalcaemia requires an understanding of the physiological regulation of plasma calcium and the key hormones and receptors that are important components. These include Vitamin D, Parathyroid hormone (PTH), the Calcium sensing receptor and renal function. The differential diagnosis for both these conditions is wide and it is important that relevant investigations are undertaken at presentation prior to the initiation of treatment.

In the assessment of Hypocalcaemia the measured PTH level at presentation will provide an important clue as to the possible underlying disorders and direct subsequent investigations. A similar approach is required in the assessment of Hypercalcaemia where the measured PTH level will categorise the condition as PTH dependent or PTH independent. The condition of the child at presentation will also influence the interpretation of the severity of the underlying disorder and the urgency of management. For example a child who is discovered to have a high plasma calcium on a blood test undertaken for other reasons who is asymptomatic may have the condition Familial Hypocalciuric Hypercalcaemia (FHH) that requires no active management.

Many conditions that present in childhood with Hypo or Hypercalcaemia have a genetic basis which may have implications for other family members. It is therefore important to include genetic confirmation once the underlying diagnosis is apparent. Long term drug treatment is required for many of the conditions which will require appropriate monitoring to ensure effectiveness but also to avoid adverse effects.

MTE7.1

Abstract not available

MTE8.1

Psychology of Childhood Diabetes: How to Motivate Children and Families with T1DM

Karin Lange

Hannover Medical School, Hannover, Germany

Type 1 diabetes in childhood is a family project challenging all members 24h/365 days a year. Parents and children have to perform a multitude of self-management tasks responding to changes in activity, food, emotional well-being and physiology. In addition parents have to combine their role as loving carer with role of the responsible 'diabetologist' of their child.

Personalized structured education and psychosocial support for all family members are the keys to successful management of diabetes and child's age appropriate psychosocial development. Diabetes education is an interactive process that supports families to acquire and apply the necessary knowledge to develop confidence to manage their life with diabetes. Age-specific curricula are based on psycho-educational principles and combine practical education with problem solving tasks, goal setting, communication skills, motivational interviewing, family conflict resolution, support of self-efficacy and psychosocial adaptation. Lifelong diabetes management requires frequent qualified education at initial diagnosis and ongoing to support and motivate children and their care givers.

During the workshop core elements of diabetes education and psychological advice will be discussed based on clinical cases: 1) basic practical 'survival skills' and psychological support in the phase of diabetes diagnosis focusing on feelings of helplessness and guilt, development of feelings of security and self-efficacy as well as on positive coping among parents and children; all measures should follow common therapeutic goals and a shared holistic approach; 2) supporting positive emotional coping with unexpected glucose variation and improving patient confidence, self-efficacy and motivation during the first year with type 1 diabetes; 3) practical tools to support better coping with (un-)realistic fear of hypoglycemia and to reduce parents' distress; 4) tools for effective use of CGM in children and their parents, e.g. worksheets on realistic expectations for adolescents and parents; discussion of parents' and adolescents' emotional reactions on alerts and unexpected glucose variation; cognitive behaviour techniques to prevent from overreaction on hypo alarms; step-by-step introduction of different alarms to prevent children, parents and other carer from overload; worksheets to support positive parent-adolescent cooperation ('coaching contract'); 5) Concerns, challenges and opportunities common to adolescents with diabetes, e.g. accepting the critical role of continued parental involvement and yet promoting independent, responsible self-management appropriate to the level of maturity and understanding, emotional and peer group conflicts, problem solving strategies for dealing with dietary indiscretions, illness, hypoglycemia, blood glucose fluctuation due to puberty, sports, smoking, alcohol, drugs, reproductive and sexual health and family planning.

Novel Advances & Controversies in Paediatric Endocrinology

The Clinical Relevance Of Metabolomics; Genomic Engineering – CRISP-R/Cas9 and its Many Implications

NA1.1

The Clinical Relevance of Metabolomics

Maria Klapa

Foundation for Research & Technology-Hellas (FORTH), Patras, Greece

High-throughput biomolecular (omic) analyses enabled the simultaneous quantification of hundreds or thousands of transcripts, proteins, metabolites in a biological system, contributing to the identification of discriminatory multi-component molecular profiles of a pathophysiology. Molecular quantities being interconnected, even subtle differences in one can carry significance if viewed in the context of the observed changes in the rest of the molecules. We can now view molecular physiology as a dynamic arrangement of interacting biomolecular networks and interpret the molecular mechanisms underlying a pathophysiology as disruptions in this network connectivity and dynamics (network medicine). Thus, omic analyses pave the way for in-depth systemic studies of human (patho)physiology. Metabolomics is the most recently introduced but fast growing omics, referring to the analysis of the metabolic profile, i.e. the concentration profile of the free small metabolite pools, of a biological system. The metabolic profile is an integral component of the epigenetic fingerprint of an individual, providing a direct link to the phenotype. Hence, metabolomics of biological fluids or tissues (when available) can be crucial for accurate disease diagnosis and design of personalized therapeutic treatments, either as singly applied or as part of multi-omic studies, foreseen to complement the classical biochemical tests in the near future.

In this lecture, the significance of metabolomics as a useful tool in clinical research and practice will be presented in the general context of systems medicine and demonstrated through examples of its application in the search for diagnostic profiles, underlying molecular mechanisms of disease and appropriate therapeutic treatments, within endocrinology, pharmacometabolomics, neurophysiology and personalized nutrition, from collaborative projects of my laboratory and the literature. The current challenges for the broad deployment of the metabolomic analytical platform to systems & precision medicine research and practice, concerning the standardization and harmonization of the involved experimental protocols and computational methods for accurate, reproducible and validated performance, will also be discussed.

NA1.2

Abstract not available

Cell Engineering for Treatment of Diabetes

NA2.1

Stem Cells as a Source of Beta Cells

Henryk Zulewski

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The ultimate therapy for type 1 diabetes is the replacement of the lost insulin producing cells instead of the actual life-saving but imperfect substitution of insulin. The isolation of embryonic stem cells (ESC) and later the reprogramming of somatic cells into induced pluripotent stem cells (iPSC) raised enormous hopes for cell based therapies in diabetes type 1. The first important stage in the differentiation process of ESC/iPSC is the generation of definite endoderm that contain cells which are positive for critical pancreatic transcription factors such as Pdx1 and Nkx6.1. At this time the decision to enter the pancreatic endocrine pathway is triggered by induction of Ngn3 and followed by the successive activation of other critical transcription factors required for differentiation and maturation of insulin secreting beta cells.

Despite recent progress in the generation of insulin secreting cells from pluripotent stem cells, there is a considerable variability in the differentiation efficacy and each cell lines require protocol adjustments. One reason for these observations is the inability to really control cell fate decisions at critical stages of the differentiation process such as the timely and efficient activation of Ngn3 for determination of the pancreatic endocrine phenotype. In order to overcome this hurdle we engineered a genetic software using the tools of synthetic biology, that allows to control the timing and intensity of Ngn3 activation as well as the following sequential induction of Pdx1 and MafA, that are required for differentiation and maturation of functional insulin secreting cells. More than 75% of iPSC that were regulated by this genetic software differentiated into insulin positive cells that displayed glucose stimulated insulin secretion. Cell fate controlling genetic software may help to unveil the real potential of iPS for the replacement of insulin producing cells in type 1 diabetes through reliable control of critical developmental steps.

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NA2.2

Induction of Pancreatic Beta-Cell Neogenesis

Patrick Collombat

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Background: The recent discovery that genetically-modified pancreatic alpha-cells can regenerate and convert into beta-like cells in vivo holds great promise for diabetes research. However, to eventually translate these findings to human, it is crucial to discover compounds with similar activities.

Results: We recently identified GABA as an inducer of alpha-to-beta-like cell conversion in vivo. This conversion induces alpha-cell replacement mechanisms through the mobilization of duct-lining precursor cells that adopt an alpha-cell identity prior to being converted into beta-like cells, solely upon sustained GABA exposure. Importantly, these neo-generated beta-like cells are functional and can repeatedly reverse chemically-induced diabetes in vivo. Similarly, the treatment of transplanted human islets with GABA results in a loss of alpha-cells and a concomitant increase in beta-like cell counts, suggestive of alpha-to-beta-like cell conversion processes also in humans. The latest advances will be discussed

Conclusions: This newly discovered GABA-induced alpha-cell-mediated beta-like cell neogenesis could therefore represent an unprecedented hope towards improved therapies for diabetes.

Should Growth Hormone Be Used in ISS?

CON1.1

PRO: Should GH Be Used in ISS?

Ron Rosenfeld

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There are few issues in pediatric endocrinology which have generated as much controversy as that of GH treatment of ISS. The genesis of this debate is totally understandable, given that ISS is not a "disease," but, rather, a heterogeneous collection of conditions that are defined auxologically as a height below -2 SD, without evidence of an underlying systemic, nutritional, endocrine or chromosomal disorder. One can quite rightfully state that no matter how many children might be treated, 5% will always be below the 5th percentile. Despite this caveat, it seems unreasonable to deny therapy to a patient who may experience benefit.

And yet, we continue to treat many ISS patients. Some of the justifications are listed below:

1. Treatment of short stature related to a wide variety of other non GH deficient states, such as Turner syndrome, SGA, Noonan syndrome, SHOX deficiency, and Prader Willi Syndrome, is widely approved
2. Recognition that ISS constitutes a heterogeneous group of disorders, many of which may have demonstrable etiologies, such as unsuspected defects of SHOX, NPR2, FGFR3 and dominant negative mutations affecting the GH-IGF axis. Indeed, all short stature that is not due to environment or systemic disease will ultimately prove to have a molecular basis. As such, it becomes extremely challenging to determine where the boundary lies between pathology and normal variation.
3. Difficulties in the diagnosis of GHD, with estimates that at least 70% of children labeled and treated as GHD are actually ISS patients.
4. Heterogeneity in the growth response to GH of patients labeled as GHD and ISS, so that considerable overlap exists between these two groups of patients.

Failure to identify an agency-approved indication for GH should not necessarily exclude a patient from potential beneficial therapy. A trial of GH treatment seems reasonable in such cases.

CON1.2

Abstract not available

CON1.3

Abstract not available

CON1.4

Abstract not available

To Prime or Not to Prime?

CON2.1

PRO - To Prime Or Not to Prime?

Ola Nilsson

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Recent progress in the understanding of growth disorders has further emphasized that growth hormone deficiency is only one of many causes for growth failure and that growth hormone deficiency (GHD) is over-diagnosed in children with short stature. Over-diagnosis of GHD is problematic as it incorrectly labels

children with pituitary disease, leads to overtreatment and misinformation of patients and families, and may sometimes prevent doctors from making the correct diagnosis. Methods that can improve the specificity of GH testing are therefore urgently needed. Estrogen priming of prepubertal children is safe and inexpensive. Available data suggest that it increases specificity and therefore improves testing performance. In this presentation, I will discuss estrogen priming and argue that it should be used if the purpose of testing is to accurately determine whether the child is GH deficient.

CON2.2

Con-To Prime Or Not to Prime

Alan Rogol

University of Virginia, CHARLOTTESVILLE, USA

The diagnosis of growth hormone deficiency (GHD) is primarily clinical and usually includes: short stature but virtually always growth failure, perhaps some physical findings that accompany syndromic causes, and alterations in body composition and in the regional distribution of body fat. Laboratory testing, whether static or dynamic, and medical imaging are mostly confirmatory to the clinical diagnosis.

Biochemical laboratory testing for GH insufficiency is fraught with many uncertainties: non-physiologic, poorly reproducible and thus the results may contain little useful information especially concerning response to rhGH therapy, rely on arbitrary definitions which are assay, age and puberty stage dependent and may be expensive and uncomfortable. Perhaps most importantly, they (easily) identify the child with severe GHD, but are of limited value in discriminating between normal short children and those with partial GHD.

Added to this murky mix is that the role of sex hormone priming is unclear. Since sex steroids cause the increase in GH secretion and circulating IGF-I levels at puberty, one assumes that exposing prepubertal children to sex steroid priming facilitates GH release and *May* make retesting unnecessary or avoid mis-classification of the condition.

Not all agree that sex hormone priming is *Required,* for a concern is that of spontaneous GH release in prepubertal children, who do not have circulating endogenous sex steroids. The "primed" test would then force an un-physiologic state for a prepubertal child. Certainly the lower bound of normal GH release would be higher than the "usual" one.

Historically, the primed test was useful when only severely children with GHD could be treated because of the inadequate supply of pituitary GH. With the present supply of rhGH available to children with idiopathic short stature, some of whom may have partial GHD, it becomes less of an issue. Perhaps a compromise would be that sex hormone priming is not required routinely but perhaps useful in the small group of peri-adolescent age children with significantly delayed puberty because children of this age "should" have greater concentrations of circulating sex steroid hormones.

The conundrum is not making a diagnosis of GHD, but of determining who is GH *Responsive*. Testing itself is expensive and not always definitive. It may very well be prudent to do a clinical trial of rhGH treatment for 6 to 12 months, for it is the early growth response that predicts, perhaps best, the long term growth response to therapy with rhGH.

Henning Anderson Award

HA1

EAP1 Mutations Cause an Impaired Transcriptional Activity on GnRH Promoter That Leads to Self-Limited Delayed Puberty

Alessandra Mancini[1], *Sasha R. Howard*[1], *Claudia P. Cabrera*[2], *Michael R. Barnes*[2], *Sabine Heger*[3], *Leonardo Guasti*[1], *Sergio Ojeda*[4], *Leo Dunkel*[1]

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Background: The initiation of puberty is orchestrated by the augmentation in the secretion of gonadotropin-releasing hormone (GnRH) from a few thousand neurons located in the hypothalamus. Recent findings identified that the neuroendocrine control of puberty is regulated by a network of transcriptional factors hierarchically organized, but this still remains not fully elucidated. Enhanced At Puberty 1 (*EAP1*) is one of the main regulators of pubertal onset and it is expressed in the hypothalamus of pubertal rats and non-human primates. Its role has been described as being involved in the initiation of female puberty by transactivating GnRH promoter. Its inhibition in the hypothalamus, causes disrupted estrous cyclicity and delayed puberty in rats. Self-limited delayed puberty (DP) (i.e. constitutional delay of puberty) runs in families with either autosomal dominant or complex inheritance patterns in >70% of families, indicating a strong genetic basis of the trait. However, only a few genes have been identified underlying DP, and to date, no *EAP1* mutations have been found in humans.

Objective, hypotheses and methods: Whole exome sequencing was performed on DNA from 160 individuals of 67 multi-generational families affected with DP. Variants returned were analysed to identify rare, potentially pathogenic variants enriched in case versus controls and relevant to the biological control of puberty. We identified two *EAP1* variants whose pathogenicity was validated *in Vitro* and tissue expression was examined in mouse hypothalamus.

Results: After filtering we identified one in-frame deletion and one rare missense variant in *EAP1* in two unrelated families (five affected individuals) and all segregated with DP trait with the expected autosomal dominant pattern of inheritance. These variants are highly conserved and were predicted to be deleterious by the main prediction software tools (i.e. SIFT and POLYPHEN 2). Expression studies on *Eap1* revealed its broad expression in the hypothalamus of peri-pubertal mice and specifically in the nuclei expressing GnRH neurons, such as the arcuate and periventricular nuclei. The pathogenicity of each variant was investigated using a promoter-reporter assay in a HEK293T cell line. For verifying the EAP1 transactivating ability on GnRH promoter, we employed a luciferase reporter gene whose expression is driven by the GnRH promoter. EAP1 mutant proteins showed a significantly reduced transcriptional activity compared to wild-type, thus impairing its function on GnRH promoter.

Conclusion: We have identified, for the first time, two human *EAP1* mutations leading to a reduced GnRH transcriptional activity resulting in the phenotype of self-limited DP.

HA2

Generating a Human Gonadal Cells Model from Terminal Differentiated Fibroblast-Derived Induced Pluripotent Stem Cells

Daniel Rodríguez Gutiérrez[1], *Wassim Eid*[1,2], *Anna Biason-Lauber*[1]

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Background: Differentiation of the gonads in men is closely dependent on Sertoli cells maturation. Differences of sex development (DSD) are caused by variations in this process. The study of the mechanisms underlying these complex conditions is crucial for optimal clinical management and Sertoli cells would be an ideal model for this purpose. However, there are two main obstacles for the study of human Sertoli cells. Firstly, mature human Sertoli cells lose their proliferation abilities in culture. Secondly, the currently available models (human NT2D1 and mouse TM4 cells) demonstrated to have limitations due to their origin as mouse or tumor cells.

Objective and Hypothesis: To establish a more suitable model to study human testis formation, we differentiated human fibroblasts-derived induced pluripotent stem cells (iPSCs) into human Sertoli-like cells.

Methods: We reprogrammed human fibroblasts into iPSCs by lentivirus transduction of reprograming factors (Oct4, SOX2, NANOG, LIN28, KLF4 and C-MYC). Subsequently, we guided the differentiation of iPSCs into SLCs by growth factors and characterized this new model by new generation sequencing techniques including 44.946 genes expression analysis. In a more detailed analysis, we selected 20 gene markers for the different stages of Sertoli cell development including SRY-Related HMG-Box 9 (SOX9), vimentin (VIM), Cytochrome P450 Retinoid Metabolizing Protein (CYP26B1) and Proto-Oncogene Tyrosine-Protein Kinase Src (SRC). We additionally tested whether SLC are able to create three-dimensional structures in gel matrix and the expression of claudin-11 (CLDN-11) in tight junctions.

Results: This approach revealed that SLCs expressed Sertoli cell markers such as SOX9 and VIM, When compared the other current models (NT2D1 and TM4 cells), SLCs showed a reduction of the germ cell markers SOX2, POU5F1, DPPA2, DPPA4 and NANOG and an increased expression of Sertoli cell markers CYP26B1, SCF and SRC ($p<0.05$ for all). We additionally demonstrated the ability of SLCs to form three-dimensional structures when grown in extracellular matrix gel and expressed CLDN-11 in the tight junctions as human Sertoli cells.

Conclusion: Harnessing the power of iPSCs we were able to generate Sertoli-like cells that show genetic and functional similarities to human Sertoli cells. Thanks to this novel approach, Sertoli-like cells may become an alternative source of patient-specific Sertoli cells models that may boost the understanding of the individual complexities of DSD patients.

Working Groups

ESPE Disorders of Sex Development & Turner Syndrome Joint Session

WG1.1

Long-Term Outcomes in Males with 45,X/46,XY Mosaicism: A Multicenter Study of 59 Males

Marie Lindhardt Ljubicic

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45,X/46,XY mosaicism is a rare karyotype and patients present with varying phenotypes from Turner females to males. Genital phenotype, gonadal function and histology, and growth are all affected to varying degrees by the karyotype. Information on these long-term outcomes is scarce and larger multicenter studies are needed. Therefore, in collaboration with 17 centers, we performed a study including 59 post-pubertal males that had reached adult height. Centers were identified and invited using the I-DSD Registry and DSDnet network.

We found that long-term outcomes such as External Masculinization Score, gonadal function in terms of spontaneous pubertal onset and the need for testosterone substitution, and the frequency of genital surgeries, namely hypospadia repairs and orchidopexies, were significantly affected by whether patients were diagnosed at birth due to genital anomalies or later in life due to reasons such as growth retardation, delayed puberty, lack of virilization in adulthood or infertility. Thus, patients diagnosed at birth had more affected genital phenotypes and poorer gonadal function than patients diagnosed later in life. However, most patients, regardless of reason for referral, entered puberty spontaneously indicative of some Leydig cell function. Moreover, 12% of gonadectomized patients had gonadal neoplasia *in Situ*, highlighting the need for thorough follow-up including ultrasound scans and possibly biopsies in this group of patients.

Additionally, growth appeared to be affected in all individuals and many patients were experimentally treated with human growth hormone. This retrospective, non-randomized study failed to find an effect of the treatment on height standard deviation scores. High incidences of renal and cardiac congenital malformations, all reflective of the Turner cell line, were seen regardless of reason for referral.

Overall, male patients with 45,X/46,XY mosaicism are affected very differently by their karyotype which is also reflected in the long-term outcomes. Thus, individual management and care is still highly recommended.

WG1.2

Abstract not available

WG1.3

Cardiovascular Pathology in Males and Females with 45,X/46,XY Mosaicism

Katya De Groote

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The phenotype of 45,X/46,XY mosaicism is heterogeneous ranging from females with Turner syndrome (TS) to apparently normal males. Cardinal features of TS include reduced final height and infertility. Apart from endocrine, renal and neurocognitive disorders, structural heart defects are frequently present (in 25% to 50%), also in TS patients with mosaicism 45,X/46,XY.

Males with 45,X/46,XY frequently show stigmata typically associated with TS but data on cardiovascular pathology are scarce. Case reports and small series show that abnormalities of the heart and the great vessels are frequent and include the same lesions that are found in female Turner patients (i.e. aortic coarctation, bicuspid aortic valve and aortic dilation). It is advised to perform cardiac screening and life-long monitoring in all males with 45,X/46,XY mosaicism according to the existing guidelines for Turner syndrome.

Based on the I-DSD registry we designed an international multicentre retrospective study to verify the prevalence of cardiovascular pathology in a larger group of 45,X/46,XY patients and to map the current policy on cardiovascular screening in males with mosaicism 45,X/46,XY. Data collection is ongoing and the preliminary results of the study will be presented.

WG1.4

Abstract not available

WG1.5

Abstract not available

WG1.6

Abstract not available

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ESPE Obesity Working Group (OWG)

WG2.1

Abstract not available

WG2.2

Abstract not available

WG2.3

Abstract not available

WG2.4

Abstract not available

ESPE Bone and Growth Plate Working Group (BGP)

WG3.1

Abstract not available

WG3.2

SHOX - From Gene to Growth Plate

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SHOX deficiency is the most frequent genetic growth disorder associated with isolated and syndromic forms of short stature. Caused by mutations in the homeobox gene *SHOX,* its varied clinical manifestations include isolated short stature, Léri-Weill dyschondrosteosis, and Langer mesomelic dysplasia. In addition, SHOX deficiency contributes to the skeletal features in Turner syndrome. Causative *SHOX* mutations have allowed downstream pathology to be linked to defined molecular lesions. Expression levels of SHOX are tightly regulated, and almost half of pathogenic mutations have affected enhancers. Clinical severity of SHOX deficiency varies between genders and ranges from normal stature to profound mesomelic skeletal dysplasia.

Zebrafish and chicken animal models together with micromass cultures and primary cell lines have been used to address SHOX function. Pathway and network analysis have identified interacting molecules, target genes, and regulators. SHOX is one of several critical factors regulating chondrocyte hypertrophy and chondrocyte maturation in the growth plate. Two decades of research support the concept of SHOX as a transcription factor that integrates diverse aspects of bone development, growth plate biology, and apoptosis.

WG3.3

Abstract not available

WG3.4

Abstract not available

WG3.5

Abstract not available

WG3.6

Abstract not available

ESPE Diabetes Technology and Therapeutics Working Group

WG4.1

Abstract not available

WG4.2

Abstract not available

WG4.3

Use of Apps for Physical Activity in Type 1 Diabetes

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Global growth in the use of mobile phones, the so-called smartphones, makes them a powerful platform to help provide tailored health, delivered conveniently to patients. These devices are developing rapidly mainly with regard to information processing, design, features and connectivity with other devices. Modern treatment and monitoring of type 1 diabetes is being supported by rapid evolving technology as pumps for continuous subcutaneous insulin infusion and sensors for continuous subcutaneous glucose monitoring, both providing data that can be processed by smartphone apps.

Systematic reviews of available studies examining the effectiveness of interventions with smartphone apps to promote lifestyle changes such as physical activity, physical fitness, modification of dietary habits, and quality of life (QoL) in patients with diabetes show that the use of such apps seems to improve lifestyle factors, to strengthen the perception of self-care and specially to decrease HbA1c. However, the results had severe heterogeneity that was explained by the frequency of health care professionals (HCP) feedback. HCP functionality was important to achieve clinical effectiveness.

Nowadays, there is an increasing number of apps designed to give guidance to patients with Type 1 diabetes during activity or exercise combining diabetes-specific with fitness data sources. Current available apps include Engine 1 by Glucose Advisors, Diabits, Glucose Buddy, MySugr, One Drop, bant and Glucozone (Type 2 diabetes only), whereas others like the "Lilly Type 1 Diabetes Exercise App" or the "T1Dexi exercise and nutrition app" are under development.

Although there is some indication that the use of diabetes apps is not associated with an excess of severe episodes of hypoglycemia, current evidence concerning the safety of diabetes apps is scarce. Thus, future long-lasting studies are necessary to further evaluate the effectiveness of these rapid evolving diabetes apps with direct attention to safety issues, particularly for apps with bolus calculator functionality.

WG4.4

The Future Role of Machine Learning and Computer Vision in Carbohydrate Estimation for Patients with Diabetes

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The recent advances in the areas of artificial intelligence, machine learning, computer vision, wearable sensors and smartphone technologies permitted the introduction of systems that allows the monitoring, analysis and assessment of food intake, in terms of energy and nutrient content.

To empower diabetic patients the Diabetes Technology Research laboratory of the ARTORG Center at the University of Bern (Switzerland) has developed GoCARB, a smartphone App, capable to translate food images into carbohydrates. How does it work? The user places a credit card-sized reference object next to the dish, and takes two photographs from different points of view. One of the photos is used to detect, segment and recognize automatically the existing food items, while semiautomatic tools are also provided for correcting the results, if needed. By using both photos and the card, we build a 3D model of the food itself. With this 3D model of the different foods, you can calculate their volume. Once you know the volume and food type and using nutrient databases, you can calculate the carbohydrate content. In house clinical studies have shown that this is superior to getting the diabetic patient to estimate the carbohydrate content and that glucose control is then more precise. But how close are we towards "real world systems"? Will artificial intelligence improve dietary assessment? What is my experience within and beyond the GoCARB project?

WG4.5

Analyzing and Reporting of Sensor Glucose Levels

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Background: Since the publication of the Diabetes Control and Complications Trial results two decades ago, glycated haemoglobin (A1c) has remained the only validated measurement of glycemic control and marker for future complications. The growing use of continuous glucose monitoring (CGM) has opened a new era of measuring and following glycemia and it associated outcomes. These new available glucose variables can provide a broader insight to personalized glycemic control and provide valuable glucose measurements beyond A1c.

Objective and hypotheses: Data from CGM enables to continuously record blood glucose levels, demonstrate glucose excursions, day to day and within day variability, provide a more accurate description of hypoglycemic and hyperglycemic episodes. Data driven by CGM can also overcome many of the limitations presented by A1c. For example; patients may have identical mean blood glucose but completely different levels of A1c. CGM reported glucose variables can be used for routine follow up of patient's glycemia level, as well as a mean to assess the impact of new technologies and therapeutics on glycemic control. Thus, there is a need to define the various CGM glycemic variables with relation to outcomes, and to standardize the analysis and report of these variables. This will create a uniform basis for evaluation and comparison of the level of glycemia.

Method: Recently several consensus reports on CGM related glucose metrics have been composed by different groups of various opinion key leaders and experts in Type 1 Diabetes. These reports include the 2017 ATTD consensus recommendations, the join report of the American Diabetes Association and the European Association for the Study of Diabetes and other groups. The consensus recommendations define different and new categories for hypoglycemia, hyperglycemia, time with in different glucose ranges and glucose variability based on clinical evidence regarding CGM use. Furthermore, the different groups emphasize the value of hypoglycemia as an adjuvant measurement of glycemia in addition to time within range and A1c outcome.

Conclusion: The new era of technology and the use of CGM have provided important information on individual parameters to define and report the level of glycemia. CGM use has a positive impact on diabetes control and provides valuable andmeaningful information on the level of glycemia. Thus, efforts should be made to encourage its daily use for all patients with type 1 diabetes, and its glucose metrics as endpoints in clinical trials.

WG4.6

Updates on the Developments of Decision Support Systems for the Treatment of Diabetes

Moshe Phillip

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With the increased number of patients with diabetes on one hand and the shortage of professional teams of health care providers (HCP) worldwide on the other hand, new ways of providing medical care to patients with diabetes are needed. Decision Support Systems (DSS) and emerging tools are developed in order to help HCP during patients' office visits and to help patients navigate their own metabolic control between office visits. Recently, tools of DSS have been tested in clinical studies and got European regulatory approval (CE) as well as USA (FDA) approval. More DSS are in development for patients with diabetes.

WG4.7

Use of Social Media for Improving Glucose Control in Patients with Type 1 DiabetesUse of Social Media for Improving Glucose Control in Patients with Type 1 Diabetes

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One potential solution in improving Type 1 Diabetes (T1D) management is the use of technology, providing additional opportunities to support management, maintain and improve communication and engagement with healthcare services. Patients use Internet to search and interact with a community of patients with similar problems; to share clinical information; and to provide and receive support. Facebook with over 2.1 billion active monthly users worldwide is important source of information, support and engagement for patients with chronic disease. It can be used as a supportive tool in disease management for patients and families, which is not necessarily available through formal professional consultation.

This paper describes several analysis and interventions among 478 T1D patients who use social media as communication tool with health providers. Practical implications for understanding the social media support, needs of T1D patients and enhancing social media for this population are discussed. Social media like Facebook and Viber can improve glucose control. Patients using insulin pumps more often use social media in communication and has significantly lower HbA1c compared to patients without social media use.

We believe that in today's challenging healthcare environment of limited budgets and resources with a desire to provide better diabetes care, new methods of patient interaction using social media can be beneficial.

ESPE Paediatric and Adolescent Gynaecology Working Group (PAG)

WG5.1

Abstract not available

WG5.2

Abstract not available

WG5.3

Influence of Adiposity as a Determinant of the Age at Pubjeanertal Onset

Frank Biro

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Multiple studies have examined the relationship between BMI and timing of the onset of puberty. The more salient measure of this relationship may be adiposity, which can be represented by fat mass, BMI z-score, or waist-to-height ratio. The relationship of greater BMI or adiposity to earlier pubertal onset in girls is generally consistent, and several mechanisms have been proposed. These potential mechanisms include impact of adiposity on leptin concentrations, altered regulation of gonadotropin production, impact of endocrine-disrupting chemicals (EDCs), and peripheral aromatization of adrenal androgens. The relationship of adiposity and maturation in boys is not as consistent, and a proposed model may help explain the discrepancies in the literature.

WG5.4

Endocrine-Metabolic Outcome of Women with a History of Sexual Precocity

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Central precocious puberty (CPP) may have endocrine and metabolic implications in adulthood. Long-term effects may be associated with the underlying neuroendocrine dysfunction leading to CPP, the GnRH analogue (GnRHa) therapy, or both. Data are conflicting on the long-term risk of polycystic ovarian syndrome in both treated and untreated women. Clinical hyperandrogenism has been more frequently reported in CPP women than in controls, with no significant difference between GnRHa-treated and untreated CPP women. Gonadal function is promptly restored in girls after cessation of treatment and reproductive potential appears normal in young adulthood. However, the assisted- fertilization rate may be higher in untreated CPP women than in treated CPP women, suggesting that pubertal suppression treatment may have a protective effect. CPP (treated or untreated) is not associated with increased risk of obesity, metabolic derangements, or cancer morbidities in young adulthood. Moreover, GnRHa therapy does not seem to have any long-term effect on BMI or a negative impact on BMD. The finding that the health status of former CPP women is similar to that of the general population is reassuring.

WG5.5

Abstract not available

ESPE Gender Dysphoria (GD)

WG6.1

Abstract not available

WG6.2

Abstract not available

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ESPE Paediatric Endocrine Nurse Specialists and Allied Health Professionals Working Group (PENS)

WG7.1

Advanced Anthropometrics in Pediatric Endocrinology: Utility and Difficulty

Jean De Schepper

UZ Brussel, Brussels, Belgium

Anthropometrics is an important part of pediatrics and public health. Its non-invasiveness, simplicity and low cost makes anthropometry attractive for several purposes. It is a valuable method for the screening or assessment of growth disorders, as well as under- and over-nutrition. Furthermore, specific anthropometric measures can be used as indicators of general fitness or cardiovascular risk factors (insulin resistance and dyslipidemia) in (obese) children, as well as markers for asthma severity, pulmonary function or sleep associated respiratory problems in (asthmatic or obese) children.

However, attention for accurate measurements and availability of reliable references values are prerequisites for its use in clinical practice. Recently, European reference values of skinfold thickness, sum of skinfolds, waist and neck circumference, and the waist-to-height ratio have been developed. Furthermore, regular practice and respecting standard conditions (in the morning and fasting) and standardized measuring techniques increase their reliability.

Measurements of body (head, neck, upper arm, waist and hip) circumferences, (biiliacal, biacromial) diameters and (truncal, leg) segments as well as of (tricipital, subscapular) skinfold thickness characterize either the body frame, body proportion or body composition.

For the assessment of total body fat, sum of skinfold thicknesses and neck circumference (NC) can be used, whereas for the determination abdominal fat, waist circumference (WC) or waist-to-height ratio can be determined. The latter measurements have been recommended to improve the assessment of cardio-metabolic risk, even in young children.

Body proportion determination may contribute to a better insight into the growth pattern of several genetic disorders, especially when affecting skeletal growth, such as Turner syndrome, Kabuki syndrome and Klinefelter syndrome. The evaluation of a morphogram of the body has been found very helpful in the detection of the typical changes in Turner syndrome, showing the greatest deficit in leg length and greatest excess in chest circumference, whereas in Klinefelter syndrome disproportionally long legs during childhood are present. In addition, segmental body measurements might be also helpful in evaluating the risk of associated diseases or the effect of growth promoting therapies. In Turner syndrome equal of greater increase in leg length SDS has been found to be a good marker of GH sensitivity. On the other hand, excessive GH dosing is known to increase feet length excessively in several growth disorders.

In conclusion, anthropometric methods can be used with efficiency for several clinical purposes, if accurate and reliable measurements are performed by dedicated nurses or doctors.

WG7.2

Next Generation Nursing: Genomic Competencies for Pediatric Endocrine Nurses

Andrew Dwyer

Boston College, Chestnut Hill (MA), USA

This presentation provides an overview of genetics relevant to pediatric endocrine nursing practice. A brief genetic primer for nurses will be given followed by discussion of patient and clinician barriers to genetic literacy. Genetic competencies for nursing practice will be reviewed and application will be demonstrated through several pediatric endocrinecase presentations. At completion, participants will be able to incorporate concepts of genetic literacy and apply genetic nursing competencies to their nursing practice in order to promote comprehensive care of patients and families.

WG7.3

Abstract not available

WG7.4

Abstract not available

WG7.5

Abstract not available

Free Communications

Adrenals & HPA Axis

FC1.1

A Novel Non-Invasive Short Synacthen Test Validated in a Healthy Paediatric Population

Charlotte Elder[1,2], *Ruben Vilela*[1], *Trevor Johnson*[3], *E Helen Kemp*[1], *Brian Keevil*[4], *John Newell-Price*[1], *Richard Ross*[1], *Neil Wright*[2]

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Introduction: Worldwide the Short Synacthen Test (SST) is the most popular diagnostic investigation for adrenal insufficiency (AI) amongst both paediatric and adult endocrinologists. Cannulation and blood sampling are required making it invasive, time-consuming and resource-intensive. We have previously validated a reliably absorbed and well tolerated formulation of nasal synacthen (Nasacthin003) in healthy adult males, measuring the glucocorticoid response in salivary cortisol and cortisone. This paediatric study establishes a novel non-invasive SST in children.

Methods: A prospective, open-label, sequence-randomised, cross-over pharmacokinetic study of Nasacthin003 in 24 healthy children aged 4-14 years. Volunteers were dexamethasone suppressed to establish a uniform glucocorticoid baseline and enable measurement of plasma Synacthen. For the intravenous comparator participants received either 250 mcg (N=12) or 1 mcg (N=12) IV synacthen. Nasacthin003 was administered via a mucosal atomiser device, 0.1ml to each nostril. During both three-hour visits 14-paired blood and saliva samples were taken (-15, -1, 2, 5, 10, 15, 20, 30, 40 50, 60, 75, 90 and 120 minutes) and measurements of plasma Synacthen (ACTH EIA), plasma cortisol (chemiluminescent immunoassay) and salivary cortisol and cortisone (LC-MS/MS) made. The paediatric data was compared to our previous healthy male adult cohorts.

Results: The Cmax, Tmax and time-concentration curves for this child cohort were essentially indistinguishable from the historic adult data for all glucocorticoid biomarkers in all three tests (250 mcg IV, 1 mcg IV and Nasacthin003). The mean plasma cortisol Cmax in children compared with adults was 568 nmol/L (+/-79) versus 558 (+/-110), 406 (+/-77) versus 400 (+/-89) and 630 (+/-54) versus 615 (+/-51) for Nasacthin003, 1mcg IV and 250 mcg IV respectively. The median Tmax was 75 minutes (IQR 30 mins) in both children and adults following Nasacthin003, 30 mins for IV 1 mcg and 120 mins for IV 250 mcg. The administeration of Nasacthin003 in children resulted in a slightly higher exposure (synacthen $AUC_{0\text{-}inf}$) compared to adults, due to smaller body size. Salivary cortisol and cortisone samples were closely correlated with their paired serum samples (r=0.88 and 0.90 respectively). Salivary cortisone was the more sensitive marker of adrenocortical response at lower plasma cortisol values compared to salivary cortisol.

Conclusions: We have developed a novel non-invasive SST, with PK parameters demonstrating that Nasacthin003 stimulation leads to an indistinguishable glucocorticoid response in both serum and saliva compared to high and low-dose IV synacthen.

FC1.2

Long-Term Effects of Prenatal Dexamethasone Treatment and Postnatal Glucocorticoid Treatment on Brain Structure in the Context of CAH

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Objective: Congenital Adrenal Hyperplasia (CAH) requires life-long replacement of cortisol. Female fetuses with classical CAH are virilized, which can be prevented by prenatal dexamethasone (DEX) treatment from gestational week 7. However, 7 out of 8 fetuses are treated unnecessarily during fetal life and are thus exposed to high prenatal glucocorticoid (GC) levels. Both prenatal exposures to high GC levels, as well as long term postnatal GC-treatment in patients with CAH are expected to affect brain development, predisposing individuals to impairments in cognition. The present study addresses effects of postnatal GC therapy in CAH, and first trimester prenatal DEX treatment in non-CAH subjects on brain structure of young adults.

Methods: 37 CAH (21 female), 43 Controls (26 female), and 19 DEX-treated non-CAH subjects (9 female), aged 16-33 years, underwent MRI scanning at 3T. T1 structural images were analyzed using FreeSurfer software, obtaining estimates of neocortical volume, surface area and thickness and subcortical volumes of atlas-based regions of interest. ANOVA's were employed to assess group differences between CAH and Controls, and between DEX-treated subjects and Controls. Gender effects were estimated with an interaction between sex and group (CAH or DEX). Results were corrected for multiple comparisons (FDR). Age, total brain volume and sex were used as co-variates.

Results: CAH subjects had reduced cortical thickness of areas involved in executive function (left middle frontal gyrus) and sensory integration (right superior occipital sulcus, left intraparietal sulcus), in addition to alterations of cortical volume in areas involved in language (left superior temporal planum polare) and language-based cognitive control (left inferior frontal orbital gyrus, H-shaped sulcus). These areas include mostly left-lateralized fronto-parietal loops that are heavily involved in verbal working memory. DEX-treated subjects had increased volumes of the bilateral amygdala, a key region of the limbic system. There were no interactions with sex.

Conclusion: The present study is the first to show an effect of prenatal DEX treatment on brain structure in individuals not having CAH and exposed to DEX during early fetal life, thus proving the existence of fetal programming effects of prenatal GC treatment. In addition, we show that long-term glucocorticoid treatment affects brain structures of working memory networks in patients with CAH. Our results provide a basis for reconsidering the cost/benefit balance of prenatal DEX treatment and stress the importance of optimizing GC treatment for CAH.

FC1.3

Targetting the Binding of ACTH to the Melanocortin Receptor by Structure Modeling and Design of Peptide Antagonists to Block Excess Androgens in 21-Hydroxylase Deficiency

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Background: The adrenocorticotropic hormone (ACTH) is a 39 amino acid polypeptide secreted by the anterior pituitary and regulates cortisol secretion from the adrenal cortex. Cortisol has negative feedback and regulates the synthesis and secretion of the ACTH. Excess ACTH is associated with a wide range of diseases including congenital adrenal hyperplasia (CAH). Classic CAH due to the 21-hydroxylase (CYP21A2) deficiency causes a reduction or loss of cortisol synthesis. Here the negative feedback is removed, causing an excess of ACTH which then leads to an increase in the production of adrenal androgens. This high level of androgens compromises both the growth and the fertility in the CAH patients.

Aim: To model the interaction of ACTH with MC2R and design ACTH antagonists for reducing the abnormal adrenal androgen production by blocking the binding of ACTH to the MC2R.

Methods: Three-dimensional protein structure models of both the MC2R and the ACTH were built by homology modeling and optimized by molecular dynamics (MD) simulations. A computational docking of ACTH to MC2R was performed and contact points of ACTH and MC2R were generated. This interaction information was then used to design peptide-based inhibitors. *In-Vitro* assays were performed to test the potency of designed peptides which were then optimized further to produce a second batch of antagonists. For assays, the OS3 cells transfected with MC receptor constructs were used and cyclic AMP (cAMP) was measured by luciferase assay. The potential to shift the ACTH concentration-response curve (CRC) was evaluated to characterize antagonist activity of the designed peptides.

Results and Conclusion: Activation and inhibition of MC2R by designed peptides were tested and the assay results confirmed the structural bioinformatics predictions. Mutation in the core sequence (M4, R8) of ACTH abolished MC2R activation as predicted. One lead peptide inhibitor was identified which shifted the ACTH CRC towards the right by half log, indicating antagonism. This study could be useful in ACTH/MC2R antagonist development and inhibiting the binding of ACTH to the MC2R could be a novel approach for CAH management.

FC1.4

Whole Exome Sequencing in Patients with Primary Generalized Glucocorticoid Resistance Identifies a Novel *TRIM28* Gene Mutation (p.R230X)

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Introduction: Primary Generalized Glucocorticoid Resistance or Chrousos syndrome (CS) is a rare sporadic or familial disorder characterized by generalized, partial tissue insensitivity to glucocorticoids. Mutations of the *NR3C1* gene, which encodes the human glucocorticoid receptor, have been identified in many but not all patients with CS.

Objective: To identify novel genes related to CS in patients without *NR3C1* gene mutations.

Patients and methods: Ten patients (6 males, 4 females) with CS but without *NR3C1* gene mutations, and two patients with CS associated with *NR3C1* gene mutations (positive controls) underwent Whole Exome Sequencing (WES) on Ion Proton platform (ThermoFisher Scientific USA). Bioinformatic analysis was carried out employing the variant annotation and filtration of the Ion Reporter and VarAFT applications; the variant annotation was carried out in comparison with the Ch37(hg19).

Results: Using bioinformatics tools and a threshold of 50 reads/variant, 500 exonic non synonymous or frameshift variants were identified. Ingenuity Pathway Analysis (IPA, Qiagen) revealed that these changes were present in 390 genes involved in 5 different pathways, one of which was that of steroid hormone biosynthesis and/or actions; however, none of the identified variants were pathogenic. An *in Silico* panel, including all the glucocorticoid-related genes, was designed to search for mutations. No pathologic variation was identified in any of the samples. The presence of common homozygous and heterozygous pathologic variants was searched and compared among the two *NR3C1* mutation carriers and the 10 patients not carrying *NR3C1* gene mutation. In all 12 patients, three genes with homozygous and six with heterozygous variants were detected. The variants were evaluated for their pathogenicity employing various *in Silico* analysis tools, and the possible interaction of the genes to the *NR3C1* was explored. Two of these variants were further evaluated: the *TRIM28* gene (*KAP1;TF1B;RNF96;TIF1B; PPP1R157*) variant c.688C>T:p.R230X and the *SLC4A2* gene variant, c.1511A>C:p.N504T. The *TRIM28* gene is ubiquitously expressed and encodes a protein that mediates transcriptional control by interaction with the Kruppel-associated box repression domain found in many transcription factors, including the glucocorticoid receptor. This mutation is not present in the 1000 Genomes or the ExAC browser. The *SLC4A2* gene encodes a member of the anion exchanger family of membrane transport proteins.

Conclusions: We identified a novel *TRIM28* gene novel stop codon mutation, R230X, in all patients with CS, irrespectively of the presence of *NR3C1* mutation. This mutant might be involved in the pathophysiology of CS.

FC1.5

Untargeted Plasma Metabolomics in Subjects with Differences in Tissue Glucocorticoid Sensitivity Identifies a Novel Metabolic Signature

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Background: Tissue glucocorticoid sensitivity is characterized by a considerable variation in terms of therapeutic response and side effects to synthetic glucocorticoids. The multi-metabolite concentration profile measured by untargeted plasma metabolomics provides a comprehensive metabolic signature that might be used in clinical practice.

Objective and Hypotheses: To investigate the usefulness of plasma metabolomics in identifying a metabolic signature that could distinguish glucocorticoid resistant from glucocorticoid sensitive subjects and provide clues of the underlying physiological differences.

Methods and Results: One hundred healthy volunteers were given a low-dose (0.25mg) dexamethasone at midnight, and polarized into the 10% most sensitive (S) and 10% most resistant (R) according to the serum cortisol concentrations in the following morning. One month later, DNA was isolated from peripheral blood mononuclear cells and plasma samples were collected. Sequencing analysis did not reveal any mutations or polymorphisms in the human glucocorticoid receptor (*NR3C1*) gene. Subsequently, we determined the metabolic profile of plasma samples, using Gas Chromatography - Mass Spectrometry (GC-MS). After appropriate data normalization and filtering, 51 metabolite profiles were used to extract biological conclusions. Multivariate significance analysis (SAM) identified 20 metabolites with significantly lower abundance in the sensitive compared to the resistant groups, including fatty acids and intermediates of serine/threonine metabolism. These results combined with the higher (but not statistically significant) glucose and lactate abundance, indicate higher lipid oxidation, aerobic glycolysis and serine/threonine metabolism rates in the sensitive compared to the resistant individuals.

Conclusions: A metabolic profile indicating oxidative stress conditions was observed in the sensitive compared to the resistant group. This is a significant result in providing a signature to differentiate the glucocorticoid resistant from glucocorticoid sensitive subjects to be useful in clinical practice, while providing clues of the underlying molecular mechanisms of the physiological differentiation.

FC1.6

A Novel Stem Cell Model for the Triple a Syndrome

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Triple A syndrome (AAAS) is a rare, incurable, recessive disorder, characterised by achalasia, alacrima, adrenal failure and a neurodegenerative phenotype. The *AAAS* gene encodes ALADIN, is a nuclear pore complex (NPC) protein necessary for nuclear import of DNA protective molecules, important for redox homeostasis. ALADIN's role is not fully characterised: its discovery at the centrosome and the endoplasmic reticulum suggests a role outside the NPC. To date, the interrogation of ALADIN's function has been limited by suboptimal disease models: knock-out mice do not exhibit an analogous phenotype, patient fibroblast cultures do not originate from the affected tissue-type, and knock-down experiments with immortalised cell lines achieve at best an 80% reduction in ALADIN expression.

Aim: To generate cellular models of AAAS with isogenic controls and undertake characterisation.

Method: We have developed induced pluripotent stem cell (iPSC) models of AAAS using CRISPR-Cas9 gene-editing: (1) Bi-allelic exon 2 deletion (*AAAS*-KO) and (2) *AAAS* homozygous patient mutation: a splice donor hotspot mutation p.G14fs (c.43C>A, exon 1) (*AAAS*-mutant). These are paired with the original healthy wild-type (WT) iPSC line and mono-allelic exon 2 deletion (*AAAS*-het) as isogenic controls.

Results: Immunoblotting did not detect ALADIN in *AAAS*-KO or *AAAS*-mutant cells. There was no difference in cellular proliferation after 24 hours between *AAAS*-KO compared to WT by cell counting (p value 0.24). Immunofluorescence with Ki67 antibody confirmed there were no significant changes in cellular proliferation (WT: 100% of cells exhibit Ki67 compared to 88.46% of *AAAS*-KO cells, p value 0.40). RNA sequencing was performed to identify differences in the transcriptome of the iPSC lines, comparing WT to *AAAS*-KO, *AAAS*-mutant and a mono-allelic exon 2 deletion (*AAAS*-het) (n=3). This identified 9 genes with significantly altered transcription (LogFC values >1.1 and <-1.1) with preliminary analysis suggesting an impact of AAAS deficiency on genes involved in oxidative stress. We demonstrated that *AAAS*-KO and *AAAS*-mutant cells will differentiate along a neurocortical lineage, expressing neuronal transcription factors OTX2 PAX6 and Nestin.

Conclusion: We present a viable alternative iPSC model for the study of ALADIN in a near endogenous environment. These can be differentiated along a neurocortical lineage, to reflect the tissue affected in the Triple A Syndrome. We present detailed transcriptome analysis, which will inform further functional experiments, designed to provide insight into the pathogenesis of AAAS.

Bone, Growth Plate & Mineral Metabolism 1

FC2.1

Burosumab, a Fully Human Anti-FGF23 Monoclonal Antibody, for X-Linked Hypophosphatemia (XLH): Sustained Improvement in Two Phase 2 Trials in Affected Children 1-12 Years Old

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In XLH, excess fibroblast growth factor 23 (FGF23) causes hypophosphatemia and consequent rickets, skeletal deformities, and growth impairment. The efficacy and safety of burosumab, a fully human monoclonal antibody against FGF23, was evaluated in two Phase 2 trials in children with XLH.

In CL201, 52 children with XLH (5-12 years old, Tanner ≤ 2) were randomized 1:1 to receive subcutaneous burosumab every two (Q2W) or four (Q4W) weeks, with doses titrated up to 2 mg/kg to target fasting serum phosphorus levels within 1.1-1.6 mmol/L. In CL205, 13 children with XLH (ages 1-4 years) received subcutaneous burosumab 0.8 mg/kg Q2W, which was increased to 1.2 mg/kg based on serum phosphorus levels. A key efficacy endpoint for each study was change in rickets severity assessed by blinded readers using two radiographic scales: Thacher Rickets Severity Score (RSS) and the Radiographic Global Impression of Change (RGI-C). Here, we present efficacy and safety data of Q2W dosing through week 64 from these studies.

Results are reported for Q2W-treated subjects (CL201 n=26; CL205 n=13). Collectively, 95% of subjects had received prior conventional therapy. Rickets was evident at baseline in both studies (mean ± SE RSS: CL201, 1.9 ± 0.2; CL205, 2.9 ± 0.4). At Week 64, Total RSS was reduced by 58% CL201 and by 69% in CL205 (both $p<0.0001$); rickets as assessed by RGI-C at Week 64 improved as well (CL201: +1.62 ± 0.16, $p<0.0001$; CL205: +2.23 ± 0.12, $p<0.0001$). Mean (SD) dose (mg/kg) at Week 64 was 1.04 (0.48) and 0.93 (0.18) for CL201 and CL205, respectively. Mean (SD) serum phosphorus (mmol/L) increased from 0.8 (0.1) at Baseline to 1.1 (0.1) at Week 64 in CL201 ($p<0.0001$); and from 0.8 (0.1) to 1.1 (0.2) in CL205 ($p<0.0001$). Mean alkaline phosphatase (U/L) decreased from 462 U/L at Baseline to 354 U/L at Week 64 in CL201 ($p<0.0001$); and from 549 to 334 in CL205 ($p<0.0001$). One subject per study experienced a serious adverse event (AE): hospitalization for fever/muscle pain that resolved within a day (CL201) and a dental abscess (CL205). Other AEs were generally mild to moderate in severity. No clinically meaningful changes in calcium or parathyroid hormone were observed. No subjects discontinued the study or developed hyperphosphatemia.

Children 1-12 years old with XLH administered burosumab Q2W showed significant improvements in phosphate homeostasis and rickets that were maintained for 64 weeks.

FC2.2

Whole Genome Sequencing Reveals Novel Intragenic Deletions of *GNAS* as Causes of Pseudohypoparathyroidism Type 1a

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Background: Pseudohypoparathyroidism type 1a (PHP1a) is characterized by Albright hereditary osteodystrophy (AHO) and multi-hormone resistance, most commonly to parathyroid hormone (PTH) and thyroid-stimulating hormone. This rare disorder is caused by inactivating mutations involving exons 1-13 of the imprinted *GNAS* gene that encodes the alpha-subunit of the stimulatory G protein (Gαs). Due to paternal imprinting of Gαs transcripts, *GNAS* mutations on the maternal allele cause PHP1a while similar mutations on the paternal *GNAS* allele cause pseudopseudohypoparathyroidism (PPHP) characterized by the physical findings of AHO but without hormone resistance. More than 200 point mutations and small coding insertions/deletions (indels) have been described in PHP1a, but small intragenic deletions are rarely reported due to limitations of Sanger and whole exome sequence analysis.

Objective and hypotheses: To identify the underlying genetic defects for three patients with clinical diagnosis of PHP1a/PPHP, negative *GNAS* sequencing, and normal SNP array.

Method: Whole genome sequencing (WGS) was applied to two patients with clinical diagnosis of PHP1a to search for genomic structural variations and Sanger was performed to confirm and define their boundaries. Pyrosequencing was used to determine percent methylation at CpGs in the exon A/B differentially methylated region (DMR).

Results: We identified two novel small genomic deletions, supported by different bioinformatic algorithms. For family 1, an 1,438-bp deletion (chr20:g.57,465,324-57,466,761) that involves partial exon 1 was identified in the proband with clinical diagnosis of PHP1a and slightly reduced methylation level (34%) at exon A/B. Subsequently Sanger confirmed the deletion is inherited from mother who is affected with PPHP. This deletion starts 923-bp up-stream of the deletion described by Reyes *Et Al*., Bone 2017 (chr20:g.57,466,247-57,468,263) in a PHP1a patient with normal (50%) methylation at exon A/B, suggesting this 923 nucleotides could potentially highlight genetic elements important for normal establishment and/or maintenance of imprinting at exon A/B. WGS, followed by Sanger, revealed another novel small deletion (chr20:57,467,470-57,473,862) that includes exon 2 of *GNAS* in the second PHP1a patient with 43% methylation at exon A/B.

Conclusion: Our results demonstrate WGS can detect relatively small deletions beyond Microarray resolution and could be used as a single test to capture nearly all known genetic variations. The first deletion identified herein in a patient with slightly reduced methylation level at exon A/B further refines a region that may be critical for normal imprinting of the exon A/B DMR.

FC2.3

Clinical Course of Hypoparathyroidism in Patients with APECED (APS1)

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Background: Hypoparathyroidism (HP) is the most common first endocrinopathy in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED or APS1), an autosomal recessive condition caused by mutations in the *AIRE* gene. Treatment of HP has not changed over the decades and parathyroid hormone is used only rarely.

Aim: To describe clinical characteristics and course of HP in a cohort of patients with APECED and evaluate treatment challenges in pediatric patients.

Methods: We collected retrospectively the data concerning diagnosis and treatment of HP in patients with APECED diagnosed in Finland after 1960. Medical histories were reviewed for all required adjustments in calcium and active vitamin D dosing before the age of 18 years. The first year after diagnosis was excluded from the analyses. Serum ionized calcium, plasma phosphate and urine calcium to creatine ratios were measured during normal follow up using fasting blood samples and second void urine samples in patients.

Results: Altogether 29 patients were included in the study; 21 (72 %) were females. Median age at diagnosis of HP was 5.77 years (Interquartile range, 4.25–7.66). In 34% of them APECED diagnosis was made before development of HP. Calcium supplement was started at the time of diagnosis in 33 % of patients in 1960-1980 (n = 12) and in 82 % of patients after 1980 (n = 17). Based on data on 148 patient years, the mean number of medicine adjustments per year was 5.74. Signs of nephrocalcinosis had been found in five patients (17 %) before the age of 18 years. The cohort included six patients who were currently followed at pediatric centers. Their median age was 12.5 years (range, 7.0 - 16.5 years) and median HP disease duration 8.8 years (range, 0.3 - 12.9 years). One patient was treated with teriparatide with an infusion pump. In the pediatric subjects the median plasma ionized calcium was 1.12 (range, 1.02 - 1.25) mmol/L and met the target range of 0.98 - 1.08 mmol/L in every third of the patients. Median phosphate level was 1.72 (1.25 - 1.84) mmol/L. Urine calcium to creatine ratio was below 0.7 in 83 % of patients.

Conclusions: Treatment of HP with calcium supplements and vitamin-D metabolites requires frequent dose adjustments in patients with APECED and indicates a need for improved treatment modalities.

FC2.4

Diagnostic Performance of Artificial Neural Network-Based TW3 Skeletal Maturity Assessment

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Purpose: To evaluate the efficacy of supervised Artificial Neural Network (sANN) in bone age assessment and compare the diagnostic performance of sANN-based TW3 skeletal maturity assessment on hand radiographs with that of experienced child endocrinologists.

Materials and Methods: This study developed an optimized artificial intelligence TW3 bone age assessment system by using the sANN and rating for the 20 hand bones (13RUS+7carpal) from A to I. 8332 of clinical hand radiographs (the chronological age range from 6 months to 17 years old, male 45.5%, female 54.5%) in our hospital were obtained from Jan 2012 to Dec 2016. Of them 6665 examples were for train set and the rest 1667 ones for validation. 200 independent examples were for the test set, the bone age was firstly assessed by four experienced child endocrinologists according to TW3 rule. Bone age assessment between the artificial intelligence model (BA-AI) and endocrinologists (BA-E) was assessed by comparing the root mean square (RMS) and mean absolute difference (MAD). And we also compared time consumption and stability between model and reviewers.

Results: The mean difference between BA-AI and BA-E was 0.4±0.3 years, with a mean RMS and MAD of 0.54 and 0.48 years. The female bone age difference assessed within six months accounted for 92.5%, and 98.4% in one year and for males 93.3% and 97.84% respectively. The average time of input hand radiographs to output bone age was 1.5±0.2s for the model, while 225.6±55.5s for the reviewers. The consistency of TW3 Carpal between the four reviewers is poor than TW3 RUS, the differences between reviewer1 and 2, reviewer 2 and 4 were statistically significant.

Conclusion: The diagnostic performance of sANN-based TW3 skeletal maturity assessment is time saving, the accuracy is similar and the stability is superior to that of experienced endocrinologists.

Key words: Bone age, Artificial Neural Network, Artificial intelligence, TW3 bone age assessment

FC2.5

Radial ESWT Stimulates Longitudinal Bone Growth in Cultured Rat Fetal Metatarsal Bones

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Background: Extracorporeal shock wave therapy (ESWT) is widely used in the clinic for non-union of fractures. However, effect of ESWT on longitudinal bone growth has not been well studied. We explored the *in Vitro* and *in Vivo* effects of low/high dose radial shock wave treatment (SWT) on growth plate (GP) cartilage. A positive or negative effect on growth could be harnessed for therapeutic growth modulation while no change establishes safety.

Methods: As a proof of principle, we studied the effects of radial SWT by varying energy levels and frequencies in an *Ex Vivo* model of cultured fetal rat metatarsal (n= 40) bones. At day fourteen, outcome was assessed by length measurement, histology, and immunohistochemistry. *In Vivo,* immature New Zealand white rabbits (n=3) received a low dose of 1500 impulse/5Hz/90mJ, 4 times/month and a high dose of 3000 impulse/5Hz/180mJ, 3 times/month on the right distal femur with contralateral limb as untreated control. Changes in GP were evaluated by histomorphometry and immunohistochemistry after four weeks. Data are expressed as mean±S.D.

Results: *In Vitro*, high energy group (10Hz/180mJ) showed an increase in bone length of 2508±205µm compared to 1900 ±555µm in control bones ($p<0.05$); increase ($p<0.001$) in the hypertrophic zone height (504±58 µm) as compared to control (158.8±13.4 µm) was observed. Immunostaining in high energy group revealed upregulation of PCNA, Bcl-x, Bcl-2, Gli1, NFkB and IGF-1 compared to untreated controls ($p<0.05$). In vivo, high energy group showed increase in cell proliferation (low dose: 79±45 vs 81±4, ns; high dose: 114±9.20 vs 67±0.60, $p<0.05$); low energy group when compared to control showed increase in thickness of GP cartilage (low dose:504±90µm vs 413±65µm, $p<0.05$; high dose: 582±123µm vs 501±26µm, ns) and area (low dose: 2.20±0.40µ2 vs 1.80±0.35µ2, $p<0.05$; high dose: 2.20±0.61µ2 vs 1.90±0.25µ2, p=ns). However final bone length remained unchanged.

Conclusion: High energy radial SWT may stimulate local bone growth by activating Ihh and NFkB pathways in fetal metatarsal bones. In contrast, short-term treatment in rabbits showed a transient increase in GP cartilage area without affecting bone length. Further refining of shock wave doses, location, and duration of treatment are warranted to study any clinically useful impact on longitudinal bone growth.

FC2.6

Final Height Is Negatively Related to Disease Burden in Mitochondrial Disease

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Context: Abnormal growth and short stature are observed in patients with mitochondrial disease but it is unclear whether there is a relationship between growth, stature and muscle phenotype.

Objectives: To examine growth and final height in patients with genetically confirmed mitochondrial disease, to describe growth patterns in the principle underlying genetic subgroups and to establish whether stature is related to disease severity.

Method: Patients were identified from the United Kingdom Mitochondrial Disease Patient Cohort from inception to January 2017. A retrospective analysis of the association between final adult height and most recent body mass index (BMI) within the key genetic subgroups of patients with mitochondrial disease and a comparison with clinical disease severity was then performed. Diseases severity was determined by a validated assessment tool, the Newcastle Mitochondrial Disease Adult Scale (NMDAS).

Results: 585 patients aged 19-89 years of age were identified with documented height, weight and a molecular genetic diagnosis of mitochondrial disease. Patients with mitochondrial disease were short, with a mean height standard deviation (SD) of -0.48 (CI 95%; -0.57 to -0.39) when compared to UK reference data. Patients with the m.3243A>G genotype, were particularly short with a mean height SD of -0.70 (+/-1.20) compared to the single large scale mitochondrial deletions sub-group (-0.27 +/- 1.18; p=0.01) or the nuclear DNA groups (0.41 +/- 1.12;p=0.06). Patients were not thin overall although the m.3243A>G sub-group demonstrated a significantly lower mean BMI SD, 0.12 (+/- 1.64) when compared to the single large scale deletions (0.68 +/- 1.55; p=0.03) and the nuclear DNA sub-group (1.13 +/-1.73; p=<0.00). NMDAS scores were negatively correlated with the height SD (r = -0.265, p=< 0.00). This association was most pronounced in the m.3243A>G group (r=-0.31, p=<0.00). An analysis of the association between NMDAS score and height in older patients (> 25 years) was similar to the data as a whole confirming that the association was not simply due to delayed pubertal development and growth. Age corrected blood heteroplasmy levels in the m.3243A>G sub-group were positively correlated with NMDAS score (r=0.361, p=<0.00).

Conclusion: Multiple mechanisms may contribute to short stature in mitochondrial disease including the impact of impaired muscle function on the growth plate and suboptimal nutrition. However we suspect that abnormal growth also reflects abnormal adenosine triphosphate (ATP) generation and higher heteroplasmy levels in growth plate chondrocytes. Further in-vitro and in-vivo studies are required to confirm this.

Diabetes and Insulin 1

FC3.1

Neonatal Diabetes Owned to Potassium Channel Mutation: Response to Sulfonylureas According to the Genotype

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Introduction / aim: Neonatal diabetes owned to potassium channel mutation can be successfully treated by sulfonylureas (SU). No study has reported SU efficiency according to the genotype.

Method: Review of literature conducted in accordance with the control criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). Search engine used: PubMed and the Cochrane Library database. Selection of clinical report, case reviews and meta-analyzes published in English, German or French before May 2017. Data collected: patient characteristics and SU treatment, success rate and presumed failure of SU treatment, characteristics of genetic mutations, HbA1c before and after switch, adverse effects. 84/150 studies selected.

Results: 393/449 patients were successfully treated by SU (87.5%). The median age at diagnosis was 60 days of age (0 to 20 years of age), and at sulfonylureas initiation was 48 months of age (0 to 63 years). In 32 patients, SU were introduced only in adulthood. The median dose of SU required to maintain a good glycemic control was 0.47 mg / kg / day (0 to 2.8 mg / kg / day). The median dose in patients with ABCC8 mutations was 0.4mg / kg / day (0.03-1.8mg / kg / day) versus 0.49mg / kg / day (0.017-2)., 6) for mutations of KCNJ1. The median HbA1c of the patients was 8.2% before SU treatment versus 6.2% after the start of treatment. 6 mutations of the KCNJ11 gene (C166Y, G334D, G334V, I296L, L164P, Q52L) on the 43 reported and 4 mutations of the ABCC8 gene ((F132V, N72S, R1182W, R825W) on the 39 reported have never been successfully treated. 5 mutations of KCNJ11 and 5 mutations of ABCC8 required high doses of SU (> 0.79 mg / kg / day) to allow insulin discontinuation (KCNJ11: C166Y, K170N, L164P, Q52R, R50P - ABCC8: A1263V, Q211K, R1182W, T229N, V86A). Digestive disorders in the days following the introduction of SU were the main reported adverse effects.

Conclusion: SU alone are efficient to allow a good metabolic control in 88% of patients with permanent neonatal diabetes owned to KCNJ11 mutation and in 84% of patient carrying a mutation ABCC8 gene. Nor significant side effects were reported. This study is, to our knowledge, the only review of the literature aimed at identifying the SU of mutant potassium channels in vivo.

FC3.2

Genome-Wide Meta-Analysis Identifies a Novel Low Frequency *STK39* Variant of Large Effect on Risk of Type 1 Diabetes

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Background: The genetic etiology of Type 1 Diabetes (T1D) is well recognized, with over 60 loci being identified to date, mainly through genome-wide association studies (GWAS). Most of these genetic associations involve common variants, while a sizable portion of the missing heritability of T1D could be attributed to unidentified rare single nucleotide polymorphisms (SNPs) (minor allele frequency (MAF) < 5%). The recent availability of large human whole genome sequencing datasets has enabled the interrogation of rare genetic variation by deep imputation from directly genotyped data, in the search of large genetic effects associated with rare alleles. Here we undertook a large GWAS meta-analysis to identify rare genetic variants with large effects on T1D risk.

Methods/Results: Through deep imputation, GWAS, and meta-analysis of 12 cohorts of European ancestry totaling of 9,684 T1D cases and 15,743 controls, we identified 43 independent genome-wide significant variants outside the major histocompatibility complex,23 of which were common, mostly at known autoimmune loci (N=14). 24 of these variants had MAF < 5%, all with large effects (OR>1.5), and only 5 were in known autoimmune loci. 17 of the 24 rare variants successfully replicated in a separate cohort including 4,329 T1D cases from T1DGC and 9,543 controls from UK Biobank. After combining discovery and replication results, 14 of these 17 variants had an OR >1.5, and 10 achieved an OR > 2. Our *in Silico* follow-up of the lead rare SNPs using a topological domain analysis prioritized a low-frequency variant at 2q24.3 (rs60587303 (C), MAF 1.8%) within the first intron of *STK39,* with a combined OR on T1D of 1.97 (95% CI 1.58-2.47, Pmeta 2.9 x 10^{-9}), an effect comparable to those of the insulin (*INS*) and *PTPN22* loci. This variant overlaps a DNase I hypersensitivity cluster of 68 cell types, and a cluster of transcription factor bindings sites including *FOS, JUN* and *STAT3.* Pharmacological blocking of Stk39 in murine T-cell lines increased activation and proliferation of effector T-cells and secretion of gamma interferon from CD4 T-cells.

Conclusion: We identified 17 novel rare variants associated with T1D, most of which have effect sizes larger than previously described common SNPs. Our findings highlight STK39 as a protein, with no previously known role in T1D, which appears to influence T-cell activation and effector functions. These findings add to the knowledge of the genetic architecture of T1D and demonstrate *STK39* as a new T1D gene with potential therapeutic implications.

FC3.3

Pediatric Patients with Type 1 Diabetes and Abnormal Nerve Conduction Studies Demonstrate Higher Neopterin Levels: Potential Role as a Biochemical Marker for Peripheral Neuropathy

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Background: Electrophysiological techniques allowed identification of sub-clinical pathological changes and early diagnosis of diabetic peripheral neuropathy (PN). Neopterin is a marker of inflammation and cellular immune response that is elevated in conditions of T-cell or macrophages activation. Diabetic peripheral neuropathy (PN) is associated with inflammatory/immune processes and therefore, we hypothesized that neopterin could be used as a marker of neuropathy in type 1 diabetes mellitus (T1DM).

Objectives: To measure neopterin levels in 60 children and adolescents with type 1 diabetes mellitus (T1DM) compared with 30 age- and sex-matched healthy controls and to assess its possible relation to glycemic control, PN and nerve conduction studies (NCS).

Methods: Sixty patients ≤18 years and >5 years disease duration were subjected to neurological assessment by neuropathy disability score (NDS) and NCS for median, ulnar, posterior tibial and common peroneal nerves. Mean fasting blood glucose, lipid profile, HbA1c, high sensitivity C-reactive protein (hs-CRP) and serum neopterin levels by enzyme linked immunosorbent assay were measured.

Results: The frequency of PN according to NDS was 40 (66.7%) patients out of 60, while NCS confirmed that 30 (50%) patients had this complication. Neopterin levels were significantly higher in patients with DPN than those without (median [IQR], 53.5 [35–60] nmol/L versus 17 [13–32] nmol/L) and healthy controls (5.0 [3.2–7.0] nmol/L) (p<0.001). Significant positive correlations were found between neopterin levels and HbA1c (r=0.560, p=0.005), serum creatinine (r=0.376, p= 0.003), total cholesterol (r=0.405, p= 0.026) and hs-CRP (r=0.425, p= 0.012) among patients with DPN. Neopterin levels were positively correlated to motor latency of tibial and common peroneal nerves as well as motor and sensory latencies of median and ulnar nerves. Logistic regression analysis revealed that neopterin was a significant independent variable related to DN (Odds ratio, 2.976). According to ROC curve analysis, neopterin cutoff value 32 nmol/L could differentiate patients with and without DPN with 100% sensitivity and 96.7% specificity.

Conclusions: Diabetic peripheral neuropathy occur in both sensory and motor nerves in children and adolescents with T1DM, even before the presence of symptoms. Nerve conduction changes in lower limbs are more common than that in the upper extremities. The strong relation between neopterin and nerve conduction parameters supports its use as a reliable serum biomarker for PN in T1DM.Our study highlights the role of inflammation and cellular immune activation in the pathophysiology of diabetic neuropathy and introduces neopterin as a future therapeutic target.

FC3.4

Is the Glycaemic Response from Fat in Meals Dose Dependent in Children and Adolescents with T1DM on Intensive Insulin Therapy?

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Background: Management of people with T1DM on intensive insulin therapy (IIT) uses algorithms based on the meal carbohydrate (CHO) content (MCC) to calculate prandial insulin dose. Typically, these calculations do not consider the meal content of fat or protein.

Objective: To determine if the postprandial blood glucose (BG) response to varying fat content is dose dependent when standard insulin bolus is given based on MCC.

Methods: Randomised repeat testing of 30 patients with T1DM >1 year duration, aged 8-18 years on IIT. A test drink was given on

6 consecutive nights, at 10 PM, in random order, without insulin, 4 hours after the regular evening meal; 5 test drinks varying in fat content (3, 13, 25, 38, 50g), but without CHO/protein, and one 20g CHO drink with no fat/protein. A continuous glucose monitoring system was used to assess BG levels at 10 minute intervals for 8 hours afterwards. Area under the BG excursion curve was calculated for each individual and analysed for each one-hour block after the drink. Generalised linear mixed models (GLM) with a random effect for the individual patients, were used to determine if there was a statistically significant difference between BG excursions after 20g CHO drink compared to drinks containing fat. The dose response was estimated using similar GLM but excluding the CHO drink and treating the BG excursions as a continuous variable.

Results: There were thirty paritcipants of whom 17 (56.7%) were female, age 8-16 years, with median BMI 19.8 kg/m^2. The CHO drink increased average BG but this increase wasn't seen with consumption of the drinks containing fat. Over the early postprandial period, patients who consumed the CHO drink had higher BG excursions than after consumption of the fat drinks (all p-values < 0.01). This remained statistically higher than some fat drinks at 3 hours after which the BG excursions of patients who had consumed the fat drinks tended to rise but did not reach significance until 6 hours. The dose response in AUC for fat became statistically significant between 6 and 7 hours (p=0.024), and 7 to 8 hours (p=0.015).

Conclusions: Fat lowers BGL in the first 4 hours after ingestion, in contrast with the increased glycaemia following a 20g glucose ingestion without insulin. Fat increases BGL 6-8 hours after ingestion in a dose dependent manner. These observations may impact on insulin dosing for high-fat meals in intensive insulin therapy.

FC3.5

Genotype and Phenotype Correlation in Syndromic Forms of Hyperinsulinaemic Hypoglycaemia – A 10-Year Follow-Up Study in a Tertiary Centre

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Introduction: Hyperinsulinaemic Hypoglycaemia (HH) is one of the commonest causes of hypoglycaemia in infancy. It is characterised by hypoketotic, hypofattyacidaemic and hyperinsulinaemic hypoglycaemia. The molecular basis of HH includes defects in pathways that regulate insulin release; to date, 12 genes have been associated with monogenic forms of HH (*ABCC8, KCNJ11, GLUD1, GCK, HADH1, UCP2, MCT1, HNF4A, HNF1A, HK1, PGM1, PMM2*). However, no genetic aetiology has been identified in 50% of patients. Recently, various syndromic genetic forms of CHI have been documented including Beckwith-Wiedemann (BWS), Kabuki (KS), Turner (TS), Sotos, Simpson-Golabi-Behmel, Costello, Trisomy 13, Timothy and Usher syndrome.

Objective: We aimed to characterise the different syndromic forms of HH, their response to treatment, and their long-term outlook.

Method: We performed a retrospective study of patients diagnosed with syndromic forms of HH in a specialist tertiary centre.

Results: We recruited 60 children with syndromes or syndromic features presenting with hypoglycaemic episodes were recruited. Investigations confirmed HH in 52 cases. The following syndromes were identified: BWS (n=19), KS (n=7), TS (n=6), Rubenstein Taybi Syndrome (RTS; n=1), chromosome 16p11.2 deletion (n=2), Prader-Willi (n=1), CHARGE (n=1), Trisomy 21 (n=1), Di George (n=1), Sotos (n=1), Costello (n=1), Allagile (n=1), Usher (n=1) and 9 cases with syndromic features (no specific syndrome identified). Forty-four were responsive to diazoxide, with one TS developing pulmonary hypertension, while 5 were unresponsive (5 BWS, 1 RTS). Octreotide was effective in 6 cases (4 BWS, 1 TS; 1 BWS partially responsive). Lanreotide monthly injections were successfully administered in one BWS case. Sirolimus was used in three cases (2 BWS, 1 RSS) and proved partially effective. Pancreatectomy was required in 6 cases: 3 BWS, 1 KS, 1 Costello and 1 with an undefined syndrome. Thirty-eight patients discontinued medication at ages ranging from 1 month to 4.5 years, while 4 stopped medication post-pancreatectomy and 14 children continue to require medication (10 Diazoxide, 3 Octreotide, 1 Lanreotide).

Conclusion: Our study highlights the association of HH with various syndromes. The early diagnosis of HH is fundamentally important for preventing hypoglycaemic brain injury. Hence, children with features suggestive of syndromes associated with HH must be closely monitored for hypoglycaemia and, when detected, be screened for possible HH. Our data indicate that most cases (70%) of syndromic forms of HH are Diazoxide-responsive and resolve over time. Further studies, including prospective, long-term follow-up data, are required to clarify underlying mechanisms and monitor disease progression into adulthood.

FC3.6

Using CRISPR/Cas9gene Editing to Study the Molecular Genetics of Congenital Hyperinsulinism

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Background: Congenital Hyperinsulinism(CHI) is characterized by the unregulated secretion of insulin in the presence of hypoglycaemia. The mutations in ABCC8 and KCNJ11, which encode the sulfonylurea receptor 1 (SUR1) and potassium inward-rectifying 6.2 (Kir6.2) subunits of ATP-sensitive potassium channel (K channel), are the most common identified cause of the condition. Defects in the HADH gene are responsible for SCHAD- HI, a rare form of the disease caused by the disruption of fatty acid oxidation.

Aims: The aim of this project is to use the novel CRISPR/Cas9 gene editing technique to create a KO mouse cell model of Congenital Hyperinsulinism. Such cellular models would play a key role in the elucidation of the function of the two genes of interest-ABCC8 and HADH. In addition, this cell model would be used to develop and screen for novel therapeutic drugs.

Methods: Several CRISPR sgRNAs were designed to target each gene and tested to identify the best sgRNAs to generate the KO cellular models. Optimisation of the delivery of CRISPR/Cas9 system included the evaluation of different formats such as plasmid DNA, mRNA and RNP complex using a reporter gene. At the molecular level, the disruption of the gene was confirmed by Sanger sequencing and T7 Endo assay. As a pilot, optimisation of ELISA using wild type (WT) TC6 cells to demonstrate glucose-stimulated insulin secretion (GSIS) has been undertaken.

Results: Progress so far has addressed the optimisation of transfection conditions to deliver CRISPR/Cas9. Several sgRNAs have been designed for the disruption of the Abcc8 and Hadh genes. The molecular validation of Abcc8 KO model had been demonstrated by heteroduplexes in the T7 Endo assay. In addition, the optimisation of the ELISA insulin assay in wild type TC6 cells has demonstrated a dose dependent GSIS which can be used as a standard to compare the GSIS from the KO cell model.

Conclusions: The results of our study so far has demonstrated the potential of the use of Cas9/gRNA system as an efficient reverse genetic tool in studying the molecular mechanisms underlying CHI. Our future aims are to: conduct further molecular interrogation to confirm the KO in Abcc8 gene; create a KO allele of hadh gene in the TC6 cell line and further, use the newly generated KO mutant cells to analyse the function of these genes and furthermore, to test and develop novel therapeutic drugs for CHI.

GH & IGFs

FC4.1

Monogenic and Digenic Gene Mutations Are Present in Children with Idiopathic Short Stature (ISS)

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Background: Several genetic defects (*GHR*, *SHOX*, *GHSR*, *NPR2*, *IGFALS*) have been reported in children classified as ISS. ISS children are GH sufficient and about one third of them show low IGF-I levels, suggesting some degree of GH insensitivity.

Objective: To explore potential genetic defects in ISS children suspicious of GH insensitivity, selected by low IGF-I levels and low response to IGF generation test.

Subjects and Methods: Levels of IGF-I, IGFBP-3, and ALS were determined in 42 ISS children (34 males; 2.1-9.4 years old, height <-2.5 SD, stimulated GH > 4.8 µg/L). Those presenting IGF-I <50 ng/ml underwent an IGF generation test (GH doses 0.033 mg/kg.day), measuring IGF-I, IGFBP-3, and ALS. Sequencing of *IGFALS* gene in all participants, and whole exome sequencing (WES) in two selected cases, were performed. *IGFALS* gene variants were generated by site-directed mutagenesis and expressed in CHO cells. ALS variants were analyzed by Western immunoblot (WIB). STAT5b variants were characterized in HEK293T cells transiently transfected with plasmids containing c.DNA variants by a dual luciferase reporter assay.

Results: From 8 children presenting IGF-I levels <50 ng/ml, one was compound heterozygous and 4 heterozygous for *IGFALS* variants (p.E35Gfs*17, p.P22L, p.R548W, and p.G506R). By WIB p.E35Gfs*17 was not detected, p.R548W was a hypomorphic variant, while p.P22L and p.G506R were variants of uncertain significance (VUS).Those 3 presenting the lower IGF-I response were further studied. Patient 1: the compound heterozygous child (p.L409F/ p.S490W) presented undetectable levels of IGFBP-3 and ALS (both *IGFALS* variants were not detected by WIB) was diagnosed as complete ALS deficient. The other two patients (patient 2, heterozygous carrier for p.R548W, and patient 3, *IGFALS*-WT) underwent WES. In patient 2, a 2.1 year-old boy, height 73.5 cm (-3.23 SD), weight 8.28 Kg (-2.5 SD), WES revealed a heterozygous novel *STAT5B* variant: c.1896G>T; p.K632N. *In Vitro* studies demonstrate that p.K632N is an inactive variant, since it showed severe diminished reporter activity, under basal conditions and in response to GH treatment. In patient 3, a 6.3 year-old boy, height

103.8 cm (-2.57 SD), weight 17.5 Kg (-1.53 SD), WES analysis did not reveal potential pathogenic variants related with his phenotype.

Conclusions: Candidate gene approach combined with WES was useful to perform a genetic diagnosis of partial or complete ALS deficiency (one or two affected *IGFALS* alleles) or double heterozygotes (*IGFALS* and *STAT5B* genes) in children with apparent GH insensitivity.

FC4.2

Effects of IGF-1R Nuclear Localization in Glioblastoma Cells

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Background: CNS tumors are the most frequent solid tumors in pediatric population. The IGF system of ligands and receptors are known to play an important role in both normal and neoplastic growth. Recently, we have shown that in paediatric gliomas, IGF-1R nuclear localization was significantly associated with both high grade tumours and increased risk of death, suggesting that nuclear IGF-1R localization may contribute to an aggressive behaviour of these tumours.

Aim: To characterize the impact of IGF-1R nuclear localization in glioma cells.

Methods: U87Mg glioblastoma cells were transfected with pEGFP-IGF1R plasmid to generate stably transfected cells overexpressing GFP-IGF-1R fusion protein. Corresponding Lys1025-1100-1120 of the mature IGF-1R were targeted by directed mutagenesis to avoid IGF-1R nuclear translocation. Cells were cultured, starved ON and stimulated 10 min or 8 h with IGF-1. Proliferation assays were carried out during 5 days, with or without IGF-1 stimulation. Wounding assay was analyzed after 18 hours incubation with IGF-1. Protein extracts were obtained from whole lysates or after subcellular fractionation of cultured cells, and processed by western blot using specific antibodies. Gene expression was quantified by rqPCR. All experiments were performed under 50nM IGF-1 stimulation and 0.5uM preincubation with OSI906.

Results: we generated stably transfected cells with 5 (B4U87) or 50 (B2U87) times basal expression of IGF-1R. In these cells an increase in pAKT, pERK and pMAPK38 was observed upon 10 min IGF-1 stimulation. Also, after 8h incubation with IGF-1, nuclear localization of IGF-1R was verified by IF and by western blot of nuclear and cytoplasmic extracts. These effects were blocked by 1h preincubation with OSI906. Although CyclinD1 levels were slightly increased in B2U87 and B4U87 cells in response to 24 h IGF-1 stimulation, proliferation and apoptosis were not different from parental cells during 5 days of culture. Wounding assay showed an increased motility in both B2U87 and B4U87 compared to parental cells. Moreover, GLUT-1 expression showed a two-fold increase after 24h rhIGF-1 stimulation that was abrogated by preincubation with OSI906. Cells expressing GFP-IGF-1R$^{1025x\text{-}1100x\text{-}1120x}$ showed no IGF-1R nuclear localization and a lower increase in GLUT-1 expression upon IGF-1 stimulation.

Conclusion: IGF-1R nuclear localization may contribute to an aggressive phenotype of glioblastoma by increasing motility and metabolism of tumor cells rather than increasing its proliferation.

FC4.3

The Reduction in Longitudinal Growth Induced by PAPP-A2 Deficiency Is Associated with Reduced Body Weight, Increased Energy Expenditure and Behavior Modification

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Background: Pregnancy associated plasma protein (PAPP)-A2 is an insulin-like growth factor (IGF) binding protein (BP) protease that regulates IGF-1 availability, affecting postnatal growth. We have recently reported the first mutations in human *PAPP-A2* causing short stature and changes in bone size and mineral density. However, the IGF system is involved in diverse physiological functions and to date it is unknown how mutations in PAPP-A2, which significantly reduce free IGF levels, might affect these functions.

Objective: The present study aimed to characterize the effects of constitutive *Papp-A2* gene deletion on energy metabolism in adult male and female mice.

Results: Mice homozygous for a *Papp-A2* gene deletion had reduced body length (5-7% reduction) and low body weight (12-16% reduction) from postnatal day (PND) 24 to PND 85 compared to wild-type mice. At 6 months of age, in addition to reduced body length and weight, these *Papp-A2* gene knock-out (KO) mice also had a reduction in bone (femur and tibia) weight and length. Analysis in metabolic cages indicated that PAPP-A2 deficiency increased energy expenditure (kcal/day/kg body weight) and altered [VO_2] consumption and [VCO_2] production (mL/min/kg body weight), resulting in an increase in respiratory quotient [VCO_2/VO_2]. Additionally, adult *Papp-A2* KO mice had a reduction in calorie intake (kcal/g body weight) and locomotor activity, with this reaching significance in males, and an increase in rearing (vertical activity) in females, suggesting that behavior may be affected.

Conclusion: These results further support a role of PAPP-A2 activity in the regulation of postnatal growth and body weight gain and suggest that this protease may be involved in the mediation of IGF-1's effects on energy expenditure and possibly behavior.

FC4.4

A Cross-Sectional Study of IGF-I Bioavailability Through Childhood and Associations with PAPP-A2, STC2 and Anthropometric Data

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Background: Insulin-like growth factor I (IGF-I) is one of the important hormonal mediators of human growth. Circulating IGF-I exists in a ternary complex bound to the acid-labile subunit (ALS) and one of its 6 binding proteins (BPs). IGF-I bound to ALS and BPs needs to be liberated by either Pregnancy Associated Plasma Protease A (PAPP-A) or A2 (PAPP-A2) to reach its receptor. Stanniocalcin 2 (STC2) is a potent inhibitor of both PAPP-A and PAPP-A2. Genome-wide association studies have linked PAPP-A, PAPP-A2, and STC2 to adult stature, and mutations in *PAPPA2* lead to short stature. Although these components are key regulators of the bioavailability of IGF-I, little is known about their concentrations throughout childhood. We aimed to evaluate the normal serum concentrations of bioactive IGF-I, PAPP-A2, and STC2 throughout childhood and the relationship between their concentrations and anthropometric measurements.

Methods: We studied serum from 838 individuals (Age: 3-18, Male: 48%, Caucasian: 83%) who participated in the Cincinnati Genomic Control Cohort, a study of generally healthy children. Subjects were evaluated at a single visit. Height and weight were measured and a blood sample was taken for serum isolation. We measured total IGF-I, bioactive IGF-I, PAPP-A2, and STC2 using ELISA kits at Ansh Laboratories. Patients on medications known to affect growth or with significant medical comorbidities were excluded. Descriptive statistics for each factor by age and sex were estimated; correlation multiple regression was used to assess associations with age, body mass index z-score (BMIz) and height z-score (HAz). Log transformation was used for analysis of the factors, where appropriate. Statistical analysis was performed using SAS®, version 9.4.

Result: Mean bioactive IGF-I, PAPP-A2, and STC2 was slightly higher in females than males. Log PAPP-A2 concentration was inversely correlated with age (r=-0.46, -0.53; (M,F), p=<0.0001). STC2 and intact BP3 concentration were positively correlated with age (r=0.26, 0.34; 0.74, 0.69; (M,F), p=<0.0001). In a multiple regression model, controlling for age and sex, log STC2 and log PAPP-A2 concentration were associated with BMI z-score (β=0.03, p=0.02; β=-0.11, p<0.0001). Log bioactive IGF-I was associated with HAz (β=0.03, p=0.01).

Conclusions: This is the first study describing PAPP-A2 and STC2 concentrations throughout childhood. Bioactive IGF-I levels increased with age as expected. Surprisingly, PAPP-A2, a positive modulator of IGF-I bioavailability, decreased with age, while STC2, a negative modulator, increased with age. Sex differences were detected suggesting differences in regulation of IGF-I bioavailability between sexes throughout childhood.

FC4.5

Prediction of Adult Height by Artificial Intelligence (AI) Through Machine Learning (ML) from Early Height Data

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Context: Growth analyses have traditionally been done by either non-structural descriptive statistics or by fitting models. While we usually describe height and weight separately, we assume reciprocity of weight and height on each other. We utilize ML to predict ages 7-18y height based on height and weight data up to age 6y.

Methods: After pre-processing the height and weight, primary and secondary features (height SDS, BMI, growth velocity) of 1596 subjects (798 boys) age 0-19y from the longitudinal GrowUp 1974 Gothenburg cohort with emphasis (~20 measurements) on infancy (0-12mo) were utilized to train multiple regressors: Linear, MultiLayer Perceptron (MLP), Decision Tree, Random Forest. For evaluating the accuracy of the model for each learning algorithm and choosing the best regressor, we cross validated the system 5-fold, and the out-of-sample performance was tested on 5X100 other subjects and 600 additional subjects of the same study. We then validated the system with the Edinburgh Longitudinal Growth Study cohort of 180 subjects that were measured at 3, 6 mo intervals from age 0-20.

Results: Random Forest Regressor with 51 trees produce the most accurate predictions. The best predicting features (top of the tree) are sex and heights at age 3.3-6.0y. Accuracy of the predictions against actual final height (R-square) increase from 0.580 at age 7 and 0.592 at age 13 to 0.837 at age 18, when actual heights are 173,8±9.2 (SD) and predicted heights 173.3±8.0cm,

with a prediction error of -0.4±4.0cm. Verification of prediction for 600 additional GrowUp children show prediction/actual R2 of 0.76; predictions accuracy correlates negatively with age 18 height (p=1.8e-15). The final height of thin 6y.o. children (1st quartile BMI) were underestimated as compared to 4th quartile (p=5.2e-4). When the algorithm is tested on the Edinburgh cohort, accuracy is 0.38 and prediction errors are 2.0±7.2cm.

Conclusions: 1. ML and AI is used here successfully for the first time to predict adult height based on early (<=6y) height and weight. 2. Prediction accuracy at age 0-6y for age 18y height is better than the bone-age based TW3 method. 3. The best features for prediction are sex and heights at age 3.3-6.0y, when childhood growth velocity has stabilized. 4. Prediction errors are greater for tall (overestimates) and thin subjects 5. The success of ML strongly depends on the structure of data sampling and cannot be easily inferred between dissimilar cohorts.

FC4.6

Absorption and Excretion of Somapacitan, a Long-Acting Growth Hormone (GH) Derivative

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Background: Somapacitan is a reversible albumin-binding growth hormone (GH) derivative in clinical development for once-weekly administration in patients with GH deficiency (GHD). Clinical data in healthy subjects, and adults and children with GHD showed that once-weekly somapacitan injections were well tolerated with no clinically significant safety or local tolerability issues. A sustained dose-dependent IGF-I response supports a once-weekly treatment regimen.

Objective: The primary objective of this study (NCT02962440) was to investigate absorption, metabolism and excretion in healthy male subjects after a single subcutaneous administration of tritium [^{3}H]-somapacitan. Secondary objectives were to assess the pharmacokinetics (PK) of [^{3}H]-somapacitan and [^{3}H]-somapacitan-related material, and the safety and tolerability of somapacitan, after a single dose of [^{3}H]-somapacitan.

Methods: Subjects (seven healthy males aged 45–62 years, BMI 22.8–27.1 kg/m^2) attended up to five clinic visits: visit 1, screening; visit 2, dosing visit (in-clinic stay [16 days]); visits 3 (21 days post-dosing) and 4 (28 days post-dosing), weekly 24-hour in-clinic PK and safety visits; visit 5 (35 days post-dosing), follow-up. Subjects received a single subcutaneous dose of 6 mg somapacitan containing [^{3}H]-somapacitan of 540 μCi/20 MBq at visit 2. Blood, serum, plasma, urine, faeces and expired air were collected for radioactivity assessment.

Results: Twenty-eight days after dosing, 94.0% of the administered dose (range: 90.8–103.5%) was recovered as [^{3}H]-somapacitan-related material, most of which was excreted in urine (80.9%); 12.9% excreted in faeces (both in wet samples) and an insignificant amount (0.19%) in expired air. PK properties of [^{3}H]-somapacitan-related material appeared to be consistent across plasma, serum and blood. Terminal half-life of somapacitan-related material was 189.0, 184.6 and 184.7 hours in plasma, serum and blood (dry samples), respectively. Results from the metabolite analyses will be reported later. Two subjects had six adverse events (AEs); all were mild in severity and considered unlikely to be related to trial product. Both subjects recovered from the AEs.

Conclusion: This is the first study reporting absorption and excretion of somapacitan in human subjects and may be of clinical interest to paediatric endocrinologists treating patients with GHD. 94.0% of [^{3}H]-somapacitan-related material was recovered 28 days after dosing. Urine was the major excretory route, followed by faeces; excretion through expired air was negligible. A single dose of 6 mg somapacitan (containing [^{3}H]-somapacitan [540 μCi/20 MBq]) in healthy male subjects was well tolerated with no safety issues identified.

Thyroid

FC5.1

Beta1-Tubulin Gene (TUBB1) Mutations Cause Thyroid Dysgenesis Associated to Abnormal Platelet Morphology and Hyper-Aggregation

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Background: Congenital hypothyroidism (CH) is the most common neonatal endocrine disorder, with an incidence of 1:3000 neonates, and one of the most frequent preventable causes of mental retardation worldwide. Most (65%) cases of primary permanent CH are due to thyroid dysgenesis (TD). However, a genetic cause is identified in less than 5% of CH due to DT.

Methods: We performed WES (Whole Exome Sequencing) for siblings with childhood-onset TD and we analyzed 270 TD cases by targeted NGS.

Results: We identified three novel *TUBB1*gene mutations that co-segregated with TD in three affected families. *TUBB1*(Tubulin, Beta 1 Class VI) encodes a member of the ß-tubulin protein family. *TUBB1* gene is expressed in the developing and adult thyroid in humans and mice. All three *TUBB1* mutations lead to non-functional α/ß-tubulin dimers that cannot be incorporated into microtubules. First, in *Tubb1*knock-out$^{(-/-)}$mice, we observed *in Vivo* impaired thyroid proliferation and migration during development. Second, final thyroid differentiation was abnormal in *Tubb1*$^{-/-}$embryos, with increased T4 within the thyroid follicular cells, probably reflecting impaired hormone secretion. Third, at 3 months of age, serum TSH levels were higher and T4 levels lower in *Tubb1*$^{-/-}$ in comparison with wild-type mice, suggesting hypothyroidism in the mutants. Moreover, thyrocytes ultrastructure examined by electron microscopy showed larger numbers of dense vesicles in *Tubb1*$^{-/-}$*Versus* wild-type thyrocytes suggesting impaired hormone secretion. In addition, *TUBB1* mutations in patients caused macroplatelets observed in blood smears with high mean platelet volume in complete blood counts and hyperaggregation of human platelets.

Conclusions: Our data highlight unexpected roles for ß1-tubulin, via the microtubules, in thyroid development and function and in platelet physiology. Special concerns should be raised for the CH patients bearing *TUBB1*mutation, as they may have an increased risk for thrombosis in adult life. Finally, these findings expand the spectrum of the rare pediatric diseases related to tubulin mutations and provide new insights into the genetic background and mechanisms involved in congenital hypothyroidism and thyroid dysgenesis.

FC5.2

Enrichment of Inherited Rare Variants in Non-Syndromic Congenital Hypothyroidism from Thyroid Dysgenesis Identified by Exome Sequencing: The Contribution of IKBKE to Vasculogenesis and Thyroid Development

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Congenital hypothyroidism from thyroid dysgenesis (CHTD) is mainly a sporadic and non-syndromic condition occurring in 1:4,500 live births. In contrast to rare cases of syndromic monogenic CHTD, non-syndromic (NS) CHTD shows low familial recurrence risk (~2%) and low concordance rate between MZ twins, suggesting a two-hit scenario combining post-zygotic events with either a *de Novo* monogenic mutation or incomplete penetrance of polygenic inherited variants,. As this latter possibility was recently proven right in cases of non-syndromic congenital heart defects, we analysed the burden of inherited rare variants in the exome of 30 cases of NS-CHTD compared to that of 495 controls sequenced and analysed on the same platform. Gene-burden analysis identified 19 genes enriched in NS-CHTD, including *IKBKE*. Three *IKBKE* rare variants were also identified in an independent cohort of 107 cases of NS-CHTD. *IKBKE* is a member of the inhibitor of κB kinase (IKK) family. It is implicated in the non-canonical pathway of NF-κB and interferon regulatory factor signalling. Furthermore, it has been associated with inflammation, cell transformation, and progression of many cancers. Functional assays showed that *IKBKE* depletion decreases migration of Nthy-Ori cells (a human thyroid cell line) *in Vitro*. Moreover, *Ikbke* depletion in zebrafish caused defective aortic arch artery formation and abnormal thyroid morphogenesis. The phenotype was observed in two different *Ikbke* morphants in which the level of *Ikbke* transcripts correlates inversely with the phenotype, suggesting a dose-effect relationship. Moreover, a partial rescue of the migration defect was observed with injection of human *IKBKE* RNA in *Ikbke* morphants. Our results further expand the growing list of predisposing genes for CHTD and confirm the association between vasculogenesis and congenital thyroid malformations.

FC5.3

Computational Analysis of the Ligand Binding Domain of the Thyroid Hormone Receptor for the Rational Design of an Efficient Protein-Based Biosensor for the Detection of Thyroid Hormone Disrupting Chemicals

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Background: Thyroid hormone disrupting chemicals (THDCs) which are present in the environment, food and everyday consumer products, interfere with thyroid hormone signaling, possibly by interacting with thyroid hormone receptors (THRs). This alters the thyroid hormone homeostasis and affects various functions regulated by the thyroid hormone e.g. macronutrient metabolism, cardiovascular function, and normal brain development. Therefore, there is a necessity for detection and monitoring these pollutants in the environment. THRs belong to the nuclear receptor superfamily and have two highly conserved domains: DNA binding domain (DBD) and ligand binding domain (LBD). The LBD is responsible for the ligand selectivity and could be used as a bio-recognition element in a protein-based biosensor for THDCs detection. However, mutant LBD with increased affinity will act as better bio-recognition elements due to their increased sensitivity towards THDCs and capability in detecting very low quantities of chemicals.

Aim: Prediction of functionally important residues from the LBD of thyroid hormone receptor for rational modification to achieve high binding affinity.

Methods: Multiple sequence alignments of LBD of thyroid hormone receptor across the species were carried out to locate the differentially conserved alignment positions. By employing information theoretic measures (Cumulative Relative Entropy (CRE)) we tried to present a structural and functional analysis of LBD of thyroid hormone receptors. Since THR belongs to thyroid-hormone like a family of nuclear receptor superfamily, we contrasted THR with estrogen receptors (ER). CRE was calculated for two sets of alignments.

Results: Based on highest CRE scoring twenty positions were selected and predicted to impart functional specificity to THR as well as other TH-like receptors.

Conclusion/Significance: Selected residues could be used for rational design of LBD with an enhanced affinity towards ligands and applied towards the development of sensitive protein-based biosensors to detect THDCs.

FC5.4

Thyroid Hormone Analog Therapy in Patients with MCT8 Deficiency: The Triac Trial

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Introduction: Mutations in the thyroid hormone (TH) transporter MCT8 result in MCT8 deficiency, which is characterized by severe intellectual and motor disability and high serum T3 concentrations inducing thyrotoxicity in peripheral tissues. At present, no effective treatment is available, although preclinical studies suggest that the T3 analog Triac is a promising candidate to 1) normalize serum T3 levels and thus alleviate the thyrotoxicosis and 2) restore TH signaling in the brain.

Objective: To study the effect of Triac on serum T3 concentrations and signs of thyrotoxicosis in patients with MCT8 deficiency.

Methods: We conduct a world-wide prospective interventional trial in which 46 patients with MCT8 deficiency receive Triac treatment for 1 year. The primary end-point is the reduction of serum T3 concentrations, and secondary end-points include normalization of heart rate (HR), improvement of body weight (BW) and serum parameters that reflect TH action in peripheral tissues. The neuro(psycho)logical phenotype is assessed before and after 1 year of Triac treatment.

Results: Currently, all patients (age: 1-66 yr) have been enrolled of which 35 completed 1 year of follow-up. Triac treatment effectively reduced serum TSH concentrations (mean ± SD: 2.9 ± 1.6 to 1.0 ± 1.0 mU/L; $p<0.001$), resulting in a strong reduction of T3 concentrations (5.2 ± 1.4 to 1.8 ± 0.8 nmol/L; $p<0.001$), when comparing baseline and end-study measurements in these 35 patients. Importantly, the age-specific SD scores for BW (-3.1 ± 1.9 to -2.7 ± 1.8, $p<0.05$) and BMI (-2.8 ± 2.6 to -2.2 ± 2.6, $p<0.05$) significantly increased, whereas basal HR (102 ±13 to 93±8 bpm, $p<0.01$) significantly decreased. Moreover, serum markers that reflect tissue thyroid state improved such as SHBG (222 ± 88 to 186 ± 76 nmol/L, $p<0.005$) and Creatinine (31.5 ± 10.3 to 36.1 ± 13.0 µmol/L, $p<0.005$). The youngest patients had some improvement in neuropsychological markers. No (severe) adverse reactions to Triac occurred.

Conclusions: This interim analysis indicates that Triac treatment effectively normalizes serum T3 concentrations in patients with MCT8 deficiency. Both clinical outcomes (BW, BMI and HR) and biochemical markers representing thyroid state in different tissues improved on Triac treatment. Future studies should aim to evaluate the effect of Triac on the neurocognitive phenotype once treatment is installed early after birth.

FC5.5

Guidelines for the Management of Paediatric Differentiated Thyroid Carcinoma; A UK Endeavour

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Objectives: Differentiated thyroid cancer (DTC) has shown increasing incidence in children and young people <19 years (CYP), and CYP present with more extensive disease than in adults and are at risk of long-term morbidity. A paucity of randomised controlled trials in the field has led to a lack of consensus on how these children should best be managed. These Children's Cancer and Leukaemia Group and British Society for Paediatric Endocrinology and Diabetes commissioned guidelines intend to provide management guidelines for all paediatricians and paediatric endocrine, oncological, surgical, genetic and radiological specialists caring for CYP with suspected or confirmed DTC, thereby improving long term outcomes.

Methods: Guidelines were developed according to the AGREE II framework. Clinical questions were formulated based on a PICO (**P**opulation, **I**ntervention, **C**omparison, **O**utcome) format by a multidisciplinary Guideline Development Group to guide systematic searches via the Ovid MEDLINE (Jan 1990–Nov 2016) and Cochrane Library (2016, Issue 12) TRIP and EMBASE electronic registries, identifying 250 separate research articles. Publications underwent a three-tier filtering process and 164 were reviewed using the GRADE approach. For areas where recommendations could not be made based on published literature, a two-stage international Delphi consensus process was conducted to inform guideline recommendations.

Results: 64 clinical questions were identified, leading to 42 recommendations which were largely based on low to very low quality evidence. 23 further recommendations achieved >70% agreement via the Delphi consensus process. Important highlights include: the recommendation that all CYP with DTC are managed in an age-appropriate tertiary centre linked to a paediatric oncology centre with care co-ordinated by a clinician with expertise in DTC in conjunction with endocrinology, surgery and oncology; the recommendation to proceed to diagnostic surgery in cases of inconclusive cytology results; the recommendation that total thyroidectomy is indicated for initial surgical management, apart from in selected low risk cases; recommendations on risk stratification based on modified BTA guidelines; recommendations to perform therapeutic central neck lymph node dissection if pre-operative evidence or intra-operative biopsy evidence of loco-regional metastases exists; recommendations on the use, timing and administered activity of radioiodine remnant ablation and therapy; and recommendations for long-term biochemical and radiological follow-up.

Conclusions: These RCPCH collaborative guidelines provide the first UK evidence- and consensus-based national recommendations for the management of paediatric DTC. Through their implementation we hope to achieve better consistency in the investigation, management and ongoing follow up of CYP with DTC and improve long-term quality of survival.

FC5.6

Alterations in DNA Methylation Status of Gene Promoters in Children and Adolescents with Autoimmune Thyroid Disease

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Background: Hashimoto Thyroiditis (HT) and Graves Disease (GD) are conditions known to be caused by abnormal immune response against self-tissues. The biological processes at molecular lever are still poorly understood. A few epigenetic studies have been published so far.

Objective: To investigate whether there are differences in DNA methylation within the HLADRB1, CD40L, FOXP3, CTLA4, FCRL3, IL2RA and PTPN22 promoters between young patients with autoimmune thyroid disease and healthy controls.

Material and Methods: 59 patients with HT (11.7±0.3 years), 9 with GD (12.0±0.4 years), 25 with concurrent type 1 diabetes (T1DM) and HT (13.8±0.5 years), and 54 healthy controls (11.1±0.3 years) without a personal or family history of autoimmune disease, at least at first-grade relatives, were recruited. DNA was extracted from whole blood and then modified with sodium bisulfite. The percentage of methylation in the above mentioned gene promoters was later quantified, using specific primers for modified DNA, by analyzing the melting curves obtained during real-time PCRs. Results are presented as 95% trimmed means ± standard errors. Comparisons were performed using one-way ANOVA tests and Tukey's post-hoc analyses. Level of statistical significance was set at $p<0.05$.

Table 1. (for Abstract no FC5.6)

	Controls	Hashimoto	Diabetes and Hashimoto	Graves	p
HLADRB1	85.2±2.8	82.7±2.3	74.1±5.7	88.3±5.0	0.078
CD40L	60.5±4.2	67.5±3.5	65.9±6.3	62.7±8.6	0.640
FOXP3	94.7±1.4	91.6±1.8	100.9±1.7	86.1±7.2	0.003
CTLA4	42.3±4.1	42.3±3.1	71.4±5.5	45.2±12.5	<0.001
FCRL3	76.8±1.8	77.1±2.3	76.6±2.4	85.0±3.8	0.508
IL2RA	41.5±1.5	36.8±1.4	35.1±2.2	26.0±4.2	0.001
PTPN22	27.1±2.7	39.9±3.3	20.3±3.0	32.6±13.2	0.001

Results: Increased methylation percentage in PTPN22 promoter was associated with HT, decreased methylation percentage in IL2RA promoter with GD, while increased methylation percentage in CTLA4 promoter was associated with concurrent T1DM and HT. Percentages (%) of methylation in CpGs sites within different gene promoters between groups are shown in Table 1:

Conclusion: This study suggests that altered methylation percentages in different gene promoters do exist in patients with autoimmune thyroid disease. These differences remain to be shown whether they are related with variability in the expression of the corresponding genes, thus shedding light in the aetiopathogenesis of autoimmune thyroid disease in childhood and adolescence.

Fat, Metabolism and Obesity

FC6.1

Correlations between Measures of Adiposity Across Childhood and Adolescence and the Intestinal Microbiota in 15–17 Year-Old Children with a Family History of Obesity: Preliminary Findings from the QUALITY Cohort

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Background: While differences in gut microbiota between obese and lean subjects have been described, few studies have examined how adiposity across childhood relates to intestinal microbiota composition and diversity in late adolescence.

Objective: To explore the correlations between measures of adiposity from childhood and adolescence with intestinal microbiota composition and diversity at 15-17 years.

Methods: Data stem from the QUALITY cohort, a cohort study of 630 children with a parental history of obesity. Adiposity was assessed at 8-10 yrs, 10-12 yrs and 15-17 yrs. Height, weight and waist circumference were measured using standardized protocols,

and body mass index z-scores (zBMI) were calculated and participants were classified into weight categories according to CDC reference standards. Percent fat mass was assessed using DXA. 16S-rRNA based microbial profiling of stool samples obtained from 22 participants at 15-17 yrs were conducted to determine the composition and diversity of microbiota. Alpha-diversity indices used to assess richness include observed OTUs and the Chao1 index, whereas the Shannon and Simpson indices measured richness and evenness. Pearson's correlations assessed associations between diversity indices and measures of adiposity.

Results: Of the 22 participants, 14 were normal weight, 6 were overweight and 2 were obese. zBMI across all ages was negatively correlated with the Shannon and Simpson indices. In particular, the correlation of zBMI at 15-17 yrs with the Simpson index was -0.41 (P=0.057). Similar, albeit weaker, negative correlations were noted with measures of evenness and percent fat mass, however none reached statistical significance. Waist circumference was also negatively associated with the Shannon and Simpson indices, with the strongest correlations being with waist circumference at 10-12 yrs and 15-17 yrs and the Simpson index (r=-0.42, P=0.067 and -0.40, P=0.065 respectively). In contrast, measures of adiposity across all ages were positively correlated with measures of richness. The strongest correlations were between zBMI at 15-17 yrs (r=0.50, P= 0.019) and waist circumference at 15-17 yrs (r=0.39, P=0.075) and the Chao-1 index. At the genus level, we found a significantly greater abundance of Roseburia in the overweight/obese group compared to normal weight youth.

Conclusions: These preliminary data in a small sample of children suggest that increased adiposity in early life is associated with differences in gut microbiota diversity indices in late adolescence. The greater abundance of Roseburia, a butyrate producing bacteria, in the gut microbiota of the overweight/obese group remains to be confirmed in a larger sample size.

FC6.2

Impaired Brain Satiety Responses to a Meal in Children with Obesity

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Behavioral studies suggest that brain satiety responses to food consumption are altered in children with obesity. We studied brain regions involved in satiety processing using functional magnetic resonance imaging (fMRI) before and after a test meal. Satiety-related hormonal changes were assessed.

Fifty-four 9-11 year-old children with obesity (OB) and 22 children with healthy weight (HW) were studied. Subjects underwent two fMRI scans, one before and one after a test meal, and finally had an *Ad Libitum* buffet meal to test satiety. Serial blood samples and measures of subjective appetite were obtained. Neural activation for the contrast high-calorie food vs. objects and low-calorie foods vs objects was assessed in brain regions of an extended satiety network encompassing ventral and dorsal striatum, amygdala, ventral tegmental area/ substantia nigra, insula and medial orbitofrontal cortex.

While subjective appetite scores of hunger and fullness changed similarly between groups around the test meal, marked differences in brain activation were noted between OB and HW children. Regarding the global average of brain activation within the extended satiety network, in HW children activation was significantly reduced from pre to post meal in response to viewing pictures of high calorie food pictures ($p<0.01$), while such change from pre to post meal was not seen in OB children, despite appropriate gut hormone (peptide YY, glucagon-like peptide-1, active ghrelin) responses to the test meal in both groups. The lack of central satiety response in OB children was associated with greater degree of insulin resistance. Even when reductions in post-prandial ghrelin were substantial, OB children demonstrated persistent post-prandial activation by high-calorie food cues. OB subjects consumed more total calories at the ad libitum buffet (1156±57 vs. HW 803±64 kcal, $p<0.001$, unadjusted).

In conclusion, HW children demonstrated physiological central satiety responses, i.e. reductions of neural activation by high-calorie food cues following a test meal in areas of the extended satiety network which was not present in OB children. Our data suggest that children with obesity exhibit an impaired central, as opposed to peripheral, satiety response, which may predispose them to overconsumption of calories or difficulty with weight loss. Clinicaltrials.gov #NCT02484976. Supported by NIH R01DK098466.

FC6.3

Role of PTEN in the Proliferation and Differentiation of Preadipocytes

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Background/aim: The PTEN hamartoma tumor syndrome (PHTS) is an overgrowth syndrome caused mainly by germline mutations in the tumor suppressor *PTEN*. Patients are predisposed for the development of malignant and benign tumors. Children and adolescents with PHTS frequently develop single or multiple lipomas. PTEN antagonizes the phosphatidylinositide3-kinase/AKT/mechanistic target of rapamycin (PI3K/AKT/mTOR) pathway, which promotes proliferation and differentiation in adipocytes. The aim of this study was to investigate the mechanisms leading to lipoma development in patients with PHTS using isolated lipoma cells from a PHTS patient and a PTEN knock-down cell model.

Methods: PTEN haploinsufficient cells from a lipoma of a PHTS patient (LipPD1) were compared to SVF cells from healthy individuals regarding differentiation capacity during long-term culturing and proliferation. Primary cells of the stromal vascular fraction (SVF) from human fat biopsies (over 20 population doublings) were transfected with siRNA against PTEN and compared to scramble siRNA transfected cells. To analyze their differentiation capacity cells were grown in adipocyte differentiation medium for 12 days after transfection. Lipid droplets were stained with Oil Red O. Proliferation was measured after 7 days incubation in growth medium via counting of cell nuclei.

Results: LipPD1 cells retained their differentiation capacity over a prolonged period of 25 population doublings (60 % lipid accumulation) compared to control preadipocytes (20 % lipid accumulation after 10 population doublings). The proliferation was 1.3 ±0.1 fold higher in LipPD1 cells compared to low passage SVF cells. To evaluate the effect of reduced PTEN in direct comparison to controls, PTEN was transiently down regulated in SVF cells via siRNA with a knock-down efficiency of 54 % ±11 % that was stable during 12 days of adipocyte differentiation. PTEN knock-down cells showed an elevated AKT phosphorylation compared to control cells. Lipid accumulation was 1.4 ±0.2 fold higher in PTEN knock-down cells compared to controls after adipocyte differentiation for 12 days. Cell count was increased 2.7 ±1.0 fold in PTEN knock-down cells after 7 days.

Conclusion: Primary human preadipocytes lose their ability to differentiate into adipocytes after several weeks in culture. Their differentiation capacity could be partly recovered with reduction in PTEN levels. An enhanced proliferation of these cells corresponds with the enhanced activation of AKT. This resembles the phenotype found in lipoma cells of pediatric patients with PTEN defects.

FC6.4

Identification of the First Obesity-Associated Mutations in Human Mesoderm-Specific Transcript (*MEST*) Result in Protein Overexpression, Adipocyte Hypertrophy and a Reduction in Adipocyte Mitochondrial Area

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Background: Mesoderm-specific transcript (*MEST*) is an epoxide α/β-hydrolase protein with catalytic activity that is determinant for the development of adipocytes. The MEST gene is an imprinted gene transcribed only from the paternal allele. Although the mechanism by which *MEST* overexpression augments fat accumulation and storage in adipocytes has not been fully elucidated, frequent subcellular contacts between MEST-positive endoplasmic reticulum, mitochondria and lipid droplets have been shown. This suggests that mitochondrial affectation might be involved. To date, no pathogenic human mutations have been reported in *MEST*.

Objective: The present study aimed to characterize potential variants in the *MEST* gene in children with early-onset severe obesity.

Results: We report a total of 14 family members from seven unrelated families presenting with hyperphagia, insulin resistance and body mass index (BMI) greater than 3.5 SDS for age and sex. These patients were shown to present *MEST* variants as a result of mCpG disruptions in chr7:130131207, chr7:130132310, chr7:130132836 or chr7:130132925 sites.

Biopsies of subcutaneous fat were obtained for histology, immunohistochemistry and ultrastructural analysis by transmission electron microscopy (TEM). *MEST* mutations, without any other obesity-related single-nucleotide polymorphism (SNP) or copy number variations (CNV), were associated with increased immunoreactivity for MEST in adipocytes and hypertrophy of adipocytes. Interestingly, ultrastructural observations of adipocytes by

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TEM indicated a reduction in the mitochondrial area in patients with *MEST* mutations and with no other SNP/CNV.

Conclusions: These observations provide important insights into the regulation of adiposity by MEST in humans, and suggest a possible implication of mitochondrial activity in this process. Moreover, affectation of this gene appears to be involved in the development of human obesity.

FC6.5

The Role of Adipocytes in Childhood Precursor B cell Lymphoblastic Leukemia

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Acute lymphoblastic leukemia (ALL) is the most prevalent cancer in childhood. Over the past decades, survival rates increased, but relapse is still associated with a poor prognosis, especially if the bone marrow (BM) is affected. Marrow adipose tissue (MAT) constitutes a major part of the BM niche, but its impact on normal hematopoiesis versus leukemia initiation, progression and relapse has only recently gained attention. MAT is very sensitive to changes in the patient's metabolic status, e.g. aging, obesity, caloric restriction, anorexia, therapy with steroids or irradiation, hampering a clear definition of its exact role during hematopoiesis and leukemia.

To further address the role of adipocytes in B cell-precursor (BCP)-ALL, we established a coculture system of human adipocytes and BCP-ALL cells. For this purpose, we made use of thehuman Simpson-Golabi-Behmel syndrome (SGBS) preadipocyte cell strain, a unique and useful tool for studies of human adipocyte biology.We found that adipocyte-conditioned media from SGBS adipocytes is able to support the survival and proliferation of four different BCP-ALL cell lines (Nalm6, Reh, UoCB6 and RS4;11) under serum-free culture conditions. By using the coculture system of leukemic cells and SGBS adipocytes in comparison to transwell assays we could show that survival and proliferation of leukemic cell lines is independent of direct cell-cell contact, but mediated by adipocyte-secreted factor/s. Interestingly, conditioned media of BCP-ALL cell lines induced the upregulation of inflammatory mediators on mRNA level in adipocytes, among them monocyte chemoattractant protein 1 (MCP-1) orinterleukin-8 (IL-8). Next, we screened a cohort of 28 patient-derived BCP-ALL xenograft samples for their survival capacity in monoculture versus coculture with SGBS adipocytes. Interestingly, survival of patient-derived xenograft cells was heterogeneous anddefined by a characteristic gene expression pattern of leukemic cells identified by Affymetrix Human Genome U133 Plus 2.0 Array.

In summary, we show that adipocytes promote survival and proliferation of leukemic cells via secretion of a yet to be identified factor. Leukemic cells in turn induce upregulation of inflammatory mediators in adipocytes, possibly to maintain their own survival. Importantly, survival of primograft cells on adipocytes is not a general phenomenon, but seems to be restricted to a certain cohort of patients defined by a characteristic gene expression profile. Further molecular characterization of this cohort will hopefully lead to the identification of novel targets for the treatment of BCP-ALL.

FC6.6

MicroRNA-141 Directly Targets and Inhibits Sirtuins 1 Gene Expression and its Elevation in Obese Subjects Is Responsible for Reduced Levels of Sirtuin1 and the Subsequent Hepatic Steatosis and Insulin Resistance

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Introduction: Obesity increases the risk of various disorders including diabetes, non-alcoholic fatty liver disease (NAFLD) and cardiovascular disorders. MicroRNAs (miRNA) are single-stranded, non-coding oligonucleotides that regulate gene expression. Sirtuin 1 (SIRT1), a regulatory enzyme in metabolic homeostasis, is regulated by miRNAs. The aim of this study was to evaluate miR-141 in obesity and whether this miRNA can regulate SIRT1 expression.

Materials and methods: Plasma levels of miR-141 were measured by real-time PCR in samples from 50 obese subjects and 50 normal-weight control subjects after thorough clinical evaluation. Peripheral blood mononuclear cells were isolated and used for the assessment of SIRT1 expression after mRNA extraction and cDNA biosynthesis. Lipid profile, glucose and insulin as well as liver function tests were also measured in serum samples. Hepatic steatosis was evaluated by ultrasound. Targeting of SIRT1 by miR-141 were first evaluated by bioinformatic tools. Then luciferase reporter assay was used to confirm direct interaction of miR-141 with 3'-untraslated region (3'-UTR) of SIRT1 mRNA after co-transfection of HEK293 cells with miR-141 mimic and the vector containing the 3'-UTR sequence. Levels of SIRT1 protein and SIRT1 activity were determined by Western blotting and a fluorimetric method, respectively, after transfection of HepG2 liver cells by miR-141 mimic and inhibitor and their negative controls.

Results: miR-141 levels were increased while SIRT1 gene expression was decreased in obese subjects compared to normal subjects. SIRT1 expression was negatively correlated with miR-141 levels. High plasma miR-141 and low SIRT1 expression were associated with fat accumulation in liver as well as insulin resis-

tance. The same alterations were observed in HepG2 cells after incubation with high concentrations of glucose and induction of intracellular lipid accumulation. Luciferase reporter assay together with bioinformatic evaluation showed that SIRT1 is a direct target of miR-141. The expression of miR-141 was up-regulated while SIRT1 was down-regulated as a result of transfection of HepG2 cells with miR-141. Additionally, the protein level of SIRT1 and its activity were decreased due to the over expression of miR-141.

Conclusion: Results showed that miR-141 could effectively suppress SIRT1 expression and inhibit its activity. Thus, increased miR141 level in obesity could be considered as a causative factor for the low expression level of the SIRT1 gene. Consequently, the decrease in the expression and activity of SIRT1 could contribute to the development of insulin resistance and NAFLD.

Fetal, Neonatal Endocrinology and Metabolism

FC7.1

Expression and Localisation of Insulin, Glucagon, Amylin, Pancreatic Polypeptide and PDX-1 in Pancreatic Tissue of Children with Congenital Hyperinsulinism

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Backgound: There is insufficient knowledge about the characterisation of insulin, glucagon, amylin, pancreatic polypeptide (PP) and Pancreas/Duodenum Homeobox Protein 1 (PDX-1) in pancreatic tissue of children with diffuse (DCHI) and focal (FCHI) congenital hyperinsulinism (CHI).

Objective(s): To understand the expression profile and localisation of insulin, glucagon, amylin, PP and PDX-1 in pancreatic tissue of children with DCHI and FCHI.

Methods: Human paediatric pancreatic samples from normal (N: 2), FCHI (N: 2) and DCHI (N: 2) were obtained. For localisation of hormones, same-slide double staining immunohistochemistry was performed and images visualised under fluorescent microscopy. PDX-1 was chosen as a marker of endocrine tissue as it stains the nuclei of β-cells. Gene expression was analysed with SybrGreen quantitative Real-Time polymerase chain reaction (RTqPCR) in the same groups. *RPL19* was used as the endogenous control gene.

Results: Immunohistochemistry did not show differences in localisation of the 5 peptides between controls, FCHI and DCHI. Amylin stains the same cells as PDX-1 in normal and all forms of CHI, therefore limited to the endocrine component of the pancreas. In all three groups of patients, insulin and amylin had a different distribution within the β-cell so they did not co-localise. In CHI tissue, amylin shows comparable fluorescence to controls, and so does PP that is localised in scarce amount in the islets. Gene expression studies (RTqPCR) showed higher expression of insulin and lower of glucagon in all CHI forms, as compared to controls; consistent with known plasma hormone concentrations. In CHI forms, the expression of amylin and PDX-1 do not parallel that of insulin. PP expression is comparable in controls and all CHI cases. Gene expression of both amylin and PP, demonstrated high variability between DCHI subjects, compared to FCHI and normal pancreas.

Conclusions: As opposed to previous reports in the literature that had not used same-slide double staining, our study shows no co-localisation of amylin and insulin in the β-cell. Localisation and expression of amylin in CHI is independent to that of insulin, potentially indicating a β-cell preserved mechanism to minimise hypoglycaemia. Based on the expression studies PP may not have an important role in glucose regulation in CHI.

FC7.2

Enteroinsular Hormone Responses During Fasting, Oral Glucose Tolerance Test and Mixed Meal in Children with Hyperinsulinaemic Hypoglycaemia

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Objective(s): To understand how plasma concentrations of pancreatic [glucagon, amylin, pancreatic polypeptide (PP), insulin] and gut hormones "incretins" [Glucagon-like peptide 1 (GLP-1) and Glucose dependent insulinotropic peptide (GIP)] change in relation to fasting and feeding (different types of nutrients) in healthy and hyperinsulinaemic hypoglycaemia (HH) children of different ages.

Methods: Plasma pancreatic and incretin hormone concentrations were determined by immunoassay MILLIPLEX® MAP Kit (Millipore, Watford, UK). Samples were taken during fast [beginning (normoglycaemia) and end of fast (hypoglycaemia in cases, normoglycaemia in controls)] and during stimulation tests: Oral Glucose Tolerance (OGTT)/Mixed Meal (MM). 9 controls and 15 cases [3 focal HH (FCHI) and 12 diffuse HH (DCHI)] where analysed during the fast. 6 controls and 8 cases (N: 4 dumping syndrome, N: 1 idiopathic postprandial HH, N: 2 DCHI, N: 1 atypical HH) were analysed during OGTT/MM tests.

Results: *During Fast*: Amylin decreased in HH cases versus controls where it increased by the end of the test. Insulin

remains detectable despite hypoglycaemia, whereas glucagon response is blunted in HH case. The concentrations of PP in HH children do not show a specific pattern in the face of hypoglycaemia. GLP-1 and GIP concentrations are higher in controls than in HH cases, but in all groups, these decrease by the end of the fast. *Stimulation Tests*: In HH cases, MM test triggers a more potent response than OGTT for: glucose, insulin, amylin, PP, GLP-1 and GIP and it does not suppress glucagon. Conversely, in control subjects, it is the OGTT that triggers a more powerful response for all these hormones. Amylin´s concentrations during stimulation tests are higher in HH cases than in controls. The pattern of PP during OGTT and MM is similar in HH patients to controls. GLP-1 and GIP are similarly released in HH as in controls after OGTT; but released in excess in HH cases following a MM.

Conclusions: In HH cases, amylin may have a protective role to avoid exacerbation of hypoglycaemia and may do so by stimulating food intake. There seems to be little, if any, role of PP in glucose regulation. OGTT/MM results may guide the clinician to decide which test is more suitable for each indication and the role of feed modification to manage HH cases. Blocking the release or action of incretins could potentially benefit HH patients.

FC7.3

Diazoxide-Induced Pulmonary Hypertension: UK Multicentre Retrospective Study on the Risk Factors, Monitoring Approach and Management Recommendations

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Objectives: Diazoxide is first line treatment for hypoglycaemia due to hyperinsulinaemic hypoglycaemia (HH). However, the FDA has raised serious concerns regarding diazoxide-induced pulmonary hypertension (PH) in 2015. Although sporadic cases of PH have been reported, no HH cohort has been systematically characterised to understand severity and risk factors for diazoxide-induced PH.

Methods: To investigate the onset, progress and associated factors in PH, patients with HH who developed diazoxide-induced PH in 4 regional centres were retrospectively reviewed. PH diagnosis was based on clinical and/or echocardiography evidence. Child and treatment-related risk factors were analysed for association. The time intervals from diazoxide initiation to onset and resolution of PH were also recorded.

Results: Twelve cases were identified (5M:7F). HH was diagnosed at median (range) 12 (1,180) days, with diazoxide started 3 (1,76) days from diagnosis, reaching a highest dose of 8.0 (2.5,20) mg/kg/day. Only 3 (25%) patients had mutations in *ABCC8*/*KCNJ11* establishing genetic causation. Total fluid intake was 170 (100,180) ml/kg/day prior to treatment. The majority developed PH within 2 weeks of diazoxide [12 (2,90) days], with 3 patients requiring intensive care ventilation (2 requiring high frequency oscillation). Two-thirds of (8/12) patients had baseline echocardiography before initiation of diazoxide. Diazoxide dose reduction did not ameliorate PH but complete diazoxide withdrawal led to PH resolution at a variable time of 32.5 (3,985) days. In 3 patients, PH has yet to resolve after 6 months. Risk factors for the development of PH included low birthweight (and/or intrauterine growth restriction) in 6 (50%) and fluid intake exceeding 130ml/kg/day in 10 (83%) patients. Eight (67%) patients also had congenital heart disease (CHD), predominantly secundum atrial septal defects and patent arterial ducts, likely related to the early transitional circulation. The presence or absence of CHD did not influence the time to develop PH [13 (2,90) v 11 (6,13) days, P=0.37] or time for PH resolution [28 (7,90) v 37 (3,985) days, P=0.99] respectively.

Conclusion: PH is a serious complication of diazoxide therapy in HH occurring at an unpredictable time from initiation of treatment. We recommend vigilance for PH in low birthweight infants with fluid intake exceeding 130ml/kg/day. PH-specific echocardiography should be performed before diazoxide treatment to identify underlying CHD, followed by weekly monitoring for at least the first 2 weeks of treatment. If PH is identified, diazoxide should be discontinued to facilitate PH resolution.

FC7.4

Altered Substrate Specificities and Metabolite Production by Aromatase (CYP19A1) Due to the R192H Mutation

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Background: Aromatase (CYP19A1) a member of cytochrome P450 protein family is a major steroid metabolizing enzyme which converts androgens to estrogens. Mutations in aromatase can lead to autosomal recessive aromatase deficiency. An R192H mutation in CYP19A1 described earlier caused severe phenotype of aromatase deficiency with regressive virilization of the 46,XX new-born, but without signs of androgen excess during pregnancy. Computational studies suggested that R192H disrupts substrate access channel in the CYP19A1 that may affect binding of the substrates and exit of catalytic products. In current study we explored the specificity of different substrates towards aromatase to find out if the R192H mutation in aromatase affects any particular substrate and metabolite more than others.

Methods: WT and R192H variants of CYP19A1 were cloned into a pcDNA3 vector for expression in COS1 cells. Three different conditions were used for cell experiments. In first case endogenous steroids produced natively by cells were used as substrates. In second case androstenedione was added to cells and in third case, testosterone (T) was added to transformed cells for use as a substrate. Steroids were measured by GC-MS analysis. Computational calculations of substrate binding were done using X-ray crystal structure of human placental aromatase available from the protein databank.

Results: We observed a range of differences between WT and R192H mutation of aromatase towards metabolism of different substrates. Without any external substrate, the level of testosterone was not affected. However, when androstenedione was added externally, an 18 fold increase in T and 7.4 fold increase in DHT was observed, while 17-β Estradiol levels were reduced to 32% of WT. With the R192H mutation the 11β-hydroxy-Androsterone was increased 2 fold, Etiocholanolone was increased 4 fold and androsterone increased by 2 fold. When T was added externally for use as substrate, the observed T levels after incubation were 16 fold higher for the R192H mutation compared to WT while DHT was elevated by 7 fold. In addition, when using T as substrate, for the R192H mutation Etiocholanolone levels increased 7 fold but Estriol dropped to 54% of the WT and 17-β Estradiol was 31% of WT.

Conclusion: Selective effects on specific substrates has been demonstrated by the R192H mutation in human aromatase. This provides an important mechanism of disease causing effect in human aromatase where metabolism of different substrates of aromatase could be affected to varying degrees.

FC7.5

Thyroid Hormone Levels in Cord Blood Are Associated with Fetal and Neonatal Growth

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Background: Normal function of the thyroid gland is essential for adequate neurological development of the fetus and child. In previous studies, associations between reduced birth weight and overt maternal and fetal thyroid dysfunction have been described. We hypothesize that also variations within the normal range of fetal thyroid function have an impact on fetal and neonatal growth.

Objective: The aim of this study is to investigate whether thyroid hormones measured at birth are associated with fetal and infant growth in healthy children.

Method: Thyrotropin (TSH), triiodothyronine (T3), thyroxine (T4), and free thyroxine (FT4) were measured in umbilical cord blood samples from the Copenhagen Baby Heart cohort, and in venous blood samples of neonates taken two hours and two months after delivery (the COMPARE cohort). Measurements of head circumference (HC), birth weight (BW) and length (BL) were extracted from medical records. Measurement of HC was repeated two months after birth on children in the COMPARE-cohort and ΔHC as growth in mm/day was calculated. Statistical analyses were performed as Pearson correlations (SAS).

Table 1. (for Abstract no FC7.5)

	HC	BW	BL	ΔHC
Cord TSH¤			r = 0.05**	r = 0.16*
Cord T3	r = 0.07***	r = 0.10****	r = 0.07***	
Cord T4	r = 0.14****	r = 0.24****	r = 0.16****	
Cord FT4	r = 0.08****	r = 0.14****	r = 0.07***	
Cord TSH/FT4 ratio¤				r = 0.18**
2-hr T3¤	r = 0.23**			
2-hr FT4¤	r = 0.25** (boys)			r = -0.20**

P-values: *<0.1; **<0.05, ***<0.01; **** <0.001. ¤ Log transformed variables.

This cohort study was initiated in June 2017 and it is expected to be finalized by December 2018. The preliminary analysis is based on the first 2316 cord blood samples, 107 2-hr samples and 83 2-mth samples.

Results: The 2-hr blood samples were collected 2h34m after birth (range 0h28m–5h25m). TSH increased from a cord blood median of 9.3mU/L (2.4-67.7) to 42.4mU/L (3.3-125.0), T3 from 1.0nmol/L (0.2-2.5) to 3.6nmol/L (1.6-7.2), T4 from 146.0nmol/L (41.0-252.0) to 214.0nmol/L (123.0-318.0) and FT4 from 13.9pmol/L (8.4-21.4) to 21.6pmol/L (14.2-38.3).

Associations between thyroid hormones and anthropometry are shown in Table 1.

Conclusion: Thyroid hormone levels increase considerably from cord blood to 2 hours post partum, likely reflecting delivery-associated stress. We found associations between thyroid hormones and body size including HC at birth, BW, BL as well as body growth from birth to 2 months. This supports the hypothesis that thyroid hormones are involved in general growth and brain development in healthy children.

FC7.6

TSH-Resistance and Remaining Low-T4 in Former Low-Birthweight Infants – A Study in Monozygotic Twins with Intra-Twin Birth-Weight-Differences

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Background: Low birth-weight (bw) and unfavourable intrauterine conditions are associated with a subsequent impact on the endocrine system. However, very little is known about the impact on thyroid function.

Objective and hypotheses: We observed genetically identical twins with intra-twin bw-differences from birth until adolescence

to objectify the impact of a lower bw on development and health in later life.

Method: Bw-difference of <1SDS was defined concordant, bw-difference >1SDS discordant. Blood sampling was performed at a mean age of 10.1 yrs (n= 27 twinpairs; 15 discordant), 15.1 yrs (n= 35 twinpairs, 15 discordant) and 17.4 yrs (n=36 twinpairs; 15 discordant). 18 twinpairs were seen at all three time-points.

Results: Group comparison revealed the following results: No significant differences in TSH, T3, and T4 levels were observed in the concordant twins. In the discordant group, a significant difference between the two twins for TSH levels was found at 10.1 yrs (p = 0.041) and a tendency at 15.1 yrs (p=0.083). The smaller twins had higher mean TSH concentrations than their larger co-twins (10.1 yrs: 3.6 vs 2.5 μU/ml, 15.1 yrs: 2.6 vs 2.2 μU/ml). Again in the discordant group, significant differences in T4-levels were observed at 10.1 yrs (p=0.05) and 17.4 yrs (p=0.03) and a tendency at 15.1 yrs (p=0.08). The smaller twins showed lower T4 mean concentrations than their larger co-twins at all time-points (10.1 yrs: 7.8 vs 8.2 μg/dl, 15.1 yrs: 6.9 vs 7.4 μg/dl, 17.4 yrs: 7.7 vs 8.4 μg/dl). Calculation of the TSH-T4-ratio revealed significant differences in the discordant group, with a constantly higher ratio in the smaller twin: at 10.1 yrs (0.5 vs 0.3; p=0.006) and at 15.1 yrs (0.4 vs 0.3; p=0.04). Thyroid-antibodies were analysed and showed no significant differences. By calculating the BMI-SDS we found that in all twin-pairs and at all time-points, the smaller twins had a significant lower BMI-SDS than their larger co-twins (10.1 yrs: -0.70 vs -0.17 SDS; p= 0.002, 15.1 yrs: -0.55 vs -0.15 SDS; p<0.001, 17.4 yrs: -0.26 vs 0.14 SDS; p<0.001).

Conclusion: In this special group of monozygotic twins with intra-twin bw-differences, we could show that birth-weight has a long-lasting impact on thyroid function. The significantly higher TSH concentrations, significantly lower T4 concentrations and elevated TSH-T4-ratios in the smaller twins who were born with a greater bw-difference indicate the possibility of a TSH-resistance and persisting "low-T4" in low-birthweight children.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

FC8.1

Estrogen Receptor 2 Variant as a Novel Cause for Dysgenetic Ovaries

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Background: Variants in the estrogen receptor α (ESR1) have previously been described in male and female patients presenting with estrogen resistance. Estrogen resistance is characterized by delayed bone-age, early-onset osteoporosis, delayed puberty and multicystic ovaries in women. So far, no clinical consequences of variants in the estrogen receptor β (ESR2) have been reported in 46,XX patients, although ESR2 variants have previously been implicated in 46,XY DSD patients. Here we describe the first case of a 16-year old woman with complete lack of estrogen action, indicated through absent breast development, primary amenorrhea and osteoporosis. Additionally, she presented with dysgenetic gonads, which has not been observed in ESR1 deficient patients.

Methods: The genomic DNA of the patient was analyzed using whole exome sequencing (WES) We could exclude variants in other genes related to 46,XX DSD, in genes up- and downstream of the estrogen receptors and in genes implicated in premature ovarian failure. We performed functional transactivation studies using wild type and variant ESR2 in ovarian, bone and breast cell lines and 3D molecular models of the wild type and variant ESR2 were created.

Results: A heterozygous missense variant of a highly conserved amino acid (AA) was identified in ESR2 (c.941A>G, p.Lys314Arg). The Lys314 was shown by the 3D model to be part of the co-factor binding site and its substitution with an Arg leads to a disrupted interaction between ESR2 and its co-factor NCOA1. The functional transactivation studies showed that the variant in ESR2 leads to a disrupted estradiol-dependent signaling in the three cell lines. In the pre-granulosa cell system, the mutant ESR2 completely lost its function and has a dominant negative effect, suggesting that ESR2 is necessary for ovarian development.

Conclusion: We describe the first case of complete ovarian dysgenesis in a woman due to a loss-of-function variant of the ESR2. This suggests that ESR1 is not sufficient by itself to advance ovarian development and that ESR2 is necessary for human ovarian determination. It remains to be established, whether estrogen resistance due to milder defects in ESR2 might account for unexplained cases of ovarian failure or infertility.

FC8.2

Partial Restoration of Biological Effects of Estrogen in a Female with Estrogen Receptor A Variant

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Introduction: Rare mutations of the *ESR1*gene, encoding the estrogen receptor alpha (ERα), have been shown to cause estrogen resistance in humans. To date, there are no effective therapeutic options. We report the case of a new inactivating mutation of ERα

and provide evidence for a partial restoration of biological effects of estrogen.

Methods: We performed clinical and biological phenotyping of the index case and sequenced the *ESR1*gene. Structural and functional studies were performed *in Vitro* in the presence of different ligands using two cellular models: HeLa transfected with the ERE-β-globin Luc+ vector (stable clones) and HepG2 transiently co-transfected with the C3 Luc reporter. A therapeutic trial was conducted with the administration of high doses of ethinyl-estradiol (EE, 50-100 µg/day) per os for 3 months.

Results: We describe a 20-year-old female, with primary amenorrhea and lack of breast development. Pelvic MRI revealed a rudimentary uterus and polycystic ovaries. The patient presented with tall stature (180 cm), continuous linear growth, delayed bone age (12 years) and severe osteoporosis (BMD -4 SD). Hormonal profile revealed LH 40 IU/L, FSH 44 IU/L, E2 1670 pmol/L (reference 220-400). Her BMI was 28 kg/m^2 with increased abdominal adiposity (DXA: trunk/limb fat ratio 1.3) and discrete hepatic fat overload (MRI spectroscopy). Metabolic profile showed severe insulin resistance (HOMA-IR 11.5), decreased insulin sensitivity (SI-OGTT Stumvoll: -0.05), increased insulinogenic index ΔIns30/ΔGluc30 (7.3), and hyperleptinemia (75 ng/ml) with normolipidemia.

Sequencing of the *ESR1* gene identified a new homozygous variant (p.Met543Thr) in the ligand binding domain (activation function-2, AF2). Functional studies *in Vitro* revealed a slight decrease in the affinity of the M543T variant for estradiol; a dramatic decrease in transcriptional activity involving AF2; and the possibility of partial restoration of the transcriptional activity in the presence of high concentrations of ligand.

Therapeutic trial with a high dose of EE improved the patient's insulin sensitivity (HOMA-IR: 5.9, SI-OGTT Stumvoll: 0.02, ΔIns30/ΔGluc30: 0.8), decreased circulating leptin (36 ng/ml) and increased several estrogen-regulated liver proteins; with no effect on the endometrium and bone.

Discussion: A new ERα receptor inactivating mutation, located in the ligand binding domain (p.Met543Thr), is responsible for a dramatic decrease in the AF2 (ligand-dependent) transcriptional activity. The structural and functional study of the receptor indicated the possibility of partial restoration of estrogen effects. The therapeutic trial with high doses of EE supports this hypothesis showing a marked improvement of insulin sensitivity.

FC8.3

Exomic Sequencing Uncovers Novel Genetic Associations for Deciphering Developmental Disorders (DDD) Study Participants with Hypospadias, Cardiovascular and Neurodevelopmental Abnormalities

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Background: Hypospadias is a common characteristic of Disorders of Sex Development (DSD). At the present time a molecular diagnosis is not reached in over 50% of cases. The DDD Study represents a useful resource of large molecular and phenotypic datasets obtained from individuals with an undiagnosed developmental abnormality including DSD.

Objective: To review associated features and identify likely pathogenic variants in previously undiagnosed DDD participants with hypospadias, cardiovascular and neurodevelopmental disorders.

Method: Retrospective review of anonymised phenotype data and bioinformatic analysis of variant call format (VCF) files of 33 DDD participants (22 family trios and 11 singleton cases) manifesting hypospadias, cardiovascular and neurodevelopmental abnormalities. A customised filter chain (using GoldenHelix, Varseq 1.4.4) specific to each inheritance pattern was created and searches were performed in databases (Online Mendelian Inheritance in Man, OMIM; PubMed and The Jackson Laboratory).

Results: Analysis was undertaken in 238 and 155 phenotype entries, recorded in 22 family trios and 11 singleton cases, respectively. Additional features included ophthalmic (34/393, 7%), skull (19/393, 5%), skeletal (18/393, 5%) and hand (17/393, 4%) abnormalities. The filter chain comprised the following criteria: read depth (DP≥20), genotype quality (GQ≥30), allele frequency (AF<0.01 or missing) and effect (loss of function) in both the trio and singleton analysis workflows. Additional filter cards specific to each inheritance pattern have been added to the trio analysis pipelines including 'Mendel error: de novo' for the autosomal dominant, 'compound heterozygous: yes' for the compound heterozygous, 'Mendel error: transmitted, Zygosity: homozygous, Mother: heterozygous, Father: heterozygous' for the recessive homozygous and 'Heterozygous' for the x-linked analysis pipeline. A final filter card entitled 'Extended DSD panel: true' was added to each pipeline to identify variants in the 57 carefully curated DSD genes that are available on the NGS DSD panel locally. 6 previously unidentified variants in 5 genes, including *EPHB4*, *DGKK*, and *PIEZO1*, in addition to the 9 variants in 9 genes reported by the DDD study,

are described in the family trios. Variant analysis of the singleton cases revealed 5 variants in 5 genes (e.g. *KIF1A*, *FMN2*) in addition to 10 reported variants in 10 genes of 6 DDD patients.

Conclusion: Exome sequencing has proven a powerful tool for the investigation of DSD with a diagnostic rate of up to 60%. Data from this study widen the phenotypic and genetic spectrum associated with DSD thus facilitating earlier recognition, improved diagnostic rates and management for affected families.

FC8.4

STARD8, a Novel Candidate Gene for 46,XY Disorders of Sex Development

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Background: An activation cascade of specific genes sets up the initiation of sex determination leading in males to testes formation and synthesis of testicular hormones. Disruption of this gene cascade may cause a spectrum of 46,XY disorders/differences of sex development (DSD) phenotypes. Here we describe for the first time two sisters suffering from 46,XY DSD, who by whole exome sequencing revealed to carry a X-linked mutation in the StAR-related lipid transfer domain protein 8 (STARD8) gene. STARD8, also known as deleted in liver cancer 3 (DLC-3) is a functional Rho-specific GAP protein, the loss of which enhances perinuclear Ras homolog gene family member A (RhoA) activity. Simultaneously, RhoA is known to play a role downregulating the expression of SOX9 and, thus, inducing the female sexual development pathway. On the other hand, available literature also linked STARD8 with the targeting of focal adhesions and the stimulation of the enzymatic activity of Phospholipase C δ1 (PLCδ1), which is known to lower the levels of active-β-catenin. Moreover, β-catenin has been identified as a key pro-ovarian and anti-testis signaling molecule.

Objectives: To gain new insights in human sex development mechanisms, we aimed to analyse the functional consequences of STARD8 mutations as a putative novel 46,XY DSD- related gene by testing the RhoA phosphorylation-dependent SOX9 expression. Since the STARD8 knockout NMRI mouse model we generated did not recapitulate the human clinical picture, we chose to test the mutation in a cell system.

Methods: COS1 cells were transfected with wild type and mutant STARD8. Quantification of activated RhoA (RhoA-GTP) levels in cell lysates was performed by a pull-down assay that specifically binds the active form of RhoA. Subsequently, the RhoA-GTP, total RhoA, SOX9 and STARD8 protein expression levels were analyzed by western blot. Quantitative RT-PCR expression profiling of STARD8, SOX9, and PLCD1 was also performed.

Results: Preliminary results showed an increase in activated RhoA levels and consequent reduced SOX9 protein expression levels with the STARD8 mutant when compared to the wild type. Also, an increase in the STARD8 protein expression levels was observed in the mutant when compared to the wild type.

Conclusions: The mentioned results suggest a STARD8-dependent Sox9 expression mediated by RhoA phosphorylation that could be triggering sex reversal in the 2 affected patients. Therefore, STARD8 resembles a strong novel candidate gene for 46,XY DSD which might have an important role in sexual differentiation.

FC8.5

DEAH-Box Helicase 37defects *(DXH37)* Defects Are a Novel Cause of 46,XY Gonadal Dysgenesis

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Background: 46,XY gonadal dysgenesis (GD) is a spectrum disorder which lead to variable degrees of atypical external genitalia, ranging from female to micropenis and absent of gonadal tissue (known as Embryonic Testicular Regression Syndrome -ETRS). Most patients with 46,XY GD remains without a molecular diagnosis.

Objective: To report the DEAH-box helicase 37 gene (*DHX37)* as a novel candidate for the GD etiology.

Patients and methods: We studied 12 familial cases from 6 non-consanguineous families by whole exome sequencing, one familial case and 69 sporadic cases by target massively parallel sequencing, including 41 patients with GD, 16 patients with ETRS and 32 patients classified as 46,XY disorder of sex development of unknown etiology (UDSD) due to previous gonadectomy or an inconclusive hormone profile. An amplicon-based capture panel of 63 genes related to DSD for targeted sequencing was used. Sequencing was performed in the Illumina platforms. Paired-end reads were aligned to the hg19 assembly of the human genome with BWA-MEM. Variants were called and annotated with Platypus and ANNOVAR, respectively. Two sporadic cases and one family with ETRS had *DHX37* studied by Sanger sequencing. Eighty-seven patients were Brazilian, including 6 families, one sporadic case was Chinese-American and two families were Argentinean and Chilean.

Results: Six different missense variants in *DHX37* were identified in 8 sporadic cases and in 11 patients from 5 families. All variants are absent or in low frequency (<0.0002) in population (gnomAD) and Brazilian databases and are classified as deleterious by at least 8 prediction tools. The variant p.R308Q was recurrent in 2 non-related ETRS families and in three sporadic cases, includ-

ing the Chinese-American patient. The p.R674W also recurred in the Argentinean and Chilean ETRS families and in one sporadic GD patient, who also bored a novel *GATA4* p.P368R. Another three *DHX37* variants were identified in three sporadic UDSD patients and one of them also harbored the novel *NR5A1* p.G26V. All these variants are heterozygous and the segregated ones disclosed an autosomal dominant inheritance. One sporadic case of ETRS from a consanguineous family was homozygous for the *DHX37* p. R151W. *DHX37* is expressed in germ cells at different stages of maturation, as shown by immunohistochemical analysis.

Conclusion: The identification of several deleterious variants in *DHX37,* as monogenic or in digenic inheritance in familial and sporadic cases of 46,XY DSD patients from different parentage, reinforces it is a strong candidate gene for the spectrum of GD phenotypes.

FC8.6

The Roles of Steroids in Gonadal Development and Maintenance – Insights from a Zebrafish Model of Androgen and Cortisol Deficiency

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Increasing evidence suggests that the aetiology of disorders of sex development cannot be solely explained by genetic alterations. It is highly likely that environmental factors hitting susceptible genetic backgrounds are partly causative. Zebrafish sex is highly plastic during development, making this species an ideal model for investigation of endocrine disruption and gonadal development and function. However, the hormonal regulation of these processes in zebrafish is poorly understood. Here, we use a model of glucocorticoid and androgen deficiency to explore such processes.

In humans, ferredoxin *(FDX1)* is an electron-providing cofactor required for steroid biosynthesis. The zebrafish homologue of *FDX1*, *Fdx1b*, plays a crucial additional role in androgen biosynthesis. To investigate the role of steroids in sex development and gonadal differentiation we analysed the phenotype of adult *Fdx1b* mutant zebrafish, which were found to be profoundly cortisol- and androgen-deficient by LC-MS/MS. Downregulation of cortisol responsive genes *Fkbp5* and *Pck1* and androgen responsive gene *Cyp2k22* confirmed systemic steroid deficiencies.

Fdx1b mutants exhibit feminised secondary sex characteristics, but may possess either testes or ovaries, and both sexes are sterile. Histological investigation showed abnormal seminiferous tubule structure and disorganisation of *Fdx1b* mutant testes, compared to those of wild-type siblings. To investigate mechanisms behind testicular disruption and sterility we measured expression of genes regulating testicular development or spermatogenesis. We observed downregulation of pro-testis gene *Sox9a,* and *Igf3,* a key factor for spermatogonial proliferation and differentiation, in *Fdx1b* mutant testes. Androgen receptor (*Ar)* expression was upregulated in mutant males, whereas putative AR target gene *Dmrt1* was expressed at similar levels in mutants and wild-type siblings. These observations suggest that increased *Ar* expression may compensate for the observed androgen deficiency, rescuing *Dmrt*1 expression, or alternatively that in zebrafish, *Dmrt1* expression is insensitive to reduced androgen levels.

Whilst androgens regulate some secondary sex characteristics, they do not promote testis differentiation, as mutants developed distinct ovaries or testes. However, it is clear that androgens have an important role in development, maturation, organisation and function of both male and female gonads, since adult males and females were sterile. Taken together, our observations provide novel insights into the roles of androgens in these processes and for the first time demonstrate a dynamic response to androgen deficiency involving compensatory upregulation of the *Ar* and rescued *Dmrt1* expression. We anticipate that these insights will support development of model organisms to study the interplay of genetic factors and environment in disorders of sex development.

Pituitary, Neuroendocrinology and Puberty 1

FC9.1

Novel Variants in the POU1F1 Beta Isoform Are Associated with Isolated Growth Hormone Deficiency and Combined Pituitary Hormone Deficiency

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Background: Hypopituitarism is characterized by deficiency of one or more anterior pituitary hormones. *POU1F1* mutations are the second most frequent known cause of combined pituitary hormone deficiency (CPHD). Patients are typically deficient in GH, TSH, and prolactin, although two unrelated cases were reported

with isolated GH deficiency (IGHD). To date, all *POU1F1* mutations have been reported for the predominantly expressed alpha isoform, which is a transcriptional activator.

Objective: We identified two heterozygous missense variants in a minor, alternative isoform of POU1F1 (POU1F1 beta), which segregated with CPHD or IGHD in two unrelated families. We report the clinical characteristics of these patients and probable mechanism of action.

Results: A German index case presented with secondary hypothyroidism one week after birth. During infancy, she developed severe GH deficiency (height SDS -5.42). Her daughter (birth length -3.45 SDS) was born with severe congenital hypothyroidism due to TSH deficiency (TSH 0.28 mU/l, fT4 5.4 pmol/l). GH therapy was started 6 months after birth because of GH deficiency (height SDS -4.93, GH <0.55 ng/ml, IGF-1 -2.62 SDS, IGFBP-3 -3.77 SDS). Prolactin was very low in both family members. MRI of the pituitaries were normal. Exome sequencing revealed heterozygous variants in POU1F1 beta (c.157T>G, p.S53A) in the index case and her daughter.

In a Brazilian family, the index case and her brother (birth length -3.96 SDS) presented with severe short stature (height SDS -4.6 and -4.0) at age 2 years. Both were diagnosed with GH deficiency (GH peak 0.9 ng/ml and 0.8 ng/ml; GH peak 0.5 ng/ml). Thyroid hormone levels were in the low normal range. The index cases father has short stature (adult height -3.7 SDS) with a low normal IGF-1 (84 µg/l, NR 84-277 µg/l), and a GH peak of 7.6 ng/ml in the insulin tolerance test. GH deficiency was also diagnosed in the index patient's daughter. Genetic analyses identified heterozygous variants in POU1F1 beta (c.152T>G, p.I51S) in the index case, her brother, father, and daughter.

Functional testing revealed that both variants ablate splicing at the acceptor site necessary for producing the alpha isoform, resulting in predominance of the beta isoform, which can act as a repressor.

Conclusion: Variants in the POU1F1 beta coding region interfere with splicing necessary to produce POU1F1 alpha, and are associated with hypopituitarism, ranging from IGHD to CPHD including GH, TSH and prolactin deficiencies.

FC9.2

Contribution of Functionally Assessed *GHRHR* Mutations to Idiopathic Isolated Growth Hormone Deficiency in a Cohort of 312 Unrelated Patients

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Purpose: Isolated growth hormone deficiency (IGHD) is a rare condition mainly caused by mutations in *GH1*. The aim of this study was to assess the contribution of *GHRHR* mutations to IGHD in a very large cohort of patients.

Methods: All *GHRHR* coding exons and flanking intronic regions were sequenced in 312 unrelated patients with non-syndromic IGHD. Functional consequences of all newly identified missense variants were assessed *in Vitro* (i.e. study of subcellular localization of recombinant GHRHRs and their ability to activate the cAMP pathway). Genotype–phenotype correlation analyses were performed according to the nature of the identified mutation.

Results: We identified 20 different disease-causing *GHRHR* mutations, among which 15 are novel, in 24 unrelated patients. Of note, 54% of those patients represent sporadic cases. The clinical phenotype of patients with at least one missense *GHRHR* muta-

tion was found to be indistinguishable from that of patients with bi-allelic truncating mutations.

Conclusion: This study, which unveils disease-causing *GHRHR* mutations in 8% (24/312) of IGHD cases, identifies *GHRHR* as the second IGHD gene after *GH1*. This finding, together with the high proportion of sporadic cases among patients with *GHRHR* mutations and the documented phenotypic impact of missense mutations, represents key data for genetic counselling and future *GHRHR* testing.

FC9.3

Mutations in *MAGEL2* and *L1CAM* Are Associated with Congenital Hypopituitarism and Arthrogryposis

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Background: Congenital hypopituitarism (CH), involving deficiencies in one or more anterior pituitary hormones, is rarely observed in combination with severe joint contractures, termed arthrogryposis. Schaaf-Yang syndrome (SHFYNG), which has phenotypic overlap with Prader-Willi syndrome, may be associated with arthrogryposis. L1 syndrome, a group of X-linked disorders including hydrocephalus and spasticity of the lower limbs, may also present with generalized contractures in rare cases. In this study, we investigated the molecular basis in five patients with CH and arthrogryposis.

Methods: Whole exome sequencing (WES) was performed in five individuals with CH and arthrogryposis (Patients 1-5). Patients 1 and 2 had growth hormone deficiency (GHD), Patient 1 also had dysmorphic features, developmental delay and mild optic nerve hypoplasia, and Patient 2 had hydrocephalus. Patients 3 and 4 were non-identical twins with diabetes insipidus, GHD, dysmorphism, macrocephaly, micrognathia, and optic nerve hypoplasia. Patient 5 had multiple pituitary hormone deficiency including GH and ACTH insufficiency and hyperprolactinaemia, with dysmorphic features. Hypothalamo-pituitary expression of implicated genes (*MAGEL2* and *L1CAM*) was studied by *in Situ* hybridization of human embryonic tissue [Carnegie stages (CS) 16, 19, 20 and 23].

Results: A *de Novo* heterozygous (*C.1996dupC*, p.Q666fs*47) mutation in the maternally imprinted *MAGEL2* gene was identified in four patients from three unrelated pedigrees (Patients 1, 3, 4 and 5). Mutations in *MAGEL2* are associated with Shaaf-Yang (SHFYNG) syndrome, a disorder characterised by hypotonia, feeding difficulties during infancy, global developmental delay/intellectual disability and sleep apnoea, often associated with arthrogryposis. The mutation reported in our patients had previously been described in a patient with SHFYNG, but with no reported endocrinopathy. A hemizygous *L1CAM* variant (*C.1354G>A*, p.G452R) known to be pathogenic in patients with L1 syndrome, was identified in Patient 2. *In Situ* hybridization revealed that *MAGEL2* was expressed in the developing hypothalamus and ventral diencephalon at CS19, 20 and 23, and in Rathke's pouch at CS20 and 23. *L1CAM* was expressed in the developing hypothalamus and trigeminal ganglia at CS19, 20 and 23, but not in Rathke's pouch at any stage.

Conclusions: We report mutations in *MAGEL2* and *L1CAM* in four unrelated pedigrees with variable hypopituitarism and arthrogryposis. The association of hypothalamo-pituitary disease with *MAGEL2* and *L1CAM* mutations respectively is extremely rare. Our expression analysis supports a role for these genes in hypothalamo-pituitary development and function. Our data suggest that patients with SHFYNG and L1 syndromes should be screened for hypothalamo-pituitary abnormalities.

FC9.4

Neuroendocrine Morbidity After Paediatric Craniopharyngioma: A Longitudinal Single Centre Analysis of 93 Patients Over 30 Years

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Context: Craniopharyngiomas are rare, suprasellar tumours with excellent 5-year survival rates of 95%. Despite their benign histology, their tendency to invade vital nearby optic, hypothalamopituitary and vascular structures, complicates resection whilst potentially causing secondary life limiting morbidity, panhypopituitarism and premature mortality. Since 1997, conservative hypothalamic-sparing surgery and radiation to the residual tumour has replaced aggressive resection at our centre.

Objective: We aimed to differentiate treatment and tumour-dependent risk factors for neuroendocrinopathy across treatment decades.

Design: This study was a retrospective longitudinal case note review and Kaplan Meier analysis of treatment and tumour-dependent factors affecting neuroendocrine outcomes in 93 children treated for craniopharyngioma at our centre between 1987-2017.

Results: Patients were aged a median (range) 8.24 (0.62-17.18) years at diagnosis and followed for 9.77 years (0.25–26.92). Despite excellent 20-year overall survival (OS) of 96.77%, progression-free survival (PFS) was 63.4% and, endocrine-event-free survival (EEFS) was just 3.3%. Time to OS (p=0.660), PFS (p=0.667) and EEFS (p=0.401) showed no difference between the different treatment decades. Hypothalamic involvement (p=0.003) more than aggressive surgery (p=0.008) were both associated with relapse. Complete resection reduced the time to first endocrine deficit (p=0.044), with TSHd being most frequently diagnosed first (frequency=84.9%) followed by GnDd (76.1%, only M>14ys/F>13ys included), GHd (93.5%), ACTHd (75.0%), CDI (63.4%) and obesity (50.6%). GHd increased with later treatment decades (p=0.002) but prompt replacement did not reduce PFS. At last review, 63 patients (67.7%) had panhypopituitarism (33 with additional CDI)

and 39 (42.0%) were obese. The BMI-SDS of the whole cohort increased by +0.96 (-2.83-+4.17) from diagnosis and was worse overall in those undergoing gross total resection, increasing by +2.16 (+0.06-+4.17) vs incomplete resection +0.87 (-0.62-+2.36, p=0.03). There was a significant reduction in overall BMI-SDS increase across the different treatment eras (p=0.011). Radiotherapy was not predictive of cognitive outcome, with intelligence quotient (IQ) scores in a subset of 22 patients with available pre- and post-treatment data showing no difference (p=0.384).

Conclusions: This large, longitudinal, single-centre analysis of children undergoing changing treatment strategies for craniopharyngioma, confirms the evolutionary hierarchical loss of pituitary and hypothalamic deficits we previously described in a cohort of optic hypothalamo-chiasmatic gliomas (Gan et al JCEM 2015). Our data suggests that changing to a conservative surgical therapeutic approach, avoiding hypothalamic harm, coupled with adjuvant radiotherapy improves neuroendocrine morbidity without reducing survival, recurrence rate or cognitive ability.

FC9.5

National Multidisciplinary Decision-Making Guideline for Children and Young People (*Idiopathic* Thickened Pituitary Stalk And/or *Idiopathic* Central Diabetes Insipidus

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Background: Thickening of the Pituitary Stalk (TPS) and/or Central Diabetes Insipidus (CDI) can occour in isolation or synchronously/metachronously in the same patient. Due to their rarity and wide spectrum of underlying aetiologies they represent a diagnostic and management conundrum. **Aim:** To develop a high-quality national multidisciplinary guideline for the assessment and management of children and young people (CYP) before their 19th birthday with *Idiopathic* TPS (iTPS) and/or *Idiopathic* CDI (iCDI), where the aetiology is not apparent at presentation. **Methods:** The interdisciplinary guideline development group (GDG) identified the objectives and 64 clinical questions which needed to be addressed. These were reviewed by guideline stakeholders and used to direct a systematic literature search (January 1990 – March 2017). 583 articles were appraised using the GRADE system. Where there was sufficient evidence, the GDG made a guideline recommendation. Where high quality evidence was lacking, the GDG drafted recommendations based on their expert opinion and reviewed these using two rounds of Delphi consensus with 30 international experts. This was a joint endocrine and oncology society (BSPED/CCLG), multidisciplinary, national endeavour, done to AGREE II methodology, produced by CCLG and endorsed by BSPED and RCPCH. **Results:** High quality evidence was lacking for the majority of the clinical questions. What constitutes a TPS was not consistently defined across studies. The GDG group recommended to consider that a pituitary stalk might be pathologically thickened and require further investigations and surveillance if there is uniform or focal thickening > 3 mm at the pituitary insertion and/or > 4 mm at the level of optic chiam. In 11 case series (684 children) the commonest individual causes of TPS/CDI were Langerhans cell hystiocytosis (16%), germ cell tumours (13%) and craniopharingiomas (12%). A range of congenital defects accounted for 19% of cases. Infectious diseases (2%), trauma (1%) and inflammatory/autoimmune conditions (1%) were rare. In 29% of the cases no etiology is identified. Causes of pituitary stalk lesions in adults, such as metastatic tumours and neurosarcoidosis, are virtually absent in children. A decision-making flowchart has been developed and will accompany the guideline. **Conclusion:** The likely aetiology of iTPS and iCDI in children differs from that in adults and justifies the development of age appropriate guidelines to inform best practice nationally. This will form the basis for future audits of practice and outcomes and is intended to improve the quality of care of CYP with iTPS and iCDI.

FC9.6

National UK Guidelines for Screening, Multi-Disciplinary Team Management and Long-Term Follow-Up of Children and Young People (CYP) with Multiple Endocrine Neoplasia Type 1 (MEN1)

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Background: The management of MEN1 in CYP<19 years is challenging due to its rarity, and diverse presentations of its component tumours to several adult and paediatric medical and surgi-

cal specialists. There is little high quality evidence for treatment recommendations.

Aim: To ensure age- and tumour-specific paediatric and adult teams are involved in co-ordinated discussions to improve high quality care and hence survival and reduce long term morbidity; to improve and expedite diagnosis (including complex screening of familial cases), acute decision making and peri-operative care.

Methods: Having recognised these challenges, a multi-disciplinary guideline development group (GDG) was convened in conjunction with the Children's Cancer and Leukaemia Group (CCLG), the British Society for Paediatric Endocrinology and Diabetes (BSPED) and the Royal College of Paediatrics and Child Health (RCPCH).

Clinical questions were formulated based on a PICO (Population, Intervention, Comparison, Outcome) format by the multidisciplinary GDG to guide systematic searches via MEDLINE and EMBASE databases using OVID. The guideline objectives and clinical questions were reviewed by previously identified stakeholders (including patients with MEN1, and support groups) to ensure no relevant areas had been omitted. The systematic literature search identified 327 articles reviewed using the GRADE approach, of which 245 were excluded and 82 incorporated into the evidence-base for recommendations. Where recommendations could not be made, a two-stage international Delphi consensus process was conducted.

Results: 18 clinical questions were identified, producing 13 recommendations largely based on low quality evidence. 24 further recommendations achieved >70% agreement via the Delphi consensus process.

Important recommendations for the care of CYP with MEN1 include:

1. This is provided in an age appropriate tertiary setting (linked to a paediatric or Teenage Young Adult (TYA) CCLG oncology centre) by a designated endocrinologist with MEN1 expertise.

2. Investigation and treatment (including decisions about the timing and extent of surgical intervention) occurs at an appropriately constituted organ specific MDT that includes adult MEN1/NET MDT members.

3. Surgery in patients under 16 years of age is performed by the Paediatric tertiary Centre's designated surgical team with a nominated surgeon from the adult organ specific MDT.

4. All are entered into a lifelong national outcomes registry to inform and improve future management.

Conclusions: These CCLG, BSPED and RCPCH-endorsed guidelines developed according to AGREE II principals provide the first evidence- and consensus-based national recommendations for the management of CYP with MEN 1 aimed at achieving better consistency in quality of care and improving long-term quality of survival.

Late Breaking

FC10.1

Burosumab Improved Rickets, Phosphate Metabolism, and Clinical Outcomes Compared to Conventional Therapy in Children with X-Linked Hypophosphatemia (XLH) – A Randomized Controlled Phase 3 Study

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In children with XLH, high circulating levels of FGF23 cause hypophosphatemia with consequent rickets, skeletal deformities, and growth impairment. Conventional therapy consists of multiple daily doses of oral phosphate and active vitamin D (Pi/D). Burosumab is a fully human monoclonal antibody against FGF23 indicated for the treatment of XLH.

In the active-control study CL301 (NCT02915705), 61 children with XLH (1-12 years old) were randomized (1:1) to receive subcutaneous burosumab starting at 0.8 mg/kg every 2 weeks (Q2W) or Pi/D as prescribed by investigators. Eligibility criteria included a Total Rickets Severity Score (RSS) ≥2.0 and prior receipt of Pi/D. The primary endpoint was healing of rickets at Week 40 assessed by radiologists blinded to treatment using the Radiographic Global Impression of Change (RGI-C).

At Week 40, burosumab significantly improved rickets compared with Pi/D (RGI-C global score least squares [LS] mean ± SE: +1.92 ± 0.11 vs +0.77 ± 0.11; p<0.0001). More subjects in the burosumab group had substantial healing (RGI-C ≥+2.0) at Week 40, compared with the Pi/D group (21/29, 72% vs 2/32, 6%; odds ratio of 39.1, p<0.0001). Additional evidence for improvement of rickets included decreased Total RSS (LS mean ± SE change, burosumab vs Pi/D: -2.04 ± 0.145 vs -0.71 ± 0.138; p<0.0001), decreased alkaline phosphatase (-131 ± 13 vs -35 ± 19; p<0.0001), and improved RGI-C lower limb deformity score (+0.62 ± 0.12 vs +0.21 ± 0.12; p=0.020). At Week 40, increases in serum phosphorous (p<0.0001) and TmP/GFR (p<0.0001) were significantly greater

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with burosumab compared with Pi/D. Standing height Z-score increased in both treatment groups from baseline to Week 40 with an LS mean change of +0.15 (95% CI: 0.05, 0.25) for burosumab and +0.08 (-0.02, 0.19) for Pi/D. Percent predicted distance walked in six minutes increased with burosumab (Baseline to Week 40: 62% to 72%) and was unchanged with Pi/D (76% to 75%). Pre-defined adverse events (AEs) of interest, including hypersensitivity and injection site reaction, were higher in the burosumab group, but were mild to moderate in severity overall, with no discontinuations. There were 4 serious AEs (3 burosumab, 1 Pi/D); none were treatment-related and all resolved.

In this randomized Phase 3 clinical trial, burosumab Q2W resulted in significantly greater improvements in rickets and phosphate metabolism compared with conventional therapy in 1-12 year-old children with XLH.

FC10.2

Efficacy and Safety of Once-Weekly Somapacitan in Childhood Growth Hormone Deficiency: Results of a Randomised Open-Label, Controlled Phase 2 Trial

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Background: Growth hormone deficiency (GHD) requires long-term daily injections with GH replacement therapy and is associated with considerable treatment burden by patients and caregivers. Somapacitan is a long-acting GH derivative that is being developed for once-weekly dosing in adults and children with GHD. A well-established protraction method, which is successfully in use to extend the half-life of insulin and glucagon-like peptide (GLP)-1, has been applied in developing somapacitan: an albumin-binding moiety (1.3 kDa) has been attached to a single point mutation in the amino acid backbone of the GH molecule (22 kDa).

Objective: To evaluate the safety, tolerability and efficacy of three different once-weekly somapacitan doses, compared with Norditropin®, a daily GH.

Design: A multicentre, open-label, randomised, controlled phase 2 trial in children with GHD (ClinicalTrials.gov: NCT02616562; REAL 3). The trial was double-blinded with regard to dose levels of somapacitan, and height measurements were performed by assessors blinded to treatment allocation.

Methods: Fifty-nine GH-treatment-naïve prepubertal children with GHD were randomised to either somapacitan (N=45) or Norditropin® (N=14). Subjects received one of three subcutaneous (s.c.) somapacitan doses: 0.04 (n=16), 0.08 (n=15), or 0.16 mg/kg/wk (n=14) administered once-weekly, or s.c. Norditropin® 0.034 mg/kg/day (0.24 mg/kg/wk; n=14). Fifty-six patients completed 6 months of treatment, as follows: n=14, 15 and 14 in the somapacitan 0.04, 0.08 and 0.16 mg/kg/wk groups, respectively, and n=13 in the Norditropin® group.

Results: Mean (standard deviation) annualised height velocity (HV) for the three somapacitan doses was 8.0 (2.0), 10.9 (1.9) and 12.9 (3.5) cm, respectively. For the 0.08 and 0.16 mg/kg/wk doses, HV did not differ statistically significantly from HV with Norditropin® (11.4 [3.3] cm). Insulin-like growth factor (IGF)-I and IGF-binding peptide 3 (IGFBP-3) showed a dose-dependent increase during somapacitan treatment. Somapacitan was well tolerated at all doses investigated, with no clinically relevant safety or local tolerability issues identified. Adverse events were mild to moderate; most were evaluated as unrelated to the trial drug by the investigator; and tolerability was consistent with known properties of GH.

Conclusions: This phase 2 trial confirms the long-acting mechanism of somapacitan. Efficacy, safety and tolerability were similar to those of Norditropin® in children with GHD. These data provide support for initiation of a phase 3 trial, using once-weekly injections of somapacitan, in children with GHD.

FC10.3

Identification of the MAPK/ERK Pathway as a Novel Therapeutic Target in Adamantinomatous Craniopharyngioma

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Adamantinomatous craniopharyngiomas (ACPs) are clinically challenging tumours, the majority of which have activating mutations in *CTNNB1*. They are histologically complex, showing solid tumor component comprised of different morphological cell types (e.g β-catenin accumulating cluster cells and palisading epithelium), surrounded by a florid glial reaction with immune cells, but also a cystic component. ACP cysts often exert substantial mass effect on critical structures, including the pituitary, the hypothalamus, visual pathways and the third ventricle, leading to severe endocrinal and neurological morbidity. This observation allowed to consider cyst-directed therapies that may offer the opportunity to control the local effect of ACP.

We have carried out RNA sequencing on 18 ACP samples and integrated these data with an existing ACP transcriptomic datasets. No studies so far have examined the patterns of gene expression within the different cellular compartments of the tumour. We

reveal that cell clusters express high levels of several members of the FGF, TGF-β and BMP families of secreted factors, which signal to neighbouring cells as evidenced by immunostaining against the phosphorylated proteins pERK1/2, pSMAD3 and pSMAD1/5/9 in both human and mouse ACP.

We determine that inhibiting the MAPK/ERK pathway results in the reduction of tumour cell proliferation and the increase of apoptosis in explant cultures of human and mouse ACP. Current experiments on genetically engineered ACP mouse model are ongoing to assess the effect of Trametinib, a MEK1/2 inhibitor, on the ACP development and to determine the potential therapeutic interest as targeted therapy in the particular environment of cysts development.

Our data support a new therapeutic opportunities for ACP patients by revealing the activation of the MAPK/ERK pathway in human ACP and showing that the inhibition of this pathway can affect tumour development.

FC10.4

Hypothalamus Sparing Surgery Improves the Outcome of Patients with Severe Initial Hypothalamic Involvement of Childhood Craniopharyngioma: Results of the Prospective Multinational Trial KRANIOPHARYNGEOM 2007

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Context: Quality of survival (QoS) is frequently impaired in childhood-onset craniopharyngioma (CP) patients due to sequelae caused by the hypothalamic syndrome. The debate, whether primary hypothalamic involvement (HI) has apriori prognostic impact or surgical hypothalamic lesions (HL) determine outcome, is controversial. Accordingly, we analyzed, whether CP patients at high risk for hypothalamic obesity due to primary HI of anterior and posterior hypothalamic structures benefit from hypothalamus-sparing surgical strategy.

Patients and methods: We included 109 CP patients with reference-confirmed initial anterior and posterior HI recruited between 2007 and 2014 in KRANIOPHARYNGEOM 2007. Progression-free survival (PFS), body mass index (BMI), QoS as assessed by **Ped**iatric **Q**uality **o**f **L**ife (PEDQOL) questionnaire, and functional capacity (FMH ability scale) were analyzed one and 3 years after CP diagnosis and at last follow-up visit with regard to the degree of reference-confirmed surgical HL.

Results: Surgical HL were reference-confirmed in 86 of 109 (79%) CP patients included in our study (23 no HL, 29 anterior HL, 57 anterior plus posterior HL). PFS and BMI at diagnosis were similar in our CP subgroups with different degree of HL. Significant increases in BMI occurred in all HL subgroups during follow-up (median follow-up interval at last visit: 6.1 yrs, range: 3.0–10.3 yrs). However, CP with anterior plus posterior HL presented with higher BMI at the time points 1 yr after diagnosis (median BMI: +5.21 SD, range: -0.32–13.09 SD) and at last visit (median BMI: +5.74 SD, range: -0.82–14.65 SD), when compared to patients without HL (median BMI at 1 yr follow-up: +1.72 SD, range: -0.07–10.37 SD, p=0.001; at last visit: +2.27 SD, range: -1.77–6.99 SD, p<0.001) and compared to patients with anterior HL (median BMI at 1 yr follow-up: +2.46 SD, range: -1.86–10.37 SD, p=0.002; at last visit: +2.87 SD, range: -0.81–11.11 SD, p=0.001). QoS was better during follow-up in CP without HL for the PEDQOL domains physical function (p=0.047), emotional stability (p=0.040), and social functionality family (p=0.002) when compared to CP patients with anterior plus posterior HL. Differences in terms of functional capacity did not reach statistical significance with regard to HL.

Conclusions: Hypothalamus-sparing surgical strategy does not result in increased relapse and progression rates, improves QoS and ameliorates the development of severe obesity also in CP patients at high apriori risk for hypothalamic obesity due to primary presurgical HI.

FC10.5

A 5-Year Single-Centre Experience on the Safety and Efficacy of Sirolimus Therapy Used for the Treatment of Congenital Hyperinsulinaemic Hypoglycaemia

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Background: Case reports have documented variable glycaemic response to the mTOR inhibitor Sirolimus in severe diazoxide+/-octreotide unresponsive forms of congenital hyperinsulinaemic hypoglycaemia (CHI). A high incidence of adverse effects has been reported in patients receiving this medication.

Objective(s): To describe the efficacy and safety of Sirolimus use over a 5-year period in the largest cohort of CHI patients treated to date.

Methods: Retrospective data were collected on CHI patients treated with Sirolimus in a single centre between 2013 and 2018. Our data were then compared with those reported in 15 previously published case reports of Sirolimus treatment in CHI (PubMed search). Complete response to Sirolimus was defined as glycaemic stabilisation exclusively on this drug, partial response as CHI

being managed on a combination of Sirolimus plus concomitant medication for CHI, and unresponsiveness as non-existent glycaemic amelioration despite combination of Sirolimus with other CHI medications.

Results: 22 CHI patients (14 female) were included. A partial response to Sirolimus was observed in 20/22 (90.9%) cases. One patient (4.5%) showed a complete response, and one patient (4.5%) was unresponsive. Compound heterozygous *ABCC8* mutations were present in 52.4% (11/21) of the partially/fully responsive patients. Complications during Sirolimus treatment occurred in 86.4% (19/22) of treated patients; infections were the most prevalent (17/22; 77.3%), of which 64.7% (11/17) were caused by bacteraemia. Three patients (13.6%) developed persistent diarrhoea, while hyperglycaemia occurred in 9.1% (2/22). Sirolimus was discontinued in 17/22 (77.3%) patients, 13 (76.4%) of whom had infections, 2 (11.7%) had hyperglycaemia, and 2 (11.7%) responded well to alternative Lanreotide treatment. When compared with existing literature on the use of mTOR inhibitors in CHI, our study shows a higher number of cases that are partially/fully responsive to Sirolimus, whilst complication rates are comparable to previously published data.

Conclusions: Frequent and potentially serious complications render Sirolimus as an agent that is only suitable for trial in selected cases of severe CHI that are unresponsive to other medications. We suggest that its use for short periods, until glycaemic stabilisation is achieved using other therapies such as Lanreotide, could be contemplated as it may avoid pancreatectomy. The potential benefit of Sirolimus in cases of CHI associated with certain genetic mutations needs to be explored further.

FC10.6

Primary Ovarian Insufficiency Incidence Rate and Etiology Among Israeli Adolescents Between the Years 2000-2016 – A Multi-Center Study

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Introduction: Primary ovarian Insufficiency (POI) occurring in youth is a devastating condition. POI is characterized by at least 4 months of disordered menses in association with menopausal follicle stimulating hormone (FSH) levels. The most common causes of POI in adolescence are iatrogenic and chromosomal abnormalities. Data are scarce regarding the incidence of POI in adolescents.

Objectives: We aimed to estimate the incidence and the distribution of etiologies of POI in a multi-center study in Israel.

Methods: Data regarding girls under age 22 years presenting with POI during the years 2000-2016 were collected from 14 medical centers. Iatrogenic cases were excluded. The incidence rate of

new POI diagnosis was calculated based on birthrate information from the Israeli Central Bureau of Statistics (CBS).

Results: 114 girls met the criteria of POI, presented at a mean age of 13.6±3.8 years, 68 (60%) with primary amenorrhea. Their mean FSH level was 77.3±39.9 mUI/mL. The distribution of etiologies was: Turner syndrome/mosaicism in 50/114 (44%), idiopathic in 36/114 (32%) and other (genetic, autoimmune, etc.) in 28/114 (24%). The incidence rate of new POI diagnoses per 100,000 births doubled between the years 2009-2016 compared to the years 2000-2008 (incidence rates 3.8 and 1.8, respectively, p-value= 0.0007). Moreover, the incidence rates of both idiopathic and other etiologies tripled comparing these two time periods (p-value=0.004 and p-value= 0.01 respectively), contrasting with Turner syndrome, whose incidence rate remained static (p-value=0.6).

Conclusions: Over the last decade a significant increase in the rate of POI was observed among adolescents, especially among non-Turner cases. We believe the findings reflect a true increase in the risk of developing POI and not a change in awareness and identification patterns. The possible involvement of environmental and epigenetic factors in this remarkable increase should be investigated.

Bone, Growth Plate & Mineral Metabolism 2

FC11.1

Successful Immune Tolerance Induction in the First Case of Neutralizing Antibody Mediated Loss of Efficacy of Asfotase Alfa Treatment in Hypophosphatasia

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Introduction: Generation of neutralizing antibodies (Nab) is a complication in enzyme replacement therapies and can lead to loss of treatment efficacy. Asfotase alfa (AA) was recently approved as the first replacement therapy in severe hypophosphatasia (congenital deficiency of alkaline phosphatase [TNSALP]). We report a case of neutralizing antibody mediated loss of efficacy of AA treatment in hypophosphatasia and the successful result of immune tolerance induction (ITI) therapy.

Clinical case: A boy affected with severe (craniosynostosis, rib cage deformity, intense metaphyseal impairment), early onset (below 6 months) hypophosphatasia due to compound heterozygosity in *ALPL* (c.542C>T/c.644T>C) started enzyme replacement therapy with AA (6 mg/kg/week in 3 doses) at age 4.42 years, showing complete biochemical (pyridoxal-5-phosphate [PLP] and inorganic pysophosphate [PPi] serum levels) and radiological (metaphyseal impairment) normalization and evident clinical improvement (bone pain resolution, achieved autonomous locomotion, improved muscle strength and endurance with no need of ambulatory-assisting devices).

After 2.5 years on therapy, clinical symptoms and radiological signs reappeared and serum TNSALP substrate PLP levels increased (343 mcg/l [N.V. 6.7-18.5]), up to a maximum of 999 mcg/l despite increasing treatment to 3-fold standard dose (18 mg/kg/week). Antidrug (ADA) and Nab titers were low (1:2), but serum neutralizing activity was 40.4% (normal <4.478%).

A Nab mediated loss of treatment efficacy was diagnosed and ITI therapy was scheduled (immunoadsorption [Therasorb®] + rituximab [375mg/m2] weekly x 4 weeks, with concomitant immunoglobulin infusion [500 mg/Kg]) in addition to stopping AA treatment for one month. During this time, the patient needed a wheelchair even for in-home movement, suffered from continuous skeletal pain, had undetectable ALP serum levels and extremely high plasma PLP (997 mcg/l), but lymphocyte B depletion was complete and the patient´s serum neutralizing activity dropped to 4.75%.

AA treatment was restarted at 6 mg/kg/week and was well tolerated, with no adverse effects. The patient showed substantial improvement in pain and physical performance (no need of ambulatory-assisting devices after 1 month, restarting school attendance, autonomous walking and physical games with classmates) and full Nab abrogation, normal PLP levels and substantial radiological healing were achieved 6 months after the ITI.

Conclusions:

1. Nab generation can engender loss of efficacy of AA treatment in hypophosphatasia.
2. The proposed ITI (weekly immunoadsorption plus rituximab for 4 weeks) can achieve Nab abrogation and restore treatment efficacy after 6 months of follow-up.

FC11.2

Elevated Phosphate Levels Inhibit Skeletal Muscle Cell Differentiation *in Vitro*

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Background: Hyperphosphatemic conditions such as chronic kidney disease are associated with muscle wasting and impaired life quality. While muscle regeneration relies on myogenic progenitor recruitment, the effects of high phosphate loads on this process

has not been investigated in detail. This study aims to clarify the direct effectsof hyperphosphatemic conditions on skeletal myoblast differentiation in an murine cell model system.

Material and methods: C2C12 murine muscle progenitor cells were differentiated with equivalents to physiological and pathological phosphate loads. Phosphate-induced changes in marker gene expression were quantified by RT-PCR. Furthermore, immunohistochemistry was performed to investigate nuclear positive cell counts under treatment. Cell viability and metabolic activity were measured by XTT and BrdU incorporation assays. All experiments were performed in ≥3 independent runs.

Results: Inorganic phosphate directly induces ERK-phosphorylation in pre-differentiated C2C12 myoblast cells. Phosphate concentrations resembling moderate and severe hyperphosphatemia (1.4mmol/l - 2.9 mmol/l) impaired the expression of differentiation markers Myogenin (-61.0%, $p < 0.0001$) and MyoD (-51.0%; $p < 0.0001$). While higher phosphate loads showed more pronounced effects, even moderately hyperphosphatemic conditions could significantly reduce Myogenin (-22.5%, p=0.015) and Myf5 (-33.3%, p=0.039) expression. Analogue effects were found on the protein level, where a significantly decreased count of Myogenin (-42.0%, p=0.004) and MyoD positive cells (-25,7%, p=0.002) was found in phosphate enriched medium. Increased phosphate concentration left metabolic

activity and cellular proliferation rate unaltered.

Conclusion: Our data point to a phosphate-induced inhibition of myoblast differentiation without effects on cell viability. Strikingly, phosphate levels corresponding to the upper normal range significantly impaired marker gene and protein expression.

Investigation of cellular responses during hyperphosphatemia may help to define serum phosphate cutoffs and modify existing treatment approaches of phosphate binders, especially in patients at risk for sarcopenia.

FC11.3

Evidence for Effects of FGF2 Aptamer in an Achondroplasia Mice Model and an *in Vitro* Chondrocyte Differentiation System Using Patient-Derived IPS Cells

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Achondroplasia (Ach) is a skeletal disorder caused by gain-of-function mutations of *FGFR3*. Ach patients suffer from various complications such as short stature, foramen magnum stenosis and sleep apnea. Disease-specific treatment is not available at present, although some drugs including a C-type natriuretic peptide analogue have been developed. The mutated FGFR3, G380R, has an elevated activity of the receptor-associated tyrosine kinase, but G380R is further activated by the binding of its ligand. Aptamer is a RNA-related drug with specificity to its cognate target or an active compound. We generated a RNA aptamer, RBM-007, specific for human FGF2 and confirmed the blocking effect in signaling pathway induced by FGF2 *in Vitro*. In the study, we investigated the effects of RBM-007 in the transgenic Ach model mouse where G380R is expressed in chondrocytes under the type II collagen promoter. The Ach mice, $Fgfr3^{Ach}$, had shorter body length than that of wild-type (wt) littermate mice, and the administration of 10 mg/kg RBM-007 sc. once every 2 days for 3 weeks significantly improved the body length (p=0.002) and femur length (p=0.0001). However, the treatment with RBM-007 did not normalized the length of the body and the femur in $Fgfr3^{Ach}$. In addition, we performed *in Vitro*chondrocytes differentiation experiments using ACH patients-derived iPS cells (iPSCs).The experiment was performed according to the protocol reported previously (Yamashita A et al. Nature 2014). In the experiments, control iPSCs differentiated into chondrocytes and produced cartilage matrix, while iPSCs derived from 3 Ach patients did not differentiate into chondrocytes. The results were consistent with those reported previously. 100 nM, but not 10 nM, RBM-007 promoted the chondrogenic differentiation of Ach-iPSCs with characteristic safranin-O-positive matrix formation and improved the expression of the chondrocyte marker genes such as *SOX9*, *COL2A1*and *ACAN*. We are now checking side effects of RBM-007 on the growth plate using young model monkeys. These results suggest that RBM-007 is a potential drug for achondroplasia.

FC11.4

Using Patient Derived Induced Pluripotent Stem Cells to Model Multiple Epiphyseal Dysplasia

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Multiple epiphyseal dysplasia (MED) is a chondrodysplasia characterised by delayed epiphyseal endochondral ossification, resulting in disproportionate short stature and early onset osteoarthritis. MED can be caused by heterozygous mutations in COMP, MATN3, COL9A1, COL9A2 and COL9A3, or bi-allelic mutations in SLC26A2. Human induced pluripotent stem cells (hiPSCs) are reprogrammed somatic cells which can differentiate to form all body tissues and have excellent potential for tissue regeneration as well as providing models of human disease. Our aim is to generate an in vitro hiPSC model of growth-plate development in order to better understand MED.

HiPSCs were generated from peripheral blood mononuclear cells (PBMCs) of 3 related MED individuals who are heterozygous for a MATN3 p.Val194Asp mutation (V194D) and 4 healthy controls, including one close relative. HiPSC were differentiated to growth-plate-like chondrocytes via an iPSC-MSC-like intermediate, followed by TGFβ3 + BMP2 induced chondrogenic pellet culture for 21 days.

Healthy and V194D hiPSCs were able to differentiate to iPSC-MSCs which displayed typical MSC morphology, expressed MSC markers (CD90, CD105, CD44 and CD73) and were capable of generating cartilage and bone. After 21 days in TGFβ3 + BMP2-containing medium V194D chondrogenic pellets were significantly larger in size, stained more strongly for cartilage associated

sulphated glycosaminoglycans (Alcian blue and Safranin O), and expressed significantly higher levels of transcript for the chondrogenic transcription factor SOX9, and the major cartilage matrix constituents COL2A1 and ACAN. These data suggest V194D mutant pellets respond differently during TGFβ3 + BMP2 induced chondrogenesis. RNA-Seq validated the high expression of chondrogenic associated transcripts in the V194D mutant pellets, recapitulating the delayed transition from cartilage to bone observed in the growth plate of MED patients.

Immunohistochemistry and confocal co-localisation analysis of matrilin-3 (usually a matrix protein) with the endoplasmic reticulum (ER) marker GRP94, suggests matrilin-3 is retained within the ER of the V194D mutant pellets. As matrilin-3 interacts with TGFβ and BMP2, this may explain the differences in response to growth factors during pellet culture. This work provides novel insight into MED disease pathogenesis. Our in vitro growth-plate model will facilitate the identification of pathogenic pathways of growth-plate diseases that are suitable for pharmacological intervention, and will allow the screening of pharmaceutical products.

FC11.5

A Recurrent 6-bp Intronic Deletion in *NESP55* with Reduced Penetrance in Pseudohypoparathyroidism Type 1b

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Background: Pseudohypoparathyroidism type 1b (PHP1b) is caused by epigenetic errors on the maternal *GNAS* allele at differentially methylated regions (DMRs) associated with exons A/B, XL, and NESP that lead to reduced production of Gαs transcripts most notably in the renal proximal tubule and thyroid follicular cells. Most PHP1b cases appear sporadically, few of which can be explained by paternal uniparental disomy involving chromosome 20q, leading to global methylation defects at all three DMRs. Familial PHP1b is most frequently associated with loss of methylation at *GNAS* exon A/B and heterozygous *STX16* deletions. A minority of familial PHP1b patients have global methylation defects at DMRs associated with exons A/B, XL, and NESP (Low-Low-High methylation) due to heterozygous deletions affecting maternal NESP and/or AS exons.

Objective and hypotheses: To identify the underlying genetic defect for PHP1b in patients with normal microarrays.

Method: Whole genome sequencing (WGS) was applied to two patients within a multigenerational kindred with clinical diagnosis of PHP1b and Sanger was used to confirm the identified variant in the entire family and screen 14 additional sporadic PHP1b patients.

Results: In a previously described PHP1b family with global methylation defects in affected subjects, WGS revealed a 6-bp intronic deletion (chr20:g.57,419,071-57,419,076) between exons AS3 and AS2 in two affecteds. Subsequent Sanger confirmed that the deletion was maternally inherited and the deletion was present in all four affecteds and one obligate carrier. However, three subjects with the maternal deletion had normal methylation and normal PTH responsiveness. We screened additional 14 sporadic PHP1b patients and found the same mutation in one patient with global methylation defects. His unaffected mother and brother both carried the same heterozygous 6-bp deletion but had normal methylation patterns and normal PTH responsiveness. The mutation was absent from 1000 Genomes Projects, gnomAD dataset with >15,000 genomes, and >10,000 samples with genome-sequencing data in Human Longevity database.

Conclusion: Our analysis indicate that this very small deletion is a recurrent *GNAS* mutation with reduced penetrance, and when maternally inherited leads to a global methylation defect (L-L-H) in only some patients. PHP1b occurs only when the methylation defect is present, indicating that the epigenetic defect rather than the genetic mutation is an accurate predictor of PTH resistance. The incomplete penetrance of this 6-bp deletion may define the limit of a cis-acting element on the maternal allele that is required for normal methylation of *GNAS* DMRs.

FC11.6

Management of Severe, Protracted Hypocalcaemia in Patients Undergoing Thymus Transplantation in a Tertiary Centre: A 10-Year Experience

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Background: Thymus transplantation is undertaken for conditions associated with severe immunodeficiency. These comprise a number of genetic and syndromic associations including 22q deletion syndrome, CHARGE association, diabetic embryopathy, and other rarer conditions. These conditions may also be associated with hypoparathyroidism and patients are therefore at risk of severe hypocalcaemia. There are no published guidelines for calcium replacement in these patients during the pre and post transplant period.

Case Series: 29 patients (age 2 months-2 years, 20 male) from the UK and 13 European centres underwent thymus transplantation between 2009-2018. The underlying diagnoses included 22q11.2 (n=17, 1 with a phenotype only of 22q11.2), CHARGE association (n=8), diabetic embryopathy (n=2), *FOXN1* mutation (n=1), and *TBX1* mutation (n=1). 93% had hypoparathyroidism prior to transplant, treated with enteral calcium supplementation on admission. 79% had hypocalcaemia (defined in this cohort as corrected calcium (cCa)<2.0mmol/L) during admission. The mean nadir in the entire cohort was cCa=1.7 mmol/L (1.2 - 2.4 mmol/L). This occurred from 45 days pre-transplant to 35 days post-transplant (mean = day +1 post-transplant). 55% of patients required intravenous calcium during admission, and 35% required continuous calcium infusions. A diagnosis of 22q11.2 was associated with a slight increase in likelihood of requiring intravenous calcium (Likelihood Ratio =1.4, 63% of patients with 22q11.2 compared to 46%

with alternate diagnosis). The mean duration of intravenous treatment was 4.7 days (1 - 39 days) and calcium requirements varied from 0.7 to 2.4mmol/Kg/day (mean = 0.7mmol/Kg/day.) Associated complications included prolonged length of stay [median=28 days (11-255)], admission to intensive care (24%), hypocalcaemic seizures (14%), nephrocalcinosis (20% of those who underwent sonographic evaluation), infection (68%), mortality (10%).

Conclusion: This case series highlights the variability and unpredictability of severe hypocalcaemia in patients undergoing thymus transplantation. This vulnerable cohort is at significant risk of hypocalcaemia due to conditioning for transplant (including anti-thymocyte globulin (ATG)), hypoparathyroidism, the surgical procedure itself and post-operative reduced enteral absorption. Our practice has evolved over the past decade to include commencement of prophylactic intravenous calcium infusions in patients with borderline hypocalcaemia at the start of conditioning. Further studies are warranted to evaluate whether early pre-operative intravenous calcium therapy reduces post-operative complications related to hypocalcaemia and length of hospital stay. The lack of standardised evidence-based guidelines for the management of these patients has important implications for morbidity, mortality and healthcare cost.

Diabetes and Insulin 2

FC12.1

Continuous Glucose Monitoring Profiles in Healthy Non-Diabetic Children and Adolescents: A Multicenter Prospective Study

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Since CGM-based outcomes that are increasingly being used in clinical pediatric diabetes research, this study was aimed at gathering normative sensor data in healthy, non-diabetic children using the recently approved DexCom G6 system.

In this multicenter study, healthy, non-diabetic children and adolescents (age 7 to <18 years, BMI between 5th and 85th percentile, and HbA1c <5.7%) were included. Each participant wore a blinded DexCom G6 for ~10 days and kept a daily log of exercise, meals, and sleep. Only participants with no positive islet antibodies and ≥72 hours of CGM data were analyzed, overall and by age group.

Among the 56 healthy non-diabetic participants who were analyzed, 54% were female, 93% non-Hispanic White, mean HbA1c was 5.1% and mean BMI percentile was 51%. Overall mean 24-hour sensor glucose level was 99 ± 6 mg/dL. Peak post-prandial glucose was 126 mg/dL. Overall, meal-related increases in sensor glucose resulted in daytime glucose levels 3 mg/dL higher than nighttime values. Sensor glucose levels >120 and <70 mg/dL were not uncommon in either age group but sensor values >180 mg/dL and <54 mg/dL were rarely observed (Table).

Table 1. Sensor glucose levels in healthy non-diabetic children and adolescents (n = 56) (for Abstract no FC12.1)

	All (n = 56)	7–11 yrs old (n = 26)	12–17 yrs old (n = 30)
Mean glucose (mg/dL)	99	99	98
Glucose CV – mean	15%	16%	15%
%Time in range 70–120mg/dL	89%	89%	91%
%Time >120mg/dL	7.4%	8.4%	7.0%
%Time >140mg/dL	1.3%	1.7%	1.2%
%Time >160mg/dL	0.2%	0.2%	0.2%
%Time >180mg/dL	0.0%	0.0%	0.0%
%Time <70mg/dL	1.3%	1.0%	1.7%
%Time <60mg/dL	0.2%	0.2%	0.2%
%Time <54mg/dL	0.0%	0.0%	0.0%

*All data are median unless otherwise noted.

As greater emphasis is placed on glycemic metrics beyond HbA1c levels, the current study provides a normative set of sensor glucose levels that can be used for comparison for clinical trials. It is noteworthy that sensor glucose levels >180 and <54 mg/dL were very uncommon in our healthy non-diabetic participants, which support these levels as the thresholds for clinically important hyper- and hypoglycemia in diabetes. With improvements in both pharmacologic agents and mechanical solutions the ultimate goal may be to attain tighter glycemic control in those living with diabetes by altering the hyperglycemic threshold to 160 mg/dL.

FC12.2

Apoptosis and Oxidative Stress Markers During the Oral Glucose Tolerance Test (OGTT)

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Background: In adults, insulin resistance is associated with vascular damage and progressive loss of the endothelial protective functions. Additionally, it further complicates the micro- and macro- vascular environment through increasing oxidative stress and inflammation.

Aim: The purpose of this study was to evaluate how apoptosis and antioxidant markers are correlated with biochemical markers in children, during the glucose tolerance test (OGTT).

Methods: A prospective study with 30 participants living in Peloponnese, Greece, 7-16 years old, was conducted. OGTT and biochemical analyses were performed. Anti-Human Cd95 (Apo-1fas) and cck18 (Kaspase-Cleaved-Keratin-18) were measured as apoptotic markers while *Superoxide Dismutase* (SOD) and Glutathione Peroxidase 3 (GPX3) were measured as antioxidant markers. Children were studied in two categories: with normal or impaired glucose tolerance.

Results: 70% of the children had BMI%≥ 95% and impaired glucose tolerance. Children with normal glucose tolerance showed that Apo1fas and CCK18 were negatively correlated with BMI % (p=0.021 and p=0.043, respectively), GPX3 was positively correlated with insulin (p=0.025), Free thyroxine (FT4) (p=0.008) and HgbA1c (p=0.01). In children with impaired glucose tolerance SOD was positively correlated with HgbA1c (p=0.031), GPX3 was positively correlated with Triiodothyronine (T3) (p=0.001) and negatively correlated with IGF-1 (p=0.016). The measurement of apoptotic and antioxidant markers during the OGTT showed a gradual increase in their concentrations reaching maximum levels at t=60min and t=90min.

Conclusions: Our study suggests that in children, apoptotic and antioxidant markers change during the post-prandial state. In children with normal glucose tolerance: (1) the decrease in both apoptotic markers, Apo1fas and CCK18, in correlation to increased BMI% may be the body's attempt to compensate for the negative effects of childhood obesity and (2) the increase in the antioxidant marker, GPX3, with increased insulin concentration during the OGTT may be part of a protective mechanism in response to increased oxidative stress. Further studies are necessary to elucidate the role of apoptosis and oxidative stress during the post-prandial state in children.

FC12.3

Impact of Insulin Sensitivity and B-Cell Function on the Development of Impaired Glucose Tolerance (IGT) in Obese European Children and Adolescents

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Objectives: Compared to the US, prevalence rates of T2DM in obese children are significantly lower in European countries. Data from cohorts of obese children living in the US suggest a concurrent worsening of insulin sensitivity and ß-cell function over the spectrum of glucose tolerance. If these results can be applied to European populations is currently unknown.

Methods: A combination of our novel method for mathematical modelling of insulin secretion and disposal from 3h, 8 sample OGTT data in children and adolescents (Am J Physiol Endocrinol Metab. 3111:E82-94, 2016) with a minimal model of glucose was used to estimate insulin sensitivity SI and β-cell responsiveness Φ in a population of n=285 (n=147 girls) obese children and adolescents (Øage 13.9 ± 3.0 years), ØBMI z-score 2.74 ±0.75. A subpopulation of n=35 subjects underwent follow-up OGTTs (median time to follow-up 1.92 years).

Results: Of the total study population, n=23 subjects were diagnosed with IGT. Regrouping into quartiles of 2h-glucose (q1: 56-95 mg/dl, q2: 96-109 mg/dl, q3: 110-122, q4 123-190 mg/dl) revealed a significant decrease of SI between each quartile of 2h-glucose (p<0.03), whereas Φ was significantly lower in q3 and q4 compared to q1 and q2 (p<0.001). IGT was associated with a 64% lower SI and 36% lower Φ compared to NGT subjects (each p<0.001). Adjusted for age and BMI z-score, only the difference in Φ remained statistically significant (p 0.004). In the follow-up cohort, n=4 subjects progressed from NGT to IGT, n=5 reverted from IGT to NGT, and n=23 remained NGT. At baseline, 'progressors' and 'reverters' were characterized by a 30% lower Φ compared to stable subjects. Furthermore, 'reverters' had a 1.6 times lower SI than stable subjects (p<0.02). Progression from NGT to IGT was associated with a 41% decline in SI while Φ remained unchanged. Conversely, reversion to NGT was associated with a 49% improvement of SI and an unchanged Φ.

Conclusions : β-cell function and insulin sensitivity continuously decline over the spectrum of glucose tolerance in obese European children and adolescents. Progression from NGT to IGT is heralded by an impairment of β-cell responsiveness, but ultimately driven by significant worsening of insulin sensitivity. Improvement of insulin sensitivity in the context of stable β-cell function leads to reversion of IGT. Therefore, stability of β-cell function may provide a pathophysiological explanation for the lower prevalence of T2DM in obese European compared to obese US adolescents.

FC12.4

How Does Thiol/Disulphide Homeostasis Change in Children with Type 1 Diabetes Mellitus?

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Introduction: Increased cytokine release, impaired antioxidation and reactive oxygen species (ROS) have been shown in β-cells in pathogenesis of T1DM. Increased ROS leads to formation of covalent bonds between the sulfur atoms, leading to disulphide conversion. Displacement to disulphide form of this thiol/disulphide balance starts the oxidative damage. This study evaluates the thiol/disulphide balance in children with T1DM.

Material- Method: Thiol/disulphide balance evaluated in 30 patients with T1DM and 30 healthy volunteer children. Total thiol, native thiol and disulphide levels studied by Erel & Neselioglu's newly developed automatic measurement method.

Results: There was no difference in age and gender of T1DM group (17 f/ 13 m, mean age:11.75±2.71 years) and control group (12 f/ 18 m; mean age:11.54±2.55 years). In T1DM group, results were as; native thiol: 388.3 ± 76.7 μmol/L, total thiol: 426.2 ± 87

μmol/L, disulphide: 18.9 ± 7 μmol/L, in control group, were as; native thiol: 423.1 ± 45.2 μmol/L, total thiol: 455.7 ± 49.9 μmol/L, disulphide: 16.2 ± 5.6 μmol/L. Disulphide/native thiol, disulphide/total thiol ratios were significantly higher in the type 1 diabetes mellitus group (p:0.005, p:0.004), but native thiol levels, native thiol/total thiol ratio were significantly lower than the control group (p:0.036, p:0.015). There was no statistically significant correlation between demographic data and thiol/disulphide subgroups.

Discussion: This is the first study demonstrating that dynamic thiol/disulphide homeostasis in children with T1DM shifts to the disulphide direction. It is suggested that this shift is caused by oxidative damage of β cells. New studies about thiol/disulphide homeostasis in children with T1DM can lead to early detection of oxidative damage of β cells.

FC12.5

Effect of Homocysteine-Lowering Therapy on Diabetic Nephropathy in Children and Adolescents with Type 1 Diabetes

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Background: Diabetic nephropathy (DN) is a major microvascular complication of type 1 diabetes mellitus (T1DM). Homocysteine levels have been found elevated in T1DM patients with DN due to several causes, including dietary deficiencies of folic acid and B Vitamins. Hyperhomocysteinemia induces renal injury and is associated with increasing urinary albumin excretion in patients with diabetes. We therefore performed a randomized-controlled trial of oral supplementation with vitamin B complex as an adjuvant therapy for diabetic nephropathy in children and adolescents and assessed its relation to homocysteine levels, glycemic control, microalbuminuria and cystatin C as a marker of nephropathy.

Methods: This trial included 80 vitamin B12-deficient type 1 diabetic patients with nephropathy, despite oral angiotensin-converting enzyme inhibitors (ACE-Is). Enrolled patients aged 12-18 years with at least 5 years disease duration and hemoglobin A1c (HbA1c) ≤8.5%. Patients were randomly assigned into two groups; intervention group who received oral supplementation with vitamin B complex once daily (Neurorubine ^{TM} –Forte Lactab ^{TM} Mepha Pharma Egypt S.A.E manufactured by Medical Union Pharmaceuticals).The tablet is composed of Vitamin B1 200 mg, Vitamin B6 - 50 mg and Vitamin B12 1000μg. The other group did not receive any supplementation and served as a control group. Both groups were followed-up for 12 weeks with assessment of plasma homocysteine, HbA1c, urinary albumin excretion (UAE) and cystatin C.

Results: The subjects in the trial groups were well matched in baseline clinical characteristics and laboratory parameters (p>0.05). Baseline homocysteine levels were elevated in both groups compared with reference control values. After 12 weeks, supplementation with vitamin B complex resulted in significant decrease of plasma homocysteine, fasting blood glucose, HbA1c, total cholesterol, triglycerides, UAE and cystatin C compared with baseline levels (p<0.001) in intervention group and compared with control group (p<0.001). No adverse reactions due to vitamin B complex were reported. Baseline vitamin B12 was positively correlated to UAE (r=-0.877, p=0.009) and cystatin C (r=-0.77, p=0.043) while negatively correlated with homocysteine levels among DN patients with vitamin B adjuvant therapy.

Conclusions: Oral supplementation with vitamin B complex for 12 weeks improved glycemic control and renal function through decreasing plasma homocysteine. Thus, it could be a safe and effective strategy for treatment of pediatric type 1 diabetic patients with nephropathy.

FC12.6

Persistent Beneficial Effects of Metformin in Children and Adolescents with Type 1 Diabetes: Adelaide Metformin Randomized Controlled Trial Follow Up

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Puberty is a critical period for the development and acceleration of vascular complications in Type 1 diabetes (T1D). We have shown that metformin in addition to insulin improves vascular smooth muscle function and HbA1c in T1D children over 12 months (1). We aimed to determine if children with T1D who received metformin in a randomized controlled trial (RCT) [Trial registration ACTRN126110001148976] have a sustained vascular function improvement 3 years after ceasing metformin compared to children who received placebo.

Design was a three year follow up study after completion of 12 months RCT of metformin (1 gram twice a day) vs placebo. Subjects had the same assessments for vascular function as in RCT using brachial artery ultrasound (Flow mediated dilatation [FMD] and glyceryl trinitrate mediated dilatation [GTN]) and laboratory methods. Ninety children with T1D (mean (SD) age 13.6 (2.5) years, 41 boys, median [interquartile range (IQR)] HbA1c 8.7[8.1-9.9]%/72 [65-85] mmol/mol) included in the original trial were invited to participate in the follow up. Metformin was not prescribed after the trial was completed.

Fifty six adolescents have completed follow up for 3.2 (0.7) years after completion of the RCT: 27 in the original metformin group and 29 in placebo group, mean age 17.4 (SD 3.1) years, 27 males, mean diabetes duration of 9.9 (4.1) years and median [IQR] HbA1c of 9.2 [8.5-10.5] %/76 [69-91] mmol/mol. There were no significant differences at baseline between the children that completed the post RCT follow up and those that did not, but completers were younger (13.3 (0.4) years vs 14.3 (0.4) years, p=0.07).

Linear mixed model analysis showed that children who received Metformin in the RCT compared to placebo had an improvement in HbA1c (effect of 0.64 % (95% CI -1.1, 0.1, p=0.002) and vascular

smooth muscle function (GTN) independent of HbA1c (effect of 2.37 percentage units, 95% CI -0.23, 4.97, p=0.07) over the follow up period. Sensitivity analysis using multiple imputation showed similar results. As in the RCT there were no significant effects observed on endothelial function or intima media thickness.

The improvement in HbA1c during 12 months of metformin intervention persisted for 3 years after discontinuation in children and adolescents with T1D. Transient use of metformin during puberty in T1D may provide ongoing benefit.

1. Anderson et al. Effect of Metformin of Vascular Function in Children With Type 1 Diabetes: A 12-month Randomized Controlled Trial. J Clin Endocrinol Metab 2017.

Pituitary, Neuroendocrinology and Puberty 2

FC13.1

Molecular Screening of Genes Associated with Central Precocious Puberty

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Central precocious puberty (CPP) results from premature activation of the hypothalamic-pituitary-gonadal axis through the activation of the gonadotropin releasing hormone (GnRH). Gain-of-function mutations of the *KISS1* and *KISS1R* genes or loss-of-function mutations of the makorin RING-finger protein 3 (*MKRN3*) have been linked with CPP. Moreover intronic and intragenic variants harbouring the imprinted loci of *MKRN3-MAGEL2* and *DLK1* genes have been associated to age of menarche.

In the present study, a cohort of 75 index girls with CPP were screened for mutations in the coding sequence of the *MKRN3*, *KISS1, KISS1R, DLK1* and *MAGEL2* genes. All patients had pubertal basal and/or GnRH-stimulated LH levels and advanced bone age. Genotypic analysis of the *KISS1R* gene did not reveal any genetic defect. Three, seven and one single nucleotide polymorphisms (SNPs) were found in the *KISS1*, *DLK1* and *MAGEL2* genes, respectively. The minor allele frequencies (MAF) for these SNPs were similar to that found in the general population. However, two novel and one known *MKRN3* gene mutations were identified in two familial and three sporadic cases of CPP. The pathogenicity of the novel missense mutation at the protein level was verified by *in Silico* structural analysis. The novel nonsense and the known frameshift mutations resulted in truncated proteins. As expected the *MKRN3* mutations identified in this study were also identified in the unaffected fathers following an imprinted mode of inheritance. Age at puberty onset was earlier among the patients with *MKRN3* mutations compared to those without *MKRN3* mutations. Our results confirm the role of *MKRN3* in the onset of pubertal development and support the fundamental role of this gene in the suppression of the hypothalamic GnRH neurons. Furthermore, these results indicate the involvement of additional genes in the regulation of pubertal timing in humans and screening using high throughput genetic analyses is under investigation.

FC13.2

Ablation of AgRP Neurons Decreases Survival In Activity-Based Anorexia Model

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Anorexia Nervosa (AN) is an eating disorder characterized by severe hypophagia, high levels of physical activity, harsh weight loss and an intense fear of weight gain. It has the highest mortality rate among psychiatric illnesses and, due to the unknown underlying neurobiology, it is challenging to treat.

Agouti-related protein (AgRP) neurons, which are localized in the arcuate nucleus in the hypothalamus, are both necessary and sufficient or feeding in adult animals.

To uncover new neural circuits that may contribute towards vulnerability to AN, we employed the specific diphtheria toxin receptor-expressing mice (AgRP-DTR) which, by the selective ablation of AgRP neurons, allow to test the impact of an impaired AgRP circuit function under the activity-based anorexia (ABA) paradigm.

ABA is a bio-behavioral phenomenon described in rodents and refers to the weight loss, hypophagia and paradoxical hyperactivity that develops in rodents exposed to running wheels and restricted food access, and provides a model for the key symptoms of AN.

Mice that express DTR only in AgRP neurons and subcutaneously injected with diphtheria toxin (DTX) at postnatal day 3 lost more than 50% of AgRP neurons on postnatal day 7 compared to control. The same percentage of neuronal loss was detected in 8 weeks old mice.

In addition, the neonatal animals developed normally after AgRP ablation, did not show any phenotypic effects and maintained normal food intake and weight when fed ad libitum. On postnatal day 36 (P36), males and females animals were housed with access on a running wheel and fed ad libitum for 4 days (accli-

mation phase). On P40, for 72 hours animals were fed for only two hours daily. Following the fasting phase, free access to food was returned and the running wheel was removed. Continuous multi-day analysis of running wheel activity showed that both controls and AgRP-DTR mice kept constant weight and food intake during acclimation. In contrast, although mice became hyperactive within the 24 hours following the onset of food restriction (FR), we noted a 10% mortality on day 2 and 70% mortality at day 4 among the AgRP DTR mice. Moreover, the survived AgRP-DTR mice failed to return to normal food intake and weight even when ad libitum food was provided.

Overall, AgRP neurons showed to be crucial for the full development of ABA symptoms. The results suggest that our new experimental setting is able to correlate particular neurons population with resilience and vulnerability to anorexia nervosa.

FC13.3

Role of GnRH Neuronal Migration and Development in Self-Limited Delayed Puberty

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Objectives: Several different pathogenic mechanisms may converge on a final common pathway to produce the phenotype of delayed pubertal timing. In our cohort of patients with familial self-limited delayed puberty (DP) we have demonstrated mutations in *IGSF10* leading to mis-regulation of the embryonic migration of GnRH neurons (Howard et al, *EMBO MM 2016*). We aimed to discover novel genetic mutations in pathways regulating GnRH neuronal migration and development in our DP cohort. In these patients with significantly delayed pubertal onset, their extreme phenotype may be inherited via one or a few genetic variants discoverable through next generation sequencing (NGS).

Methods: We performed whole exome sequencing (WES) in 160 members of 67 families from our self-limited DP patient cohort, and analysed the data looking for genes with rare, predicted deleterious variants that segregated with trait, and that were significantly enriched for pathogenic variants in our cohort by whole gene rare variant burden testing (RVBT). These data were filtered by biological relevance to GnRH neuronal development via pathway analysis: by comparison with microarray expression data from GnRH neurons and by integration of data from multiple annotation tools (e.g. Uniprot, KEGG, OMIM, Genego MetaCore and Ingenuity Variant Analysis), expression and variant databases.

Results: Rare, potentially pathogenic variants were found in 19 genes related to GnRH neuronal migration or development in our cohort of self-limited DP patients. Variants in 7 genes were excluded by Sanger sequencing due to lack of segregation within families. 3 of these 19 genes were highly enriched by RVBT: *HS6ST1, ZC3H3* and *SHANK1*. 2 genes were already known to be associated with GnRH deficiency: *FEZF1* and *HS6ST1*. Biochemical analysis showed that the pathogenic variant identified in *HS6ST1* led to reduced biological activity of the mutant protein *in Vitro*. *Hs6st1* mRNA was expressed in peri-pubertal wild type mouse hypothalamus. Vaginal opening, a proxy of pubertal onset, was delayed in *Hs6st1*$^{+/-}$ mice despite normal postnatal growth. Additionally, we identified as novel candidates for DP regulation the G-protein coupled receptor *LGR4, SIX Homeobox 6*, and several modulators of cell migration and adhesion including *Neurocan*, *Fibulin 2* and a member of the semaphorin family.

Conclusions: These data lend further weight to the evidence that abnormalities of GnRH neuronal development, migration and function can present as a phenotype of delayed puberty without defects in fertility. Extracellular matrix proteins and chemotaxtic factors may be particularly relevant to aberrant development of the GnRH neuroendocrine network.

FC13.4

The Kallman Syndrome Gene Product Is Specifically Expressed in ACTH-Expressing Cells and Dysplays Sexual Dimorphism Expression in Human Fetal Pituitary

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Kallman syndrome is defined by the association of anosmia due to an agenesis of the olfactory bulbs and hypogonadotropic hypogonadism due to a GnRH deficiency which is currently explained by a deficit of GnRH neuron migration from the olfactory placode toward the hypothalamus. In fact, the X-linked form of KS is due to loss of function mutations in *ANOS1* which encodes an extracellular protein (ANOSMIN) interacting with cell membrane heparin sulfate proteoglycans but also growth factor receptors. ANOSMIN has been implicated in cell-cell adhesion, axon guidance, neurite outgrowth as well as differentiation of neuronal progenitors within cranial placodes. However, associated developmental defects are relatively frequent in KS patients suggesting that ANOSMIN may participate to other developmental pathways. Recently, we observed an expression of *ANOS1* in fetal human pituitary mRNA microarray. The aim of this study was to characterize the pituitary expression of ANOS1 during development in human fetus.

We first confirmed *ANOS1* expression in fetal anterior pituitaries by RT-qPCR along pituitary development. Our results revealed a higher expression of *ANOS1* in female pituitaries when compared to males during the second trimester of development and a peak of expression of ANOS1 at midgestation in males. Two antibodies directed against different domains of ANOSMIN showed an intracellular staining in a minority of hormonal cells. To specify the cell types expressing ANOSMIN, a dual immunostaining was performed with an antibody against ANOSMIN and an antibody against each anterior pituitary hormone. ANOSMIN staining was restrained to intracellular vesicles of ACTH expressing cells. Surprisingly, these ANOSMIN/ACTH cells were also positive for SOX2, a marker of stem cell. The expression of SOX2 was in fact only observed in ACTH+ cells.

This study has revealed a fine control of ANOS1 expression during pituitary development. It also showed an unexpected expression of ANOSMIN in corticotropes. Altogether, these studies raise two interesting questions: 1/ What could be the molecular function of ANOSMIN in corticotropes. 2/ Do ACTH expressing cells have stem cell potential compared to other pituitary hormonal cells ?

FC13.5

Study of the Serum Kisspeptin Level in Healthy and Hypogonadotropic Boys

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Background: Kisspeptins, ligands of G protein–coupled receptor 54 (GPR54) encoded by the KiSS-1 gene, have recently emerged as key players of the gonadotropic axis.

It was found that KiSS-1/GPR54 system plays an important role in the neuroendocrine control of gonadotropin secretion, brain sex differentiation, puberty onset and fertility. It is important to know if the kisspeptin serum level could be used as a diagnostic criterion to the stage of puberty or impairment of it in boys.

Objective To investigate the possible relation between the serum level of kisspeptin and different stages of puberty in healthy boys and boys with delay of puberty onset due to hypogonadotropic hypogonadism.

Methods: 39 boys in total were examined. They were divided into three groups. Group 1 (control, prepubertal boys aged 4-10 years old, Tanner I, n=15). Group 2 (control, pubertal boys aged 14-17 years old, Tanner IV-V, n=16). Group 3 (hypogonadotropic boys aged 14-17 years old, Tanner I, n=8). Hypogonadotropic hypogonadism in boys was confirmed by the median (Me) of basal level of testosterone (T) 0,33 nmol/l, Me LH 0,3mU/l, a Gn-RH-stimulated LH value less than 5 IU/l. In all the groups the serum level of kisspeptin was examined by immunoassay (Cloud-Clone Corp., USA). The data was expressed as mean values (M+m).

Results: The level of kisspeptin in blood in group 1 and 2 did not have any differences (16,27+2,23 pg/ml and 14,11+1,71 pg/ml respectively, p>0,05). Unlike the above, the level of kisspeptin in group 3 was significantly higher than in both groups 1 and 2 (50,91+14,43 pg/ml as opposed to 16,27+2,23 pg/ml, p<0,01; 50,91+14,43 pg/ml as opposed to 14,11+1,71 pg/ml, p<0,002 respectively).

Conclusions: The serum level of kisspeptins was found to be equal in boys, sexually developed regardless of their age and stage of puberty. In contrast, the level of kisspeptins was significantly higher in boys affected with gonadotropic hypogonadism. It can be caused by GPR54 insensitivity or loss of biological activity of kisspeptin. The latter condition can be corrected by novel therapeutic technologies such as treatment with exogenous kisspeptin.

FC13.6

Teamwork Saves Lives: How Pediatric Multidisciplinary Care Can Prevent 'Unexplained Deaths' in Adults with Prader-Willi Syndrome

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Introduction: Prader-Willi Syndrome (PWS) is a complex hypothalamic disorder, causing hypotonia, intellectual disability (ID), pituitary hormone deficiencies and hyperphagia. Up to 4% of young patients with PWS die unexpectedly, every year. The mean age of reported deaths in PWS is 29.5 years; 20% of deaths even occur below age 18 years. Mortality data show that more than 50% of deaths are of cardio-pulmonary origin. Morbid obesity, diabetes and hypertension are strong risk factors for cardiovascular mortality. Lack of satiety, the primary problem in PWS, rapidly leads to this morbid obesity if combined with 1) an inadequate diet, 2) insufficient exercise, 3) a lack of education and training of caregivers with regard to PWS-specific behavioural problems and / or 4) pituitary hormone deficiencies reducing exercise tolerance. Growth Hormone (GH) treatment and physiotherapy, often combined, have been shown to improve body composition in the past. We believe that addressing the multifactorial aetiology of PWS in a multidisciplinary (MD) setting can strongly reduce cardiovascular mortality.

Methods: In order to continue MD care for PWS patients after transition to adult endocrinology, we launched a MD outpatients clinic (OPC) for adults with PWS which consists of a specialised dietitian, a physiotherapist, a psychologist and an endocrinologist. We collected clinical data of the first 100 adults with PWS who visited the MD-OPC. We compared patients who had received GH and MD care during childhood (GH/MD+), with those who had not (GH/MD-).

Results: Of the first 100 adults with PWS who visited our MD-OPC, 37 were GH/MD+ and 63 were GH/MD-. We found a striking difference in co-morbidity and cardiovascular risk factors between GH/MD+ and GH/MD- patients. Mean BMI was 26.6 in the GH/MD+ group versus 34.4 in the GH/MD- group (p=0,000077). Diabetes prevalence was ten times higher in the GH/MD- group: 30% versus 3% in the GH/MD+ group (p=0,016). Hypertension was five times more prevalent in the GH/MD- group: 20% versus 4% in the GH/MD+ group (p=0,05).

Conclusion: PWS has a high mortality at very young age of 4%, which is often (50%) due to cardio-respiratory failure. Part of this 50% could stay alive if obesity, diabetes and hypertension are prevented. Multi-disciplinary care from childhood is associated with a lower prevalence of obesity, hypertension and diabetes. By reducing cardio-vascular risk, MD care can prevent painful and expensive complications

Multisystem Endocrine Disorders

FC14.1

Awareness & Participation in Rare Disease Registries Within the European Reference Network on Rare Endocrine Conditions (Endo-ERN)

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Background: Registries are of key importance for a centre of expertise. Endo-ERN consists of 71 reference centres (RCs) that cover several groups of rare endocrine conditions within 8 themes (www.endo-ern.eu). It is unclear if awareness, participation and availability of registries is uniform for all conditions within Endo-ERN.

Objective: To determine the extent of engagement in registries of Endo-ERN members.

Methods: Endo-ERN RC leads were invited to participate in a survey of their awareness and participation in local, national and international registries and their views on future priorities using a Likert scale of 1-5 where 5 was the greatest priority.

Results: A RC response rate of 82% was obtained. Of the 29 centres surveyed within the glucose theme, 62% reported anawareness of an international registry for rare diabetes with a 48% participation rate. A priority score of 5 was only attributed to rare diabetes. Of the 33 centres within the adrenal theme, awareness of an international registry was 61% for adrenocortical tumours (ACT) and participation was 39%. Pheochromocytoma, ACT and CAH were rated as 5. Of the 37 centres within the sex development theme, 50% reported awareness and participation was 37% for DSD; all conditions were rated as 5. Of the 43 centres within the pituitary theme, international registry awareness was 33% for pituitary adenoma whilst participation was 23%. Pituitary adenoma was the only condition rated as 5. Of the 31 centres within the rare genetic tumour theme, 19% reported an international registry awareness for MEN1 and 6% reported participation; all conditions were rated as 5. Of the 30 centres within the growth theme, international registry awareness was 17% for Prader Willi Syndrome and participation was 10%. All conditions were rated as 5. Ofthe 29 centres within the Calcium/Phosphate theme, international registry awareness was 14% for phosphate disorders and participation was 7%. Hypocalcaemia and hypophosphataemia were rated as 5. Of the 35 centres within the thyroid theme, international registry awarenessfor thyroid carcinoma was 14% and participation was 0%,with 4 of 6 conditions being rated as 5.

Conclusion: Whilst there is a clear need to develop new detailed disease registries, there is also a need to improve the awareness and signposting of existing registries. A common platform that is used by the whole endocrine community and which directs the user to high quality detailed disease registries has the potential to achieve this objective.

FC14.2

National UK Guidelines for the Clinical Assessment, Diagnosis, Treatment and Follow-Up of Children and Young People (CYP) Under 19 Years of Age with Phaeochromocytoma (PCC) and Paraganglioma (PGL) – *On Behalf of the UK Paediatric Phaeochromocytoma and Paraganglioma Guideline Development Group (GDG)*

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Background: PCC and PGL are rare in CYP. National children's registry data reveal an annual incidence of 0.2 and 0.3 per million in 5-9 and 10-14 year age groups respectively. Almost all result from a genetic predisposition, can present with non-specific symptoms, and represent a significant management challenge.

Aims: We aimed to provide the first interdisciplinary national management guidelines using the AGREEII framework for CYP

with confirmed or suspected PCC/PGL, and endorsed by the Royal College of Paediatrics and Child Health, UK Children's Cancer & Leukaemia Group and the British Society for Paediatric Endocrinology & Diabetes.

Methods: 113 PICO clinical questions were formulated by a specialist GDG, and systematic literature searches conducted via Ovid MEDLINE and Cochrane Library databases identifying 526 articles. Publications were filtered and 397 reviewed using GRADE. Where evidence was lacking or conflicting, a two-stage international Delphi consensus process was conducted to make recommendations.

Results: 39 recommendations on assessment, investigations, medical/surgical management and long-term follow-up of survivors are made; 21 were sent to consensus and achieved agreement. Importantly, the GDG recommend CYP with PCC/PGL are managed in a specialist endocrine centre, linked to tertiary paediatric oncology, by a designated, age-appropriate multidisciplinary team and experienced lead clinician. Clinical assessment, including a three-generation family history, should be targeted to identify genetically determined PCC/PGL (Von Hippel Lindau (VHL), familial paraganglioma (mutations in succinate dehydrogenase genes, *SDHx*), Multiple Endocrine Neoplasia 2, Neurofibromatosis 1), and genetic testing offered for all CYP with PCC/PGL after counselling. For CYP who undergo bilateral/completion adrenalectomy or cortical sparing surgery, peri-operative steroid replacement should be led by a nominated endocrinologist. Subspecialist, including critical care, input is required for timely identification of peri-operative hypertension, hypotension and hypoglycaemia (the latter two prompting exclusion of hypocortisolism/adrenal crisis and commencement of stress-dose steroid). CYP who have undergone adrenocortical sparing surgery should continue maintenance steroid replacement until adrenocortical reserve is tested post-operatively. Patients with *SDHB* mutations/VHL have a high risk of recurrent disease and malignancy, however all CYP diagnosed with PCC/PGL should have life-long follow up because of the propensity for new events.

Conclusions: These guidelines provide the first evidence- and consensus-based national recommendations for the management of PCC/PGL in CYP, and highlight a need for further audit and research in this rare, but potentially serious, condition. Their implementation should improve the quality of care and long-term health-related survival of CYP with PCC/PGL.

FC14.3

Regulation of Salt, Sugar and Sex Steroids in Humans by Genetic Variations in NADPH Cytochrome P450 Oxidoreductase (POR) Identified in 1000 Genome Samples

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A broad spectrum of human diseases, including abnormalities in steroidogenesis, are caused by mutations in the NADPH cytochrome P450 oxidoreductase (POR) (1-4). Human POR is a diflavin reductase that transfers electrons from NADPH to small molecules, non-P450 redox partners and cytochrome P450 proteins in the endoplasmic reticulum. Cytochrome P450 proteins perform a very wide range of reactions, including metabolism of steroids, drugs and other xenobiotics. Therefore, genetic variations in POR can impact many different metabolic pathways by changing the activities of its redox partners like cytochromes P450 (1). Due to this unique role of POR in metabolism, it was believed for a long time that genetic defects in POR are unlikely, and indeed a POR knockout mouse is embryonically lethal. However, in 2004 the first human patients with defects in POR were reported, and since then over 200 different variations in POR have been found in patients and from large scale sequencing projects (4).

Recently, we have turned our attention towards characterization of POR variations from non-clinical samples. By analyzing the POR sequences from 1000 genome and other sequencing projects, we identified potentially disease-causing variations and characterized these by functional studies using recombinant proteins produced in bacteria, yeast and mammalian cells.

Identification of severe effects of POR mutations on both the drug and the steroid metabolizing cytochrome P450s, indicates that likely pathogenic mutations may be found in apparently normal (non-clinical) population. Their combination as compound heterozygotes or homozygous may lead to a severe impact on both steroid and drug metabolism by modification of POR redox partner activities. Variations in POR need to be evaluated individually. Changes in drug and steroid metabolism due to genetic variations can be addressed using personalized metabolic profiling and supplementation using modified dosages of drugs and steroids.

References

1. Pandey AV, Flück CE. NADPH P450 oxidoreductase: structure, function, and pathology of diseases. Pharmacol Ther 138:229-54 (2013).
2. Udhane SS et al. Altered CYP19A1 and CYP3A4 Activities Due to Mutations A115V, T142A, Q153R and P284L in the Human P450 Oxidoreductase. Front Pharmacol. Aug 25;8:580 (2017). doi: 10.3389/fphar.2017.00580.
3. Parween S et al. P450 Oxidoreductase Deficiency: Loss of Activity Caused by Protein Instability From a Novel L374H Mutation. J Clin Endocrinol Metab. 101:4789-4798 (2017).
4. Burkhard FZ et al. P450 Oxidoreductase deficiency: Analysis of mutations and polymorphisms. J Steroid Biochem Mol Biol. 165:38-50 (2017).

FC14.4

Glucocorticoid Deficiency Causes Differentially Dysregulated Oxidative Stress Depending on the Steroidogenic Defects

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Glucocorticoids regulate a wide range of biological processes including metabolism. Patients with adrenal insufficiency show impaired glucocorticoid biosynthesis either caused by adrenal defects (primary adrenal insufficiency) or by defects in the pitu-

itary gland or hypothalamus (secondary or tertiary adrenal insufficiency).

The systemic consequences of differentially disrupted steroid hormone biosynthesis remain unclear. Increasing evidence suggested steroid hormone precursors can feed into differential pathways and exert biological functions. With similar steroidogenic pathways, zebrafish has been established as an organism for modelling human steroidogenesis. Here, we analyzed the phenotypes of two profound glucocorticoid-deficient zebrafish lines with null mutations in *Ferredoxin* (*Fdx1b*), an electron donor required for mitochondrial steroid biosynthesis, and in *21-Hydroxylase* (*Cyp21a2)*. Both of these glucocorticoid-deficient mutant lines showed low cortisol concentrations, systemic glucocorticoid deficiency as indicated by decreased expression of glucocorticoid-responsive genes (*Fkbp5*, *Pck1*), and enlarged interrenal glands (the counterpart of mammalian adrenal glands).

Further in-depth analysis revealed the two glucocorticoid-deficient models showed a distinct oxidative stress response. Antioxidant genes *Heme Oxygenase* (*Hmox1a*) and *Prostaglandin Reductase 1* (*Ptgr1*) which are induced by oxidative stress for cell protection are significantly downregulated in *Cyp21a2*$^{-/-}$, but unchanged in *Fdx1b*$^{-/-}$, while *Dual Oxidase* (*Duox*), involved in formation of superoxide for microbial killing has opposing expression changes in *Fdx1b*$^{-/-}$ and *Cyp21a2*$^{-/-}$. These observations suggest differential expression is regulated by multiple, distinct pathways rather than directly regulated by glucocorticoids. Interestingly, further induction of oxidative stress by pro-oxidant tert-butylhydroperoxide (tBHQ) induced greater levels of lethal toxicity in wild-type and *Fdx1b*$^{-/-}$ mutants than in *Cyp21a2*$^{-/-}$ mutants, implying oxidative stress may be better 'buffered' in *Cyp21a2*$^{-/-}$ mutants. To elucidate the molecular mechanisms behind this apparent buffering, we performed expression analysis by RT-qPCR on a set of antioxidant genes with tBHQ-treated larvae. *Hmox1a* was upregulated in *Cyp21a2*$^{-/-}$ whilst downregulated in *Fdx1b*$^{-/-}$ and unchanged in wild-type, suggesting *Hmox1a* could be serving as one of the crucial factors in the differential oxidative stress responses. Finally, as a potential route to developing glucocorticoid-deficient models for pharmaceutical screening, we successfully restored the normal expression levels of the majority of antioxidant genes (except for *Duox*) in *Cyp21a2*$^{-/-}$ mutants with both dexamethasone and hydrocortisone.

Taken together, our results demonstrate for the first time alterations of oxidative stress and antioxidant balance in glucocorticoid deficiency. Moreover, our results reveal glucocorticoid deficiency due to two different steroidogenic defects has distinct systemic consequences. Thus, our research will contribute to better understand the specific pathophysiological consequences of inborn errors of steroidogenesis.

FC14.5

Pubertal Females Produce an Enhanced Interferon-Alpha, Anti-Viral Response Compared to Males, Which Is Associated with X Chromosome Number, and Not Sex Hormones

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Introduction: Very little is known about the development of the immune system during puberty. Autoimmune diseases, like juvenile onset systemic lupus erythematosus (jSLE), have an unexplained female bias and a higher incidence after puberty. IFN alpha (IFNα) is a potent antiviral cytokine, and jSLE has a strong IFNα transcriptional signature. Toll like receptors 7 and 9 (TLR7/9) sense viral RNA and DNA respectively, and trigger plasmacytoid dendritic cells (pDC) to produce IFNα.

Objectives: To discover whether sex differences in IFNα production by pDC are present in young people, and influenced by puberty, sex hormones or sex chromosomes.

Methods: Blood was collected, with informed consent, from cis-gender healthy (n=110, age=6-18); Turner's syndrome (n=9, age=13.8-19.6) and transgender volunteers (n=27, age=17.3-19.5) undergoing pubertal blockade and cross-sex hormone treatment. Clinical data and puberty self- assessment were recorded. Peripheral blood mononuclear cells were separated by Ficoll gradient centrifugation. Cells were stimulated with TLR7 agonist, R848, or TLR9 agonist, CPGODN2216, before assessing for the production of IFNα by pDC by flow cytometry. Serum testosterone, oestradiol and oestrone were measured by high performance liquid chromatography/mass spectrometry. Statistical analysis was performed using SPSS via univariable and multivariable linear regression.

Results: In cis-gender healthy volunteers, with TLR7 stimulation, on average 9.3% more pDC produced IFNα in females (p=0.03) and 6.3% more after puberty, independent of sex (p=0.043). Adding Turners syndrome and transgender volunteers, allowed for a model that controlled for the effect of sex hormones, and X chromosome number. This showed that, regardless of hormonal environment, two X chromosomes are associated with on average 10.9% more pDC producing IFNα after TLR7 stimulation specifically (p=0.002). There were no sex or pubertal differences if cells were stimulated with TLR9 agonist.

Conclusion: These data show for the first time that, in young people, female derived pDCs produce more IFNα than male pDCs upon TLR7 stimulation. Puberty is associated with an increase in pDC producing IFNα, regardless of sex. In addition, possessing two X chromosomes is associated with a higher production of IFNα regardless of hormone levels. These findings are specific to TLR7 induced IFNα production, which is interesting as TLR7 is coded for on the X chromosome. A novel collaboration between endocrinology and rheumatology has enabled us to provide novel insights into the development of the immune system over puberty, but also into the risk profile of patients with immune disorders with sex bias, such as jSLE.

FC14.6

Sex Differences in Autoimmune Disease: Testosterone is Associated with a Decrease in Expression of Key Anti-Viral Genes During Puberty, Which May Decrease the Risk of Autoimmunity in Males

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Introduction: There are well described sex differences in the immune system. It has been shown in both innate and adaptive immunity that females have a more robust response than males. Various autoimmune diseases have a strong sex bias towards females. It is the accepted dogma that oestrogen in females relates to an increased risk of autoimmunity, but evidence to this end is scarce. Interferon alpha (IFNα) is a potent anti-viral innate cytokine, and many autoimmune diseases (juvenile lupus, juvenile dermatomyositis, Sjögrens) display an interferon gene expression signature. Toll like receptors (TLR) and cytoplasmic receptors (RIG, MAVS, MDA5) sense viral RNA and DNA and trigger production of IFNα.

Aim: To investigate whether sex hormones oestradiol or testosterone correlate to gene expression in IFNα production pathways.

Methods: Blood was collected, with informed consent, from healthy, typical volunteers (n=110, age=6-18); Turner's syndrome (n=9, age=13.8-19.6) and transgender volunteers (n=27, age=17.3-19.5) undergoing pubertal blockade and cross-sex hormone treatment. Clinical data and puberty self-assessment were recorded. Peripheral blood mononuclear cells were separated by Ficoll gradient centrifugation. RNA was extracted and gene expression measured with Nanostring Plex Set. Serum testosterone and oestradiol were measured by high performance liquid chromatography/mass spectrometry. Statistical analysis was performed in SPSS using Spearmans rank correlation, and Bonferroni post hoc correction.

Results: In healthy, typical controls, serum testosterone levels correlated negatively with expression of the potent DNA viral sensor TLR9 (spearman's correlation coefficient rs=-0.408, p=0.001). In addition, testosterone levels correlated negatively with expression of intracellular cytoplasmic RNA sensors RIG1(rs =-0.356 p=0.015), MDA5(rs =-0.419 p=0.004) and MAVS(rs =-0.373 p=0.011). Interestingly, testosterone also correlated negatively to gene expression of Line-1 (L1),(rs=-0.301 p=0.037), an endogenous retroelement that may provide substrate for endogenous IFNα pathway activation. When using the stringent Bonferroni correction for multiple testing however, a corrected p-value of 0.01 represents significance. In healthy controls, there was a significant decrease in L1 (p=0.001), and TLR9 (p<0.001) after puberty. There was no effect of oestrogen on the expression of these anti-viral genes. When Turners syndrome and transgender volunteers were added to the analysis to provide an inbuilt variation in X chromosome number and sex hormone distribution, the negative correlations with testosterone remained significant.

Conclusion: Testosterone, and not oestrogen, is associated with a downregulation of expression in innate IFNα pathway signalling. This implies that in IFNα related autoimmune diseases, testosterone may be protective in males.

Growth and Syndromes

FC15.1

The Diagnostic Yield of a Targeted Next Generation Sequencing Panel in Children with Short Stature of Undefined Aetiology

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Background: Currently, data on the diagnostic yield of targeted gene panels using next generation sequencing (NGS) in children with short stature of undefined aetiology (SSUA) are limited. EPIGROW (ClinicalTrials.gov ID NCT00710307) was a prospective European epidemio-genetic study in which a targeted NGS panel including 69 genes associated with short stature (e.g. primordial growth disorders and skeletal dysplasias) was performed in 263 patients and 263 controls. In these patients, there were no clinical features suggestive of a given disorder.

Aim: To determine the diagnostic yield from a targeted NGS panel in children with SSUA.

Methods: NGS was performed on genomic DNA (exons, exon–intron junctions, and promoter regions) using the Agilent SureSelect (Agilent Technologies, Inc., Santa Clara, California) platform for target enrichment and Illumina TruSeq (Illumina Inc., San Diego, California) for sequencing. To identify potentially pathogenic variants, we selected those which were present in cases but not controls, were exonic, had a minor allele frequency <2% and where carriage of the variant allele fitted the mode of inheritance of the known short stature disorder. For missense variants only those predicted to be potentially damaging by Polyphen2 were included. To identify known mutations a combination of Ensembl and Leiden Open Variation Database (to access a range of gene specific databases) were used.

Variants identified through this strategy were classified as probably pathogenic where they had previously been reported to be associated with the condition or if they were nonsense/frameshift (loss of function) mutations. Where the variant did not fit these criteria they were classified as possibly pathogenic.

Results: We identified 43 variants of interest in 37 patients. 13 of these were classified as probably pathogenic - 11 were previously known mutations in *FANCB*, *IGF1R*, *MMP13*, *NPR2*, *OBSL1* and *PTPN11* (all missense) and 2 in *ACAN* were nonsense mutations. An additional 30 possibly pathogenic mutations were identified in these genes and in others, including *GH1*, *GNAS*, *HRAS* and

LHX4. 9 were insertions or deletions and 21 were missense variants predicted as damaging.

Conclusion: This gene panel led to a potential diagnostic yield of 5% (13/263) to 14% (37/263) in a cohort of pre-pubertal children with SSUA. Therefore, the use of such panels may improve diagnosis in SSUA.

We Would Like to Acknowledge the EPIGROW Investigator Group for Their Participation and Contributions.

FC15.2

Effects of Caloric Restriction During Gestation on the Methylome of Offspring's Adipose Tissue and Reversibility of Such Effects by Metformin in a Swine Model

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Introduction: Maternal caloric restriction during gestation leads to offspring's metabolic programming through epigenetic changes, which increase the risk of developing cardiovascular diseases in adulthood.

Objectives: To study in a swine animal model: (1) DNA methylation changes associated with caloric restriction during gestation in the adipose tissue of the offspring; and (2) the reversibility of these changes by metformin treatment.

Materials and methods: Commercial production sows (Landrace x Duroc) were fed either a standard or a calorie restricted diet (30% reduction compared to standard) throughout gestation, to deliver control (C) or growth-restricted (R) piglets, respectively. Piglets from each group (n=32) were treated with 50mg/kg/day oral metformin (n=16) or placebo (n=16) across lactation. At sacrifice (weaning, age 28 days) piglets were weighed, adipose tissue was collected and metabolic markers were measured in serum. Adipose tissue methylome was analysed by RRBS (Reduced Representation Bisulphite Sequencing; n=8 per subgroup of gestation and pharmacological treatment). As for the study of differential methylation, annotated CpG sites were analysed, SNPs were filtered and a methylation difference >15% and a *Q-Value*<0.05 were considered relevant for further analyses.

Results: R piglets showed similar weights than C piglets at weaning, together with a partly altered metabolic profile [higher CRP and lower circulating adiponectin ($p<0.01$)]. In retroperitoneal adipose tissue, maternal restriction triggered hypermethylation of 163 CpG and hypomethylation of 109 CpG, all these lists being enriched in CpGs corresponding to genes that regulate growth and metabolism (FDR<10). Piglets receiving metformin showed methylation differences compared to those receiving placebo in 221 CpG sites (88 hypermethylated and 133 hypomethylated). The CpG sites that were associated with *FASN*, *PRKCZ* and *NELFB* showed differential methylation in both situations but in opposite directions: *FASN* and *PRKCZ* were hypermethylated upon gestational restriction and hypomethylated in metformin treated piglets; *NELFB* was hypomethylated upon gestational restriction and hypermethylated during metformin treatment.

Conclusions: Gestational caloric restriction induces changes in the methylome of the offspring's adipose tissue, including methylation variations in *FASN* (a key enzyme in fatty acid biosynthesis), *PRKCZ* (a member of the PKC family of serine/threonine kinases involved in cell proliferation and differentiation) and *NELFB* (a regulator of the RNA polymerase II involved in embryonic development and homeostasis in adult tissue). Metformin may contribute to reverse the deleterious effects on these genes.

FC15.3

Methylation of the C*19MC* microRNA Locus in the Placenta: A Mechanism Whereby Maternal Body Size Links to That of the Child

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Background: The *C19MC* locus microRNA gene cluster is imprinted in the placenta. Imprinted genes control prenatal development and placental functions, and are epigenetically regulated. The factors that affect the DNA methylation status of *C19MC* regulatory region are unknown, as is the impact of this differential methylation on the offspring's body size.

Objectives: To study in humans 1) the association of placental *C19MC* DNA methylation levels with parental body size and with transmission of haplotypes for the rs55765443 SNP in *C19MC*, and 2) the link between *C19MC* methylation and the offspring's body size and/or body composition at birth and in prepubertal childhood.

Study design: A cohort of 72 healthy pregnant women (information available from 63 fathers) was studied. Pre-gestational maternal weight, height, body-mass index and gestational weight gain were registered. At birth, placentas were collected, and the infants' weight and length were assessed (gestational age 40 ± 1 wk; birth weight z-score 0.1 ± 0.9). DNA methylation at the imprinting control region (ICR) of *C19MC* (hg38 chr19:53648001-53648160) was quantified in placentas by bisulfite pyrosequencing. Genotyping of the rs55765443 SNP was performed for both parents in leukocytes, and for the infants in placental tissue, using restriction fragment

length polymorphisms. The children's body size and body composition were assessed at age 6 years.

Results: Less methylation in the placental *C19MC* ICR associated independently with larger body size of mother and child, more specifically with higher pre-gestational and pre-delivery weight and height of the mother (β=–0.307, p=0.011, R^2=0.05; β=–0.371, p=0.003, R^2=0.10; and β=–0.294, p=0.019, R^2=0.04 respectively), and with higher weight (β=–0.552, p=0.003, R^2=0.44), height (β=–0.486, p=0.009, R^2=0.39), waist (β=–0.497, p=0.003, R^2=0.33), hip (β=–0.449, p=0.004, R^2=0.41) and fat mass (β=–0.428, p=0.004, R^2=0.56) in the child. Parental transmission of the G or T alleles for rs55765443 did not significantly affect the methylation status of placental *C19MC* ICR.

Conclusions: Methylation of the *C19MC* locus in the placenta may be a transient, primate-specific, epigenetic mechanism whereby the father can link the body size of the mother to that of their future child.

FC15.4

The Metabolic Profile Associated with RASopathies

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Background: Noonan syndrome (NS) is a frequent autosomal dominant disorder characterized by facial dysmorphisms, heart defects, short stature and learning disabilities. It is caused by mutations in genes within the RAS/MAPK signaling pathway, thus called RASopathies. The RAS/MAPK pathway can also impact the signal transduction of hormones involved in body weight, carbohydrate, and lipid metabolism features scarcely studied only in animal models. This study aimed to describe metabolic profile in children with RASopathies.

Subjects and Methods: We evaluated 102 prepubertal NS patients (40 males), 41 with identified *PTPN11* mutation (*PTPN11*+) and 61 without *PTPN11* mutation (*PTPN11*-). We accessed height and body mass index (BMI) expressed as SDS for age and sex. We compared fasting insulin, glycemic, HOMA-IR, triglycerides, HDL-cholesterol, and LDL-cholesterol levels between NS groups and with a eutrophic prepubertal control group. We excluded patients with family history of obesity, hypertension, and diabetes mellitus.

Results: Patients with NS were shorter than the control group. BMI-SDS were similar among groups NS groups and control. NS patients had overweight and obesity frequency of 8% and 1%, while in Brazilian population aged 5 to 9 this frequency is 33.4% and 14.3%, respectively. *PTPN11*+ patients had higher fasting insulin levels [median 4.6; (3 to 13.9)], than *PTPN11*- [2.9; (1.3 to 18.7)] and control [3.3; (2.5 to 7.3 μU/mL); p=0.01]. HOMA-IR were higher in *PTPN11*+ [1.0;(0.4 to 3.2)], than *PTPN11*- [0.6;(0.3 to 4.4)], and control [0.6; (0.4 to 1.4); p=0.008]. The frequency of low HDL-C levels was higher in both NS groups 57% (21/37) in *PTPN11*+, and 54% (32/60) in *PTPN11*- than control group 20% (9/44); p<0.001. The LDL-C concentration was similar between groups. Frequency of elevated triglyceride levels were higher in NS groups, 57% (21/37) in *PTPN11*+ and 18% (11/60) *PTPN11*-, than control group 2% (1/44); p=0.007.

Conclusions: NS patients may have particular protection against obesity and overweight. Despite that, *PTPN11*+ patients seem to have an impaired insulin signaling (higher insulin fasting levels and higher HOMA-IR), that could be associated with SHP2/*PTPN11* mutations. *PTPN11*+ patients also had low HDL and an increased triglycerides levels in comparison to control. To the best of our knowledge, this was the first report concerning metabolism in children with NS. More studies are necessary to expand the knowledge about possible consequences that this metabolic profile could have on the cardiovascular risk to these patients.

FC15.5

Utility of BDNF and MMP-1 as Markers of Cardiometabolic Risk in Turner Syndrome Girls

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Background: It remains unclear whether cardiometabolic and vascular risks in Turner syndrome (TS) are the consequence of unidentified intrinsic factors or, conversely, the result of modifiable risk factors, such as overweight. New markers that could explain the pathogenesis of metabolic complications are under investigation.

Objective: the comparison of the selected biochemical cardiometabolic risk markers between TS patients and healthy controls.

Method: Concentration of circulating metalloproteinases (MMP-1, -2, -9), their inhibitors (TIMP-1), Brain-Derived Neurotrophic Factor (BDNF), Glial Cell-line Derived Neurotrophic Factor (GDNF) and (Vascular Endothelial Growth Factors) VEGF were measured in 28 girls: in 17 girls with TS and in 11 healthy girls with non-pathologic short stature (control group-CG). None of the participants had BMI >97 pc.

Results: No differences in chronological and bone age, the mean weight or z-score BMI were noted in TS and CG. The mean baseline values of MMP-1 and BDNF were significantly lower (both $p<0.01$) in the CG in compare to TS population. Regression analysis in the entire group revealed positive correlation between z-score BMI and both MMP-1 and BDNF concentration ($p<0.05$, $r=0.36$; $p<0.01$, $r=0.50$, respectively). There were no significant differences between TS and CG in the concentrations of other biochemical cardiovascular risk markers.

Conclusion: MMP-1 could be recognized as a potential indicator of higher risk of cardiometabolic complications in TS girls. The higher concentrations of BDNF in normal-weight TS girls need further study in which the influence of estrogens-androgens imbalance should be taken into consideration.

FC15.6

Vosoritide for Children with Achondroplasia: A 30 Month Update from an Ongoing Phase 2 Clinical Trial

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Objectives: Achondroplasia (ACH), caused by a mutation in the fibroblast growth factor receptor 3 gene (*FGFR3*), leads to inhibition of endochondral bone growth. Vosoritide is a biological analogue of C-type natriuretic peptide (CNP), a potent stimulator of endochondral bone growth. A Phase 2, open-label, sequential cohort, dose-escalation study was conducted to evaluate the safety, tolerability, and efficacy of vosoritide for 24 months in children with ACH aged 5-14 years. An extension study assesses long-term safety and efficacy for up to 5 years.

Methods: All subjects completed ≥6 months of growth measurements in an observational study prior to enrollment to establish their baseline annualized growth velocity (AGV) before treatment. 35 children (mean age 7.6 ± 1.68 years; range: 5-11) were enrolled into 4 separate dose cohorts: 2.5 μg/kg (Cohort 1, n=8), 7.5 μg/kg (Cohort 2, n=8), 15 μg/kg (Cohort 3, n=10) and 30 μg/kg (Cohort 4, n=9) given daily by subcutaneous route. Vosoritide was maintained at these doses for the initial 6-month period for each cohort. Patients were dose-escalated to higher doses in Cohort 1 (to 7.5 μg/kg and 15 μg/kg) and Cohort 2 (to 15 ug/kg). Patients in Cohort 3 and Cohort 4 remained on their initial doses (15 μg/kg and 30 μg/kg, respectively). At 30 months, 24/35 patients had completed the open-label study; 22 enrolled in the extension study.

Results: Vosoritide was generally well-tolerated at all doses tested up to 30 months. The majority of adverse events (AEs) were mild; no serious AEs were reported as study drug-related. The most common AEs were injection site reactions, which were all mild and transient. The mean (SD) baseline AGV for Cohort 3 was 4.04 cm/year (2.275). After 30 months at 15 μg/kg, the mean (SD) increase in AGV over baseline was +1.58 (1.873) cm/year. The mean (SD) height Z-score at baseline was -4.61 (1.136) and increased by +0.88 (0.369). There was slight improvement in upper-to-lower body segment ratio of -0.08 (0.054) from baseline of 1.91 (0.229). An increase in urine cGMP, a biomarker of vosoritide pharmacological activity, was sustained at 30 months.

Conclusions: Vosoritide was generally well-tolerated for up to 30 months administration. There was no evidence of tachyphylaxis with growth velocity and biomarker activity being sustained over 30 months. These data support the continued development of vosoritide for the treatment of children with ACH.

Rapid Free Communications

Adrenals & HPA Axis

RFC1.1

The Relative Contributions of Genetic and Environmental Factors on Cortisol Metabolism at Pre-, Mid- And Post-Pubertal Ages

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Background: inter-individual differences in the metabolism of cortisol have been postulated to emerge during puberty, and might be explained by a complex interplay of genetic and environmental factors. The aim of the current study was to estimate the relative contributions of genetic, shared environmental, and unshared environmental factors on cortisol metabolism in a longitudinal twin cohort assessed at pre-pubertal, mid-pubertal and post-pubertal ages.

Methods: males and females born between 1995 and 1996 were enrolled from a population-based twin register. Early-morning urine was collected at pre-pubertal (9years), mid-pubertal (12years) and post-pubertal (17years) ages. Cortisol metabolites were measured, and ratios were calculated, representing the activities of various enzymes involved in cortisol metabolism. Data were analyzed using a model-fitting approach to obtain estimates of the relative influences of additive genetic effects, either dominance effects, or shared and non-shared environmental factors. Data were adjusted for batch and sex effects.

Results: 94 monozygotic and 124 dizygotic twins were included and 213, 167 and 162 samples were analyzed at pre-, mid- and post-pubertal ages, respectively. At these ages, the additive genetic (A), dominance (D), shared environmental (C) and unshared environmental influences (E) were estimated as: 5a-reductase-activity (allo-THF/cortisol): 9yr 14% (A), 45% (C), 41% (E), 12yr 39% (A), 39% (C), 22% (E), 17yr 26% (A), 24% (C), 50% (E), 5b-reductase-activity (THF/cortisol): 9yr 0% (A), 51% (C), 49% (E), 12yr model not suitable, 17yr 1% (A), 26% (D), 73% (E), 5b-reductase-activity (THE/cortisone): 9yr 40% (A), 32% (C), 28% (E), 12yr 19% (A), 42% (C), 39% (E), 17yr 26% (A), 25% (C), 50% (E), Renal 11b-HSD-type-2-activity (cortisol/cortisone) 9yr model not suitable, 12yr 60% (A), 8% (C), 32% (E), 17yr 4% (A), 34% (C), 63% (E), 11b-HSD-activity ((THE+allo-THF)/THE): 9yr 29% (A), 33% (C), 38% (E), 12yr 27% (A), 3% (D), 69% (E), 17yr 18% (A), 11% (C), 71% (E), Cytochrome-P450-activity (6-OH cortisol/cortisol): 9yr 13% (A), 22% (C), 65% (E), 12yr 56% (A), 9% (C), 35% (E), 17yr 26% (A), 28% (C), 46% (E).

Conclusion: there were considerable differences in the relative contributions of genetic and environmental factors to the ratios indicating activities of various enzymes involved in the metabolism of cortisol at pre-, mid- and post-pubertal ages. With few exceptions, the contribution of unshared environmental factors to these ratios was found to increase with age, implicating that individual circumstances seem to play a predominant role in later life.

RFC1.2

Changes in CYP19A1 and CYP3A4 Activities Due to Population Genetic Variations in Human P450 Oxidoreductase

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Background: Cytochromes P450 proteins metabolize several steroid hormones, drugs and xenobiotics. All cytochromes P450s in the endoplasmic reticulum require P450 oxidoreductase (POR) for their catalytic activities. Earlier it has been shown that mutations in POR cause metabolic disorders of steroid hormone biosynthesis and also affect some drug metabolizing P450 activities. We aimed to characterize the mutations identified in nonclinical samples to access their effects on steroid and drug metabolism.

Methods: WT and mutant POR proteins, as well as cytochrome P450s, were recombinantly expressed in bacteria and purified. We prepared liposomes embedding the P450 and POR proteins to create a functional P450 metabolic system. Metabolism of androstenedione, testosterone as well as small molecule dyes(MTT, ferricyanide) and tracer compounds was evaluated by radioactive ligand metabolism, fluorescent substrate metabolism and colorimetric assays. Enzyme kinetic analysis was performed using Prism.

Results: The variant P284T identified from normal subjects had severe loss of both CYP19A1 and CYP3A4 activities, indicating this to be a potential disease-causing mutation. As compared to WT, P284T showed 91% and 77% decrease in supporting CYP19A1 and CYP3A4 activity respectively. MTT reduction activity of P284T was also severely affected with only 15% residual activity as compared to WT.

Conclusions: These results suggest that likely pathogenic mutations may be found in non-clinical(apparently normal)population. Their combination as homozygous or compound heterozygous may have severe impact on steroid and drug metabolism by modification of its redox partner activities.

RFC1.3

Sphingosine-1-Phosphate Lyase (SGPL1) Deficiency Is Associated with Mitochondrial Dysfunction

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Background: Loss of function mutations in *SGPL1*, a key component of sphingolipid metabolism, are associated with accumulation of sphingolipid intermediates giving rise to a multisystemic disease incorporating primary adrenal insufficiency (PAI) and progressive renal and neurological disease. Sphingolipids are implicated in mitochondrial apoptosis via induction of mitochondrial outer membrane permeabilization, cytosolic release of inter-membranal cytochrome c and activation of executioner caspases.

Objective and hypotheses: To investigate the impact of SGPL1 deficiency on mitochondrial morphology and function using patient derived human dermal fibroblasts and a *SGPL1*- knockout HeLa cell line.

Methods: Primary cell cultures of dermal fibroblasts were established from two patients with *SGPL1* deficiency (Patient 1 - p.F545del; PAI, later onset renal/neurological compromise; Patient 2 - p.S65Rfs*6G, PAI, early onset renal/neurological compromise). Mitochondrial architecture was examined by confocal microscopy with volumetric analysis using Z-stack images of stained cells. Mitochondrial oxidative phosphorylation rate was measured by Seahorse XF Extracellular Flux Analyser in control/patient fibroblasts. RT-qPCR for expression levels of genes regulating mitochondrial fusion and fission, *MFN1/2* and *DRP1*.

Results: Total mitochondrial volume in patient fibroblasts and *SGPL1*-KO-HeLa cell lines vs controls was reduced: (**p.F545del**; $p<0.05$; n=20; **p.S65Rfs*6G**; $p<0.001$, n=20), SGPL1-KO-HeLa, $p<0.01$; n=20. Additionally, the number of fragmented mitochondria was increased in **p.S65Rfs*6G** compared to control ($p<0.0001$; n=20).

The respiratory flux profile of **p.F545del** fibroblasts was unaltered, however, **p.S65Rfs*6G fibroblasts** showed a significant reduction in non-mitochondrial respiration ($p<0.01$, n=3, maximal respiration ($p<0.05$), ATP production ($p<0.05$) and spare respiratory capacity ($p<0.05$). Mitochondrial morphology differed; SGPL1-KO-HeLa and **p.F545del** had elongated and hyper-fused mitochondria whereas **p.S65Rfs*6G** had rounded, fragmented mitochondria. *MFN1* and *MFN2* expression were markedly upregulated in SGPL1-KO- and **p.F545del** fibroblasts ($p<0.0001$; n=3) while the opposite was seen in **p.S65Rfs*6G** ($p<0.0001$; n=3). However, *DRP1* was uniformly downregulated in SGPL1-KO-HeLa and patient fibroblasts ($p<0.0001$, n=3).

Conclusion: Aberrant sphingolipid metabolism leads to disruption of mitochondrial morphology/function. The significant decreased *DRP1* expression suggests an imbalance tilted towards reduced fission. The expression levels of fusion proteins *MFN1/2* differed between cell lines; up in SGPL1-KO-HeLa and **p.F545del**, down in **p.S65Rfs*6G** fibroblasts, in keeping with the morphology observed. The degree of SGPL1 deficiency or other genetic modifiers may account for differences seen. However, importantly, in both patient fibroblasts and *SGPL1*-KO-HeLa cells mitochondrial volume is reduced. Further work is required to characterise mitochondrial effects of SGPL1 deficiency, including fusion-fission imbalance and effects on steroid output.

RFC1.4

Mass Spectrometry-Based Assessment of Childhood Androgen Excess in 487 Consecutive Patients Over 5 Years

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Background: Androgen excess in childhood is a common clinical presentation and might signify serious pathology. We have recently explored patterns and severity of androgen excess in a large female adult cohort to differentiate common polycystic ovarian syndrome (PCOS) from non-PCOS pathology, including congenital adrenal hyperplasia (CAH), ovarian hyperthecosis and adrenal and ovarian tumours (Elhassan et al., JCE&M 2018). Herein, we undertake a similar approach for the differential diagnosis of childhood androgen excess.

Objective: To examine the diagnostic utility of simultaneous measurement of serum dehydroepiandrosterone sulfate (DHEAS), androstenedione (A4), and testosterone (T) to delineate the biochemical signatures of conditions underlying childhood androgen excess.

Design: Retrospective review of all children undergoing serum androgen measurement at a large tertiary care referral centre over 5 years (2013-2017). Serum A4 and T were measured by tandem mass spectrometry, DHEAS by immunoassay; results were interpreted using Tanner-stage defined cut-offs for androgen excess. Patients with at least one increased androgen underwent phenotyping by clinical notes review.

Results: 1525 children underwent serum androgen measurements in the 5-year period; in 487 children, DHEAS, A4, and T were measured simultaneously, with at least one increased andro-

gen in 41% (n=199; 141 girls and 58 boys). Premature adrenarche (PA) was the most common diagnosis (42%), followed by PCOS (12.6%) and CAH (7.0%). In 13% of children, the cause of borderline androgen excess could not be established. There was one case of adrenocortical carcinoma (ACC). PA is characterised by raised DHEAS levels in 85 % of cases. A4 was raised in 26% of PA children, T in only 9%. CAH is characterised by A4 excess in 86% of patients; T was raised in 35% and DHEAS in only 21% of CAH cases. In adolescent PCOS, the distribution of androgen excess levels was similar for DHEAS, A4 and T (50, 42 and 42%, respectively). In the ACC case, we observed an isolated, severe increase in DHEAS (28-fold above upper limit of normal).

Conclusions: To our knowledge, this is the first systematic analysis of mass spectrometry-based serum androgen profiling in a large sample of childhood androgen excess. PA was the commonest condition and is characterised by DHEAS excess in the majority of cases, whereas CAH most frequently presents with A4 excess and normal DHEAS. In adolescent PCOS, DHEAS, A4 and T excess are evenly distributed. ACC is extremely rare in childhood and severe DHEAS excess should prompt urgent investigations for this condition.

RFC1.5

Quantitative Urinary GC-MS Based Steroid Analysis for Treatment Monitoring of Adolescents and Young Adults with Autoimmune Primary Adrenal Insufficiency

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Background: Autoimmune primary adrenal insufficiency (PAI) is a rare and life-threatening disease. Standard replacement therapy consists of multiple daily doses of hydrocortisone combined with fludrocortisone. A recent Endocrine Society guideline argued against hormonal monitoring of glucocorticoid replacement. However, about 50% of adolescents and young adults (AYAs) with chronic diseases are non-adherent to their prescribed treatment regimens. Pervasive nonadherence places patients with PAI at an increased risk for morbidity and mortality. As a consequence, useful hormonal monitoring of glucocorticoid replacement would be mandatory in AYAs with PAI.

Objective and hypotheses: The suitability of 24 hour urinary steroid metabolites analysis for treatment monitoring for AYAs with autoimmune PAI.

Method: We retrospectively analyzed 21 daily urinary steroid hormone metabolite profiles obtained by GC-MS of four AYAs aged 15.6 ± 2.0 years with autoimmune PAI on hydrocortisone and fludrocortisone treatment. Urine was collected over a period of 1.5-4.2 years, with 4-9 collected urines each patient. Urinary glucocorticoid metabolites (GCM) were summed and were transformed into z-scores using references of healthy children.

Results: Mean oral hydrocortisone replacement dosage was 12.1 ± 1.1 mg/m^2 BSA/d. Three patients showed good treatment adherence (17 of 21 samples). Daily urinary GCM excretion of these samples was 7.36 ± 1.78 mg/ m^2 BSA/d, consistent with a GCM z-score of 1.77 ± 1.08. In these samples, urinary GCM reflected 59.7 ± 14.5% of orally prescribed hydrocortisone dosages. The forth patient initially showed an adequate treatment-adherence (GCM 5.20 mg/ m^2 BSA/d; 0.83 z; 49.4% of the prescribed hydrocortisone dosage). However, later the patient showed clinically symptoms of PAI, but assured regular treatment adherence. In this 24-hr urine sample, GCM excretion was only 0.32 mg/ m^2 BSA (-3.36 z), reflecting only 3.1% of orally prescribed hydrocortisone dosage. The patient later confirmed that treatment was stopped. During the next visits treatment adherence was better, but still inadequate. The morning dose was taken regularly under parental control, but the following dosages were taken inconsistently. Accordingly, urinary GCM excretion in the following two samples were 3.57 mg/ m^2 BSA/d (-0.34 z; 27.4 %) and 1.88 mg/ m^2 BSA/d (-1.63 z; 17.2%).

Conclusion: We could demonstrate that analysis of 24-hr urinary hydrocortisone metabolite excretions rates were suitable to monitor glucocorticoid replacement treatment in patients with autoimmune Addison's disease. It allows assessment of treatment adherence and helps to avoid overtreatment.

RFC1.6

A Laboratory Harmonization Strategy for Steroid Hormone Profiling by MoM-Transformed, Normalized Reference Ranges Independent of Age, Sex and Units

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Background/Aims: The high complexity of Pediatric reference ranges across age, sex and units impairs clinical application and comparability of steroid hormone data, e.g., in CAHs. We developed a Multiples-of-Median (MoM) normalization tool to overcome this major drawback in Pediatric Endocrinology.

Methods: LC-MS/MS data comprising 10 steroid hormones representing 905 controls (555 males, 350 females, 0 to >16 years) from two previous datasets were MoM-transformed across age and sex. 24 genetically proven CAH patients were included (21OHD, N=19; 11OHD, N=5). MoM cut-offs for single steroids predicting 21OHD and 11OHD were computed and validated through new,

independent patients (21OHD, N=8; adrenal cortical carcinoma, N=6; obesity, N=40).

Results: 21OHD and 11OHD showed disease-typical, easily recognizable MoM-patterns independent of age, sex and concentrations units. Two single-steroid cut-offs indicated 21OHD: 3.87 MoM for 17Hydroxyprogesterone (100% sensitivity, 98.83% specificity) and 12.28 MoM for 21Deoxycortisol (94.74% sensitivity, 100% specificity). A 13.18 MoM for 11Deoxycortisol indicated 11OHD (100% sensitivity and 100% specificity).

Conclusions: Age- and sex-independent MoMs are straightforward for clinically relevant display of multisteroid patterns. In addition, defined single steroid MoMs can serve alone as predictors for 21OHD and 11OHD. Finally, MoM-transformation offers substantial enhancement of routine - and scientific steroid hormone data exchange due to improved comparability.

Bone, Growth Plate & Mineral Metabolism 1

RFC2.1

High-Resolution MRI Imaging of Bone-Muscle-Fat in Glucocorticoid Treated Boys with Duchenne Muscular Dystrophy: Results from the ScOT-DMD Study

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Background: The pathophysiological mechanism of skeletal fragility in Duchenne Muscular Dystrophy (DMD) is unclear.

Objective: To compare trabecular bone microarchitecture, cortical geometry, muscle area and fat fraction (FF) at distal femur and vertebral bone marrow adiposity (BMA) between DMD and controls.

Method: Bone-muscle and muscleFF were assessed using 3T MRI and Dixon technique. BMA was assessed using 1H-MRS. Results expressed as median (range). Cortical parameters were adjusted for femur length, muscle area, and age.

Results: Sixteen boys with DMD, aged 11.7 years (8.8, 18.9) treated with 5.9 years (1.8, 10.5) of glucocorticoid (GC) were compared with 22 healthy boys, aged 12.6 years (8.1,17.0). Of 16 boys, nine (56%) were non-ambulant for 2.1 years (1.1,5.3). Three previously had intravenous bisphosphonate and two had testosterone therapy. Of the 16 boys, vertebral fractures (VF) were observed in 5/16(31.3%), non-VF in 6/16(37.5%) and both VF and non-VF in one (6.3%). Muscle area in DMD and controls was 3000mm^2 (889, 12295) and 5400mm^2(33234, 10847), respectively [p=0.0004]. MuscleFF in DMD and controls was 52%(3.5,93.1) and 1.5%(0.4,4.9), respectively [p<0.0001]. Apparent trabecular bone volume/total volume (appBV/TV) in DMD and controls was 0.54(0.51,0.62) and 0.56(0.51,0.60), respectively [p=0.0027]. Apparent trabecular thickness (appTb.Th) in DMD and controls was 0.25 mm(0.23,0.30) and 0.28 mm(0.25,0.31), respectively [p<0.0001]. Trabecular appBV/TV (r=0.35, p=0.19) and appTB.Th (r=-0.29, p=0.32) were not associated with GC duration. Boys with DMD had significantly lower cortical thickness (β=-0.67, 95% CI:-0.95 to -0.39) and area (β=-83.2, 95% CI:-113.0 to -53.5). Cortical thickness (r=0.01,p=0.97) and area (r=0.1,p=0.26) were not associated with GC duration. BMA in DMD and controls was 49.6%(28.7,78.9) and 21.1%(8.0,52.3), respectively [p<0.0001]. BMA was not associated with muscleFF (r=-0.20,p=0.56), appBV/TV (r=0.58,p=0.07), appTb.Th (r=-0.16,p=0.65), cortical thickness (r=0.27,p=0.42), and area (r=0.59,p=0.07) in DMD. Similarly BMA was not associated with muscleFF (r=-0.03,p>0.99), appBV/TV (r=-0.70,p=0.15)], appTb.Th (r=-0.19,p=0.73), cortical thickness (r=0.22,p=0.61) and area (r=0.24,p=0.58)] in controls.

Conclusion: This first study using high-resolution MRI identified several abnormalities in trabecular microarchitecture and cortical geometry in DMD. The lack of a relationship of bone microarchitecture and geometry to the GC duration raises the possibility that these deficits may not be solely due to GC. The novel finding of increased marrow adiposity in DMD and its role in osteoporosis requires further exploration.

RFC2.2

S-25OHD Is Associated with Hand Grip Strength and Myopathy at Five Years in Girls: An Odense Child Cohort Study

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Context: Severe vitamin D deficiency may lead to myopathy in adults. Little is known about vitamin D and muscle strength in children.

Objective: To test whether hand grip strength (HGS) in 5-year-old-children associates with serum 25-hydroxyvitamin D (s-25OHD) from pregnancy to five years.

Methods: Observational study in the population-based Odense Child Cohort, Denmark. At five years, anthropometrics, body fat percentage by skin fold measurements and HGS were obtained (n=881). Myopathy was defined as HGS <10th percentile. S-25OHD$_{2+3}$ was analyzed with liquid chromatography mass spectrometry (5-y; n=499).

Results: Mean (SD) HGS was higher for boys compared to girls, 8.76 (1.76) *vs.* 8.1 (1.64) kg, p<0.001. Mean (SD) 5-year s-25OHD was 70.7 (24.5) nmol/L. HGS was directly associated with height in girls, and with weight (directly) and body fat percent-

age (inversely) in both sexes (p<0.01 for all). In girls, 5-year s-25OHD was associated with HGS, adjusting for height, weight and body fat percentage, β=0.011 (95% CI 0.004;0.019), p=0.003. S-25OHD ≥75nmol/L associated with higher HGS compared to values <50nmol/L, adjusted β=0.783 (0.325;1.241), p=0.001. The odds of having myopathy were reduced by approximately 70% for s-25OHD ≥50 *vs.* <50 nmol/L, adjusted odds ratio 0.310 (95% CI 0.126;0.762), p=0.011. No associations were seen for boys. S-25OHD at other time points did not associate with 5-year HGS.

Conclusions: Five-year s-25OHD was independently associated with HGS and myopathy in girls, but not in boys. Muscle strength may be dependent on vitamin D status even in the higher range in preschool girls. The sex difference remains unexplained.

RFC2.3

Measured Free 25-Hydroxyvitamin D in Healthy Children and Relationship to Total 25-Hydroxyvitamin D, Calculated Free 25-Hydroxyvitamin D and Vitamin D Binding Protein

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Introduction: Vitamin D deficiency in children is still a global health problem. Measuring free 25-hydroxyvitamin D concentrations could provide a better estimate of the vitamin D status than total 25-hydroxyvitamin D (25(OH)D) levels.

Objective: To assess the relationship between measured free vitamin D (m-f25(OH)D) and calculated free 25(OH)D (c-f25(OH)D), total 25(OH)D, intact parathyroid hormone (iPTH) and other markers of phosphocalcic metabolism.

Establish serum m-f25(OH)D concentrations corresponding to a total 25(OH)D>20 ng/mL which is accepted as vitamin D-sufficiency status in children.

Material and Methods: Prospective cohort study setted between January and February 2017 in healthy children of a Mediterranean population The measurements of m-f25(OH)D and vitamin D binding protein (VDBP) were made by ELISA. Free 25(OH)D was calculated using the formula described by Bikle.

Results: m-f25(OH)D directly correlated with total 25(OH)D (r:0.804, p<0.001), serum calcium (r:0.26,p:0.035), and c-f25(OH)D (r:0.553, p:0.016); and inversely with iPTH (r:-0.374, p:0.002), alkaline phosphatase (r:-0.28, p:0.026), and age (r:-0.289, p:0.018). Total 25(OH)D correlated with the same parameters than m-f25(OH)D except for serum calcium. Whereas, c-f25(OH)D correlated only with total 25(OH)D and VDBP, both included in the calculation formula.

Multiple regression analysis showed that m-f25(OH)D variations were independently explained by calcium (β:0.156, p:0.026) and total 25(OH)D (β:0.043, p<0.001).

The optimal m-f25(OH)D cut-off for discriminating between insufficient and sufficient total 25(OH)D was ≥3.9 pg/ml (Area Under Curve (AUC): 0.897 (95% confidence interval (CI): (0.798-0.958); p<0.001; sensitivity:72.7% (95%CI: 49.8-89.3); specificity: 95.4% (95%CI: 84.5-99.4))

Conclusions: Directly measured free vitamin D correlated better with markers of phosphocalcic metabolism than total 25(OH)D and c-f25(OH)D in a population of healthy children.

RFC2.4

Novel Severe Skeletal Dysplasia with Under-Mineralisation Associated with Reduced *in Utero* Calcium Transport and *TRPV6* Compound Heterozygous Variants

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Background: Fetal skeletal bone development and mineralisation depends on placental calcium transfer. Although Parathyroid Hormone (PTH) pathway has some contribution, *TRPV6* (the sixth member of the Transient Receptor Potential Vanilloid family) is a recently identified receptor involved in calcium transport and is predominantly expressed in the placenta. It has not previously been linked with skeletal development disorders.

Case: This infant had thoracic insufficiency with significant skeletal and biochemical abnormalities. Pregnancy featured polyhydramnios. Antenatal ultrasound identified a small chest, unusual rib configuration and short long bones. Antenatal CGH array and UPD14 testing showed no abnormalities. Delivery was by emergency caesarean due to fetal distress. Intubation and ventilation was required from birth. Conventional mechanical ventilation with maximal pressures of 30cmsH20 and FiO2 0.6 was needed, followed by tracheostomy for long term ventilation.

Postnatal skeletal survey showed generalised marked under-mineralisation, bell-shaped chest, fractures of ribs and metaphyses and extensive periosteal thickening of femoral, tibial and humeral diaphyses. Biochemistry featured markedly elevated PTH (53.4 progressing to 101pmol/L), predominantly normocalcaemia (corrected calcium 2.43mmol/l), although transient mild hypocalcaemia and hypophosphataemia weeks 3-4, normal ALP (289IU/L), normal urinary Calcium/Creatinine ratio (1.05), Vitamin D insufficiency (29nmol/L). Parental biochemistry was normal.

PTH elevation with periosteal reaction suggested Neonatal Severe Hyperparathyroidism (NSHPT), although the absence of hypercalcaemia was uncharacteristic. Treatment of the metabolic bone abnormality included pamidronate, cinacalcet (calcimimetic), calcium and Vitamin D supplementation. NSHPT was subsequently excluded as molecular genetic analysis found no causative variants in *CASR*, *GNA11*, *APS21;* Mucolipidosis Type II also excluded biochemically and genetically (*GNPTG).*

The significant skeletal abnormalities were investigated by whole exome sequencing (WES) and no abnormalities were found using a 336 gene skeletal dysplasia panel. Meanwhile, resolution of biochemical abnormalities and progressive mineralisation radiologically was evident by 8 weeks. This changing clinical picture suggested an alternative hypothesis of an *in utero* pathology with normalisation *ex utero*. Consequently, placental calcium transfer candidate genes *TRPV6, CABP9K* and *VDR* were explored.

Trio exome analysis identified compound heterozygous *TRPV6* likely pathogenic variants: a novel maternally inherited missense variant, c.1978G>C p.(Gly660Arg), and a paternally inherited nonsense variant, c.1528C>T p.(Arg510Ter), confirming recessive inheritance of this novel dysplasia.

Conclusion: We report the first case of *TRPV6* compound heterozygous variants in a novel dysplasia. This rare bone disease case illustrates that astute clinical interpretation of evolving perinatal abnormalities remains valuable in complex calcium and bone pathophysiology and informs whole exome sequence interpretation.

RFC2.5

Identification of Characteristic Neurological Complications in Infants with Achondroplasia by Routine MRI Screening

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Background: Achondroplasia is the commonest type of skeletal dysplasia with an incidence of 1 in 20,000 and is due to recurrent and dominantly transmitted, activating mutations in Fibroblast Growth Factor Receptor 3 (*FGFR3*). Complications during infancy include foramen magnum stenosis and hydrocephalus which may lead to neurological morbidity and sudden unexplained mortality. Early detection and appropriate neurosurgical management can prevent these complications. However, consensus around routine screening has not been reached and imaging practices between centres are inconsistent.

Aim: The Achondroplasia Multi-Disciplinary Service at the Evelina London Children's Hospital provides regular surveillance for over 140 affected children. Since 2016 all infants under one year have undergone routine MRI brain imaging, aiming to identify early changes and document natural history of pathology, with a view to informing recommendations for management.

Study Design: This retrospective cohort study investigated all children under one year with a confirmed diagnosis of Achondroplasia from January 2016 to January 2018. Details were collected of clinical evaluation, which included a detailed neurological examination and MRI scans. The presence of hydrocephalus or craniovertebral junction (CVJ) changes were evaluated by a paediatric neuroradiologist. In order to provide a more objective assessment of foramen magnum stenosis a novel scoring system was developed; The Achondroplasia Foramen Magnum Severity Score (AFMSS).

Results: Only 1 out of 18 infants who underwent surveillance MRI brain had abnormal neurological findings on clinical examination. 77% had abnormal MRI changes (n=14). 5 patients demonstrated CVJ narrowing with preservation of the cerebrospinal fluid (CSF) space around the cord (AFMSS 1). 3 patients demonstrated CVJ narrowing with loss of CSF space (AFMSS 2). 3 patients demonstrated CVJ narrowing with flattening of the cervical cord (AFMSS 3). 3 patients demonstrated CVJ narrowing and cervical cord signal change (AFMSS 4). Hydrocephalus was also present in 2 patients with AFMSS 1 and AFMSS 3. Only those with AFMSS 3 or AFMSS 4 underwent foramen magnum decompression (n=5). One patient with hydrocephalus underwent ventriculoperitoneal shunt insertion. Overall, 43% of infants required neurosurgery (n= 6)

Conclusion: This data demonstrates a high prevalence of pathological neuraxis changes in infants with Achondroplasia detected on routine MRI screening without clinical signs or symptoms. Further studies are needed to explore the evolution of foramen magnum changes in children over 12 months of age. The results of this study indicate that all infants with Achondroplasia should undergo routine neuroimaging screening, given the high incidence of significant complications in this unselected population.

RFC2.6

The Novel R211Q *POP1* Homozygous Mutation Causes Severe Short Stature But Uniquely Only Subtle Skeletal Dysplasia

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Background: Processing of Precursor 1 (POP1) is a core protein component of the Ribonuclease-Mitochondrial RNA Processing (RNase-MRP) enzymatic complex, an essential complex in all eukaryotes. Mutations in *RMRP*, encoding the RNA moiety of the complex cause cartilage-hair hypoplasia – anauxetic dysplasia (CHH-AD) spectrum disorders, characterized by severe disproportionate short stature. Recently, five patients harboring mutations in *POP1* have been reported with anauxetic dysplasia (spondylo-epi-metaphyseal dysplasia with extremely short stature) involving the spine, and long bones' epiphyses and metaphyses in all these cases.

Patients & Methods: A 6y old boy, born to consanguineous parents, presented with severe short stature (height 90.5 cm, SDS -5.68). Physical exam revealed mild legs shortness (US:LS ratio is 1.15:1) and mild brachydactyly. A male sibling (20y) and a female cousin (25y) are extremely short (138 cm and 135 cm, respectively), with no apparent skeletal deformities. Skeletal survey and whole exome sequencing were performed for the proband. Relative abundance of the RMRP RNA and unprocessed pre5.8s rRNA

(a substrate of RNase-MRP complex) were measured in affected siblings, non-affected parents and control.

Results: Skeletal survey exemplified relatively short forearm, mild shortness of metacarpals, subtle widening and irregularity of metaphyseal borders of long bones and delayed bone age by 2.5 years. There was no epiphyseal involvement, and no skeletal abnormalities in cranium, vertebral bodies or pelvis. Using exome sequencing the proband, his affected brother and cousin were found to be homozygous for the R211Q novel mutation in *POP1* gene. Parents and healthy siblings were all heterozygous. The arginine residue at position 211 is highly evolutionarily conserved. The RNA moiety of the RNase-MRP complex quantified in RNA extracted from peripheral lymphocytes was dramatically reduced (20 times less) in affected patients compared to non-affected parents, sibling and control. Pre5.8s rRNA was not increased in patients' RNA. 3-dimentional complex modeling of the mutation to explain the relative subtle pathophysiology is underway.

Conclusions: This study identified a novel homozygous *POP1* mutation in three patients causing a unique phenotype of skeletal dysplasia. Unlike the few previously reported cases, the skeletal dysplastic changes are subtle and merely metaphyseal. Gene expression assays indicate dramatically reduced RMRP RNA levels but no elevation in pre5.8s rRNA levels possibly explaining the uniquely mild phenotype. POP1 mutations should be considered in familial cases with severe short stature even when skeletal dysplasia is not strongly evident.

Diabetes and Insulin 1

RFC3.1

Diagnostics of Early Atherosclerosis Risk in Kids (DEAR-Kids): Retinal Vessel Analysis in Pediatric Type 1 Diabetes – Retinal Arteriolar Narrowing Caused by High HbA1c

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Background/Objective: Micro-and macrovascular changes are the cause for diabetes complications. Retinal vessel analysis is a unique method to examine microvascular changes in brain derived vessels.

Subjects/Methods: 67 pediatric and adolescent type 1 diabetes patients and 58 healthy control persons underwent nonmydriatic retinal photography of both eyes. Arterioles and venules positioned in the region 0.5 to 1 diameter of the optic disc measured from its margin were identified and measured. Central retinal arteriolar and venular equivalents (CRAE/CRVE) and arteriovenolar ratio (AVR) were calculated.

Data were analysed by students T-test. Multiple linear regression was used to determine factors influencing measurements of arteriolar and venular vessels. In multiple linear regression analysis, several models were used for adjustment. Model 1 included sex, age, body length, BMI, diabetes duration and average HbA1c of the recent year as covariates. Model 2 and 3 added systolic and diastolic blood pressure, respectively. Model 4 additionally comprised waist circumference and model 5 included current blood glucose as covariate.

Results: Patients did not differ in sex distribution, age, height, weight, BMI and BMI-SDS, total cholesterol, LDL and HDL. Diabetes patients had higher triglycerides (Mean 115 vs. 87 mg/dl; $p< 0.01$), systolic blood pressure (117 vs. 112 mmHg; $p=0.023$) and waist circumference (69.8 vs 66.4 cm; $p=0.046$) than control subjects.

Diabetes patients did not differ in CRAE, CRVE and AVR compared to healthy controls overall. Per percent increase in HbA1c, CRAE was reduced by 4.3 µm (95%-CI 0.2 - 8.0 µm) up to 5.4 µm (95%-CI 8.2 - 2.6 µm), depending on model of adjustment. CRVE was not associated with diabetes duration or HbA1c.

Conclusion: Microvascular arteriolar changes caused by poor diabetes control are already present in childhood and may indicate early atherosclerosis and increased risk for diabetes complications. Multiple studies in adults show that retinal arteriolar narrowing is associated with diabetes sequela and cardiovascular disease in adulthood. Further investigation warranted this may lead to end organ damage based therapeutic goals in pediatric diabetes patients.

RFC3.2

Personalized and Predictive Medicine for Pediatric Diabetes Through a Genetic Test Using Next Generation Sequencing

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Introduction: Monogenic diabetes (**MD**) accounts for at least 3% of all pediatric diabetes cases. **MD** is often misdiagnosed as type 1 or type 2 diabetes, because of its wide phenotypic spectrum. While clinical and biochemical parameters can suggest **MD**, a definitive diagnosis requires genetic analysis. We conducted a broad study to diagnose **MD** cases. Then, with the gained knowledge, we designed a new diagnostic tool to obtain a comprehensive analytical instrument for the diagnosis of **MD**. A correct diagnosis of **MD**

is crucial to optimize treatment and thereby improve metabolic control.

Method: Diagnostic tool (Haloplex technology): This custom assay, designed based on liquid phase capture, allows for the trapping of all coding regions of the 42 genes and the respective splicing regions. Known enhancer regions and introns associated with diabetes were also included in the panel.

Results: Here, we developed a new diagnostic panel of 42 genes, including the genes causing Maturity onset diabetes of the Young (MODY) and neonatal diabetes. The panel was validated with independent samples of known MD patients. We have now analyzed the first 19 patients, sent in from all over Switzerland, and identified a variant in 53% of the subjects. We found three different variants in the *GCK* and four in the *HNF1A* gene, one in the *EIF2AK3, ABCC8 and PAX4* genes. In nine patients the result remained negative. Interestingly, the *ABCC8* variant was reported to be functionally inactivating and therefore compatible with the congenital hyperinsulinism presented by the newborn patient. This is in contrast to activating *ABCC8* mutations known to cause neonatal diabetes.

Discussion and Conclusion: Our newly developed next generation diagnostic panel shows an actual pick-up rate of 53% in the 19 consecutive patients, which is above the published rates of 21% to 37 % in the UK and 25% to 30% in France. The panel detects missense variants, insertions, and deletions, as well as activating or inactivating mutations, and large deletions extended from one exon to entire gene. These results indicate that the three patients with *GCK* diabetes didn't need any treatment, the patients with *HNF1A* mutations could be switched to oral sulfonylurea or glinides. The congenital hyperinsulinism could successfully be treated by diazoxide and the neonatal diabetes due to the homozygous *EIF2AK3* mutation needed insulin injections. These cases illustrate how applied precision medicine can tailor treatment to the needs of the individual patient with the aim to reduce long-term complications.

RFC3.3

Significant Prevalence of Severe Monogenic Immune Defects Among Children with Type 1 Diabetes and Low T1D-Genetic Risk Score

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Introduction: Monogenic Type 1 diabetes (T1D) is a rare disease caused by pathogenic variant in a single gene leading to dysregulation of immune system. T1D is combined with other autoimmunity like immune cytopenias, inflammatory bowel disease, rheumatoid arthritis, atopic eczema, autoimmune thyroid disease etc in these patients. Pathogenic variants in the *AIRE*, *FOXP3*, *LRBA*, *IL2RA*, *CTLA4*, *STAT3* and *STAT1* genes have been described as causal for monogenic T1D.

Patients and methods: Out of 519 paediatric patients with T1D from single tertiary center, 18 patients had at least two additional autoimmune conditions or a combination of T1D and autoimmune hepatitis, cytopenia or rheumatoid arthritis. In four patients with specific phenotype, the *FOXP3*, *STAT3* and *CTLA4* genes, were directly sequenced. DNA from the additional 14 patients was investigated using whole exome sequencing (WES). In addition, the T1D-genetic risk score (T1D-GRS) was used to discriminate monogenic autoimmunity from polygenic T1D.

Results: All four clinically highly suspected patients carried the causal variants in selected genes: One patient was diagnosed with IPEX syndrome with variant in the *FOXP3* gene (p.Ser241Pro). He developed early-onset T1D at six weeks of age, atopic dermatitis and progressive failure to thrive. Second patient manifested with recurrent episodes of immune thrombocytopenic purpura (ITP), autoimmune haemolytic anemia (AIHA) and T1D. He presented total alopecia and optic nerve neuritis. His younger brother manifested with T1D at age 1 year. Later on, he also developed ITP and AIHA. They carried a heterozygous variant in the *CTLA4* gene (p.Tyr60Asn). The fourth patient was diagnosed with multiple early-onset autoimmune conditions due to the activation mutation in the *STAT3* gene (p.Pro715Leu). No other causal variant in selected genes was found in remaining 14 highly suspicious patients. These four children have the T1D-GRS below 40th centile. Twelve of all investigated patients had the T1D-GRS below the 50th centile and seven even below the 30th centile suggesting high likelihood of a monogenic cause of diabetes in these children, with the possibility of identification of causative variants in the genes for regulation of immune system in future studies.

In conclusion, we found four of the 18 patients with genetically confirmed monogenic form of T1D representing 22% in our specific cohort with severe T1D associated multiple autoimmunity. The T1D-GRS is a novel tool that can be helpful for discrimination between monogenic and polygenic forms of diabetes and combined with analysis by WES will be useful for searching genes causing monogenic T1D.

RFC3.4

Functional Characterization of a Novel *KLF11* Mutation Identified in a Family with Autoantibody-Negative Type 1 Diabetes

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Objectives: KLF11 is a member of the Sp1/KLF family transcription factor which contains three C_2H_2 zinc finger domains. To date, two *KLF11* mutations (p.T220M and p.A347S) have been

identified in three families clinically diagnosed with type 2 diabetes. The aim of our study is to report clinical and molecular characteristics of a *KLF11* mutation-carrying family clinically diagnosed with type 1 diabetes (T1D).

Methods: The proband was a 10-year-old girl. She was accidentally found to have hyperglycemia when she was suffered from upper respiratory infection at age 1 year. She was subsequently diagnosed as T1D although she was negative for diabetes-associated autoantibodies. Her elder brother and mother also had been diagnosed with autoantibody-negative T1D at 1 and 4 years of age, respectively. All of them required insulin therapy. To clarify the etiology of diabetes, we performed whole exome sequencing in this family. To evaluate the pathogenicity of the identified *KLF11* variant, we performed functional analyses including western blotting, immunofluorescence and luciferase reporter assay.

Results: A heterozygous missense variant in *KLF11* p.H418Q was identified in three affected family members. Three-dimensional structure modeling suggested that the H418Q variant affects a functionally important histidine residue in the C_2H_2 zinc finger domain. The protein expression level and intracellular localization of H418Q-KLF11 were comparable with wildtype-KLF11. To analyze the transcriptional regulatory activity of wildtype and mutant KLF11, CHO cells were transiently transfected with the KLF11 expression constructs (wildtype, H418Q, A347S and T220M) along with the luciferase reporter which contains six tandem GC box of KLF11-binding sites. H418Q-KLF11 and A347S-KLF11 demonstrated significantly decreased transcriptional repression activities as compared with wildtype-KLF11. Furthermore, co-expression of H418Q-KLF11 with wildtype-KLF11 caused significant loss of repression, indicating that H418Q-KLF11 had a dominant-negative effect. The dominant negative effect was not observed in A347S-KLF11.

Conclusions: This is the first report of a *KLF11* mutation identified in patients clinically diagnosed with T1D. Functional analyses provided evidence for a dominant-negative effect of H418Q-KLF11 that could explain severer phenotypes observed in our patients. Our findings expand the phenotypic spectrum of *KLF11* mutation-carrying patients.

RFC3.5

Recent Secular Change in Pre- And Postnatal Growth and Adiposity in Infants of Mothers with Gestational Diabetes

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Objective: Typically, infants born to mothers with gestational diabetes mellitus (IOGDM) have greater risks for macrosomia, later obesity and metabolic diseases. However, we have noticed that birth weights of IOGDM have reduced over the last decade even with uniform application of the International Association of Diabetes and Pregnancy Study Group's (IADPSG) consensus definition. We therefore compared infancy growth outcomes from two IOGDM cohorts born during non-overlapping time periods.

Methods: We compared growth outcomes measured using identical protocols at birth, 3, 12, and 24 months between a 'recent' IOGDM cohort (N=139) born in 2011-2013, with an 'older' IOGDM cohort (N=98) born in 2001-2009 and also a control population (N=876) all from a single maternity unit. Anthropometry outcomes included weight, length and skinfolds thicknesses. In both cohorts, IOGDM was defined by the same IADPSG threshold of OGTT glucose concentrations: >5.1 mmol/L at 0 minutes, 10.0 mmol/L at 60 minutes, or 8.5 mmol/L at 120 minutes.

Results: At birth, 'recent' IOGDM had similar weight and length SDS (0.1±1.0 and -0.1±0.9, respectively) compared to non-GDM controls, but had lower mean skinfolds SDS (-0.4 vs. 0.0, $p<0.001$). The 'older' IOGDM demonstrated higher birth weight SDS (0.6±1.0), length SDS (0.2±1.0) and mean skinfolds SDS (0.3±0.9). This 'older' IOGDM group had subsequent weight, length, and skinfolds at all time points until 24 months that were greater than controls. By contrast, 'recent' IOGDM showed lower growth outcomes, except for 3-months weight. At 24 months, the mean weight and length SDS of recent IOGDM were lower than both 'older' IOGDM and control populations (weight 0.0+1.1 vs. 0.4+1.1 vs. 0.2+1.0, respectively; length 0.3+1.1 vs. 0.4+1.1 vs. 0.4+1.1, respectively), with lower adiposity (mean skinfold SDS -0.3+0.7 vs. 0.2+0.6 and 0.0+0.8, respectively, both $p<0.001$). Compared to the control and 'older' IOGDM populations, mothers of 'recent' IOGDM had higher BMI, higher OGTT 60 minutes glucose concentrations, were a more ethnically diverse subgroup, and delivered at earlier gestational ages.

Conclusions: In contrast with an older IOGDM population born 10 years earlier, 'recent' IOGDM were not larger at birth than controls, possibly due to enhanced pregnancy glucose management. Furthermore, 'recent' IOGDM showed poorer postnatal growth than controls, which could reflect inherent defects in their insulin sensitivity and/or insulin secretion. While avoidance of large size at birth may be advantageous, the longer-term health implications of these changing growth patterns are uncertain.

RFC3.6

Treatment Adherence and Weight Loss Are Key Predictors of HbA1c One Year After Diagnosis of Childhood Type 2 Diabetes in UK

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Background: Type 2 Diabetes (T2DM) is increasing in childhood especially among females and South-Asians.

Objective: To report outcomes from a national cohort of children and adolescents with T2DM 1-year post diagnosis.

Subjects and Methods: Clinician reported 1-year follow-up of a cohort of children (<17years) with T2DM reported through British Paediatric Surveillance Unit (April 2015-April 2016). This followed the same methodology as the survey in 2005, allowing direct comparisons across the decade.

Results: One hundred (94%) of 106 baseline cases were available for review. Of these, five were lost to follow up and one had a revised diagnosis. Mean age at follow up was 15.3 years. Mean BMI SDS was 2.72 with a mean increase of 0.13 SDS over a year. 15% of patients attained a normal HbA1c losing an average of 4% (CI -9.63 to 1.64) body weight. HbA1c <48mmol/mol (UK target) was achieved in 38.8%. HbA1c was predicted by clinician reported compliance and attendance concerns (B=18.5 p=<0.0001). In over 50%, clinicians reported issues with compliance and attendance. Mean clinic attendance was 75%. Metformin was the most frequently used treatment at baseline (77%) and follow-up (87%). Microalbuminuria prevalence at 1-year was 16.4% compared to 4.2% at baseline and was associated with a higher HbA1c compared to those without microalbuminuria (60 vs. 49 mmol/mol, p=0.033). The median HbA1c was higher in 2015 compared to 2005 (53 vs. 48mmol/mol) and BMI SDS fell by 0.11 a year after diagnosis in 2005 compared to an overall rise of 0.13 in 2015. In 2005, GLP-1 agonists were not used in the cohort of T2DM, however in 2015 4% of patients were reportedly on these drugs.

Conclusions: Adherence to treatment appears key to better outcomes a year after T2DM diagnosis. A body weight reduction of around 5% for patients may lead to diabetes resolution. Retention and clinic attendance are concerning. The prevalence of microalbuminuria had increased four-fold in the year following diagnosis and was associated with higher HbA1c.

GH & IGFs

RFC4.1

Metabolomic Changes in Patients with PAPP-A2 Deficiency in Response to rhIGF1 Treatment

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Background: We previously described two siblings with a frameshift mutation (c.1927_1928insAT, p.D643fs25*) resulting in loss of function in the gene for pregnancy-associated plasma protein A2 (*PAPP-A2*). The female was 10.5-years of age (1.7 SDS below target height at diagnosis). Her brother was 6-years of age and 1.3 SDS below target height. These patients presented elevated serum GH, total IGF-1, IGFBP-3 and ALS levels, but extremely low free/bioactive IGF-1 levels. Hence, they were treated with rhIGF-1. The growth response and improvement in bone mineral density have been previously reported.

Objective: To better understand the overall metabolic response, a GC-MS-based untargeted metabolomics approach was employed.

Results: The acute and long-term metabolic effect of the treatment were investigated using serum samples collected at 0, 60, 120, 240, 360 minutes after administration of the rhIGF-1 treatment, and before the treatment and every 6 months after the first day of treatment, respectively. Principal component analysis (PCA) and descriptive statistics were employed to explore effects of treatment with rhIGF-1 on the metabolism of carbohydrates, proteins and lipids. The metabolic fingerprinting identified 70 serum metabolites consisting of: amino acids (46%), organic acids (21%), carbohydrates (16%), fatty acids (14%) and purine bases (3%). PCA analysis showed a naïve sample clustering between samples as a result of rhIGF-1 treatment, highlighting changes in the metabolic profile of the siblings during the acute phase, as well as over two years of treatment. Free fatty acids (FFAs) and amino acids showed the greatest changes in the metabolic profiles, suggesting that lipid and protein metabolism are the most altered pathways in PAPP-A2 deficient subjects under rhIGF-1 treatment, with only subtle changes in carbohydrate and organic acid metabolites. There was a decrease in serum FFAs and glycerol levels both in the acute phase and over two years of treatment. Interestingly, 4-hydroxyproline was the metabolite showing the greatest change, increasing at 240 and 360 minutes (acute) and 6 and 12 months (long-term) after treatment.

Conclusion: These results are consistent with the direct and indirect actions mediated by IGF-1 on the skeletal muscle and adipose tissue. As 4-hydroxyproline is a marker of collagen catabolism and bone resorption, this observation could represent an increase in bone turnover. Indeed, the greatest increase in 4-hydroxyproline corresponded to the period of highest growth velocity.

RFC4.2

Data Mining and Computational Analysis of Human Growth Hormone Gene (GH1) Sequence in Normal Population to Identify Potential Variants with Disease-Causing Effects

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Background: Mutations in GH1 gene cause isolated growth hormone deficiency. Several disease-causing mutations from patients with IGHD have been reported. These mutations have been shown to (a) produce shorter isoforms of GH that does not bind to growth hormone receptor, (b) cause diminished secretion of GH or (c) result in misfolded GH protein. Large sequencing studies from the non-clinical population show several hundred genetic variations in GH1 gene. Role of common polymorphic variants in GH1 gene in relation to effects of GH protein has not been systematically studied.

Aim: Searching the genomics data to find and analyze the effects of potentially disease-causing variants in GH1 gene.

Methods: We used hidden Markov Model methods to generate position-specific scoring matrices for analyzing the sequence conservation of GH amino acids across species using both structural and genomics data. A potential list of structurally and functionally important residues was compiled for further analysis. Computational molecular dynamics using AMBER and GH-GHR interaction analysis was performed to study the effects of potentially disease-causing variants.

Results: We generated an evolutionary conservation score of all the amino acids in the human growth hormone sequence by comparing with all the GH sequences in the Uniref90 database. The Arg16, His21, Gln84, Asp169, Lys172, Cys189 residues are functionally conserved while residues Ala17, Ala24, Cys53, Ser79, Leu162, Cys172 structurally conserved. A detailed contact map of GH with amino acids in GHR revealed that GH residues His18, His21, Phe25, Leu45, Pro48, Ser62, Asn63, Tyr164, Lys172, Glu174, Ile179, Cys182, Cys189, Gly190 and Pro2, Ile4, Arg8, Asn12, Leu15, Arg16, Asp116, Glu119, Gly120, Thr123 interact with the GHR via hydrogen bonding or Vander Waal interactions.. We found several potentially disease-causing variants in the GH1 gene from sequencing data deposited from non-clinical samples. Three different categories of changes in the amino acid sequence of GH were observed. Mutations at the interface of GH-GHR interactions were predicted to affect binding and affinity of GH towards GHR, while 31 mutations were found to cause structural instabilities. An overview of GH1 variants with the potential to cause IGHD will be presented.

Conclusion: Identification of potentially negative effects of variations in GH1 gene from non-clinical populations can be utilized to study links to growth variations. Identification of potentially disease-causing variants in GH1 will help in the further functional characterization of these variants when these are later found in patients with growth hormone deficiency.

RFC4.3

A Deletion Encompassing Exon 2 of the ALS Gene: Analysis of a Patient with ALS Deficiency and His Family

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The main role of the acid-labile subunit (ALS) is to stabilize the IGFBP3/IGF complexes. Pathogenic variants in the gene coding for ALS (*IGFALS*) results in IGF1 and IGFBP3 deficiency, short stature, delay puberty and insulin resistance. The aim of these study was to identify the genetic cause in a patient with suspected ALS deficiency.

The proband is the third son of non-consanguineous parents, evaluated for the first time at 17.3 years due to short stature (-2.84 SD) and delayed puberty (Tanner 2) and a bone age of 16 years. He showed IGF1 basal concentrations of 45 ng/mL (reference range: 193-731 ng/mL) and undetectable IGFBP3. GH concentrations after Clonidin test suggested GH insensitivity (11.2-19.3-10.7-7.25ng/mL). No increases in IGF1 and IGFBP3 concentrations were found after 2 weeks of GH administration (0.1 and 0.2 U/kg/d). Neither the parents nor the 4 siblings had abnormal IGF1 or IGFBP3 concentrations. Since the findings in the proband suggested ALS deficiency, but ALS measurement was not available, Sanger sequencing of *IGFALS* was performed in the patient and his family. An apparently homozygous missense variant (c.1871C>T, p.Pro624Leu; NP_001139478.1) in exon 2 was found in the index case and on one allele in his father. This missense variant has been reported by the Exome Aggregation Consortium in only 1 allele among 44,672 individuals, but not in a clinical context. In silico analysis with PolyPhen-2 predicts that it is probably damaging with a high score. Since this point mutations was not found in the mother, MLPA analysis of the *IGFALS* gene was performed. The index case, as well as his mother and siblings, and not the father, showed a deletion encompassing at least a major part of exon 2, on one of their alleles.

Conclusion: To our knowledge, these is the first report of a large deletion in the *IGFALS* gene. The patient was the only one in his family with two affected alleles (p.[Pro624Leu];[deletion]) which is consistent with the phenotype. Identification of pathogenic variants in *IGFALS* is a useful tool to confirm the diagnosis of ALS deficiency as a probable cause of growth retardation in children with low IGF1 and very low IGFBP3. We suggest deletion/duplication analysis should be considered in the genetic analysis of ALS deficiency.

RFC4.4

A Longitudinal Study on miRNAs Circulating Levels in a Cohort of SGA and AGA Subjects, Evaluated During Childhood and Young Adulthood

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Background: Low birth weight is associated with increased cardio-metabolic diseases in adulthood. Specific circulating miRNA seem to be predictive of cardio-metabolic risk.

OBJECTIVE: Our aim was to investigate the circulating levels of mir-122, mir-16, mir-126, and mir-486 in a cohort of SGA and AGA subjects, evaluated longitudinally in childhood and early adulthood.

Method: Anthropometric and biochemical-metabolic evaluations were performed in 23 SGA (13 F/10 M) and 28 AGA (17 F/11M) subjects at the age of 9 and 21 years. IGF-I and IGF-II levels were assessed. Serum levels of mir-122, mir-16, mir-126, and mir-486 were analyzed by qPCR.

Results: All SGA subjects had shown catch-up growth though were shorter than AGA, both at 9 years (0.08 ± 1.06 SDS vs 0.76 ± 1.2 SDS, p< 0.05) and at 21 years (-0.21 ± 0.76 SDS vs 0.65 ± 1.32 SDS, p<0.05) whereas metabolic profiles and IGF levels were not significantly different. miRNAs expression did not differ between females and males. mir-122 and mir-486 expression was not influenced by age, whereas mir-16 and mir-126 levels were higher at 9 years than at 21 years. Mir-122, mir-16, mir-126, and mir-486 expression was not different between SGA and AGA subjects, both at 9 and 21 years.

In SGA subjects, mir-122 expression at 9 years was inversely related to adiponectin levels at 21 years (r=-0.48, p=0.05) and mir-486 expression at 9 years was inversely related to WBISI (whole-body insulin sensitivity) at 9 years (r=-0.52, p<0.05) and directly related to Hb1Ac at 21 years (r=0.52, p< 0.05). In AGA subjects, mir-122 expression at 9 years was directly related to BMI (r=0.5, p<0.05) and LDL-cholesterol levels (r=0.5, p<0.05) at 21 years. mir-486 expression at 9 years was directly related to leptin at 9 years (r=0.5, p=0.02) and mir-486 expression at 21 years was inversely related to adiponectin levels at 21 years (r=0.5, p=0.02).

Conclusion: SGA subjects with catch-up growth and AGA subjects do not show significant differences in biochemical and endocrine markers of metabolic risk and in miRNAs circulating levels. Specific miRNAs correlate with single parameters of metabolic risk. The relationship between miRNA levels and metabolic parameters in SGA and AGA subjects requires further studies aiming at evaluating the possible use of miRNAs as markers of increased cardio-metabolic risk.

RFC4.5

12-Month Effects of Once-Weekly and Twice-Monthly Administration of Hybrid Fc-Fused Human Growth Hormone, GX-H9, Treatment in Pediatric with GHD Deficiency

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GX-H9 is a long-acting form of recombinant human GH under clinical development for both adults and children with GH deficiency (GHD). This study was designed to compare 12-month effects of once-weekly and twice-monthly (every other week; EOW) administration of GX-H9 treatment to that of Genotropin®, in pediatric patients with GHD.

A randomized, open-label, active-controlled, parallel study was conducted at 27 endocrinology centers in 10 countries (Europe and Korea). Subjects were randomly assigned to receive either one of the three doses of GX-H9 (0.8 mg/kg/weekly, 1.2 mg/kg/weekly or 2.4 mg/kg/EOW) or 0.03 mg/kg/daily of Genotropin® for up to 24 months. Among fifty-six pediatric GH naïve GHD subjects randomized, 6 subjects withdrew from the study, and remaining 50 subjects were treated longer than 12 months.

The annualized height velocity(aHV) at 12 months of treatment were comparable between all doses of GX-H9 and Genotropin® (10.65 cm/year, 11.76 cm/year, 11.48 cm/year and 9.07 cm/year; 0.8 mg/kg, 1.2 mg/kg weekly, 2.4 mg/kg twice-monthly and 0.03 mg/kg/daily Genotropin®, respectively). No significant slow-

down of growth rate was observed after 12 months of GX-H9 or Genotropin® treatment compared to aHV calculated after first 6 months of treatment. Height SDS improved steadily from baseline to 6 and 12 months of GX-H9 or Genotropin® treatments (change from baseline, after 6 and 12 months of treatment: 0.66 SDS and 1.15 SDS, 0.66 SDS and 1.37 SDS, 0.69 SDS and 1.14 SDS, 0.70 SDS and 0.85 SDS; 0.8 mg/kg, 1.2 mg/kg weekly, 2.4 mg/kg twice-monthly and 0.03 mg/kg/daily Genotropin®, respectively). Pre and post body mass index SDS were comparable throughout the 12 months of treatment period for all GX-H9 doses and Genotropin® (change from Baseline:+ 0.44 SDS, + 0.11 SDS, -0.18 SDS, -0.24 SDS; 0.8 mg/kg, 1.2 mg/kg weekly, 2.4 mg/kg twice-monthly and 0.03 mg/kg/daily Genotropin®, respectively). No lipoatropy or injection site nodule formation or insulin resistance was observed in this study. Safety profiles were comparable across the treatment groups and with Genotropin®.

Twelve-month effects of once-weekly, twice-monthly administration of GX-H9 and daily Genotropin® were comparable with no significant slowdown of growth rate compared to first 6 months. Long term safety profiles were similar to that of Genotropin®.

RFC4.6

Effect of 2 Years of Growth Hormone Treatment on Glucose Tolerance in Adults with Prader-Willi Syndrome

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Background: In children with Prader-Willi syndrome (PWS), the benefits of growth hormone (GH) treatment are well established. GH has substantially changed the phenotype of children with PWS. Discontinuation of GH after adult height (AH) attainment leads to a decrease in lean body mass and an increase in body fat percentage.

Due to their abnormal body composition, adults with PWS are predisposed to develop impaired glucose tolerance (IGT) and diabetes mellitus type 2 (T2DM). Reports on the prevalence of T2DM vary from 7-24% in adults with PWS. Studies in adults with PWS showed positive effects of GH on body composition and metabolic health parameters, but GH is known to induce insulin resistance, which might lead to IGT. In children with PWS, GH has no adverse effects on glucose homeostasis, but data in GH-treated adults are limited.

Aims: To investigate the effect of continuation of GH after AH attainment on glucose homeostasis.

Methods: 40 young adults (mean age 19 years) received at least 2 years of GH after attainment of AH in a standard dose of 0.33 mg/m2/day (≈0.035 mg/kg/day). Dose was adjusted according to serum IGF-I and Fat Mass Percentage by DXA scan. An oral glucose tolerance test (OGTT) was performed at baseline (after GH discontinuation for 2-12 months; N=22) and at 1 and 2 years after GH re-start (n=40). IGT and T2DM were defined as glucose levels at 2 hours after glucose load between 7.8 and 11.0 or >11.0 mmol/l resp.

Results: After 2 years of GH, fasting insulin and HOMA-IR were significantly higher than at baseline (p=0.011 and p=0.009, resp.), but fasting glucose, glucose and insulin at 2 hours after glucose load and glucose and insulin AUC had not significantly changed.

Of 22 patients, with an OGTT at baseline and after 2 years, one had IGT at baseline and at 2 years, one had T2DM which returned to IGT at 2 years and two patients had developed IGT after 2 years of GH. Four patients who did not have an OGTT at baseline had IGT at 2 years. None of 40 patients developed T2DM after 2 years of GH.

Conclusions: Two years of GH in young adults with Prader-Willi syndrome leads to higher fasting insulin levels, without changes in 2 hours glucose, insulin and AUC. Thus, GH reduces insulin sensitivity, but does not lead to diabetes mellitus in young adults with PWS.

Thyroid

RFC5.1

Serum Levels of the Soluble Receptor for Advanced Glycation End Products Are Reduced in Children with Hashimoto's Thyroiditis

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Objective: Advanced glycation end products (AGEs) increased oxidative stress and promote inflammation, resulting in the cellular damage, by interacting with their receptor (RAGE) on cell membrane. By contrast, the soluble receptor for AGE (sRAGE), that is proteolytically cleaved from cell surface receptor via matrix metalloproteinases, sequester RAGE ligands and act as a cytoprotective and anti-inflammatory agent. AGEs-RAGE/sRAGE interaction is deemed to play a role in the pathogenesis of several disease related to oxidative stress. Moreover, oxidative stress has been implicated in the pathogenesis of several autoimmune disorders, including thyroid diseases. Mostly, it has been correlated to thyroid dysfunction, but recently increased levels of AGEs have been reported in adult individuals suffering from euthyroid Hashimoto's thyroiditis (HT) (Ruggeri et al. Thyroid 2016). No data are available on such oxidative stress parameters in pediatric HT patients. The aim of our study was to investigate the changes in oxidative balance in pediatric patients with euthyroid HT.

Materials and Methods: We enrolled 19 HT pediatric patients (3 M, 16 F; mean age 12.3 ± 2.4yr) and 18 age- and sex-matched healthy controls (6 M, 12 F; mean age 12.0 ± 2.4 yr). None was on L-T4 therapy. Exclusion criteria: autoimmune, inflammatory and infection comorbidities. Patients did not differ significantly from controls with regard to lipid and glucidic profile neither for anthropometric parameters. In sera from each subject, sRAGE levels were measured by ELISA (kit sRAGE Elisa, R&D System, Minneapolis, USA). AGEs, compounds formed by the transformation of proteins, were determined on spectrophotometric detection.

Results: sRAGE levels were significantly lower in HT patients (median 414.30 pg/ml, *range 307.30 - 850.30*) than in controls (558.30, *265.80 - 1132.30*; p = 0.046). These values correlated negatively with BMI (r = -0.365, p = 0.026) and anti-thyroid antibodies positivity (r = -0.364, p = 0.027), irrespective of TSH values and thyroid functional status. No differences emerged between patients and controls with regard to serum AGEs (124.25 AU/g prot, 71.98 - 186.72 vs 139.26, 94.06 - 251.05, p = 0.358).

Conclusions: sRAGE levels were decreased in HT children/adolescents, and autoimmunity *per se* seem to play an important role in such a reduction of sRAGE, irrespective of any functional alteration. Given the protective effects of sRAGE, children and adolescents suffering from HT may exhibit increased susceptibility to oxidative damage, even when in euthyroid status.

RFC5.2

Analysis of Chosen Polymorphisms Rs7138803 A/G - FAIM2, Rs7093069 C/T - IL-2RA, Rs5742909 C/T - CTLA-4 in Pathogenesis of Hashimoto's Thyroiditis in Children

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Introduction: Autoimmune thyroid diseases are multifactorial diseases with a genetic susceptibility and environmental factors. A potential role of the Fas apoptotic inhibitory molecule 2 (FAIM2) gene, the high-affinity alpha subunit (CD25) of the interleukin-2 receptor (IL-2RA) gene, the cytotoxic T cell antigen 4 (CTLA-4) gene polymorphisms on autoimmune thyroid diseases (AITDs) in children has not been established equivocally yet.

Objective: To estimate the association of polymorphisms of FAIM2, IL-2RA and CTLA-4 genes with the predisposition to Graves' disease (GD) and Hashimoto's thyroiditis (HT) in children.

Methods: The study was performed in 170 patients with GD, 81 with HT and 110 healthy volunteers from two endocrine centers (Białystok, Messina). The three single nucleotide polymorphisms (SNPs): Rs7138803-FAIM2, Rs7093069-IL-2RA and Rs5742909-CTLA-4 were genotyped by TaqMan SNP genotyping assay with platform QuanStudio 12K Flex - OpenArray plates using the real-time PCR.

Results: Rs7138803 A/A genotypes were more frequent in HT and GD patients in comparison to healthy subjects (p=0.009 with OR=3.5; p<0.0075 with OR=2.9, respectively). Rs7138803 A alleles were more frequent in GD patients in comparison to healthy subjects (p=0.019 with OR=1.5).

Rs7093069 C alleles were more frequent in HT patients in comparison to healthy subjects (p=0.032 with OR=1.61). That means that risk for development of HT is exactly 1.6 higher for C allele in comparison to T allele.

Rs5742909 C alleles were more frequent in HT patients in comparison to healthy subjects (p=0.045 with OR=1.8).

Conclusions: Rs7138803 A/G, Rs7093069 C/T and Rs5742909 C/T polymorphisms could contribute to development of HT in children. The main risk factor for rs7093069 and rs5742909 is allele C. In case of rs7138803 the main risk factor is allele A for development of both GD and HT.

RFC5.3

Incidence and Treatment Outcome of Childhood Thyrotoxicosis

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Aim: To study the incidence of childhood thyrotoxicosis in five counties in central Sweden during 1990–2009 and to study the treatment outcome.

Methods: Children below the age of 16 years diagnosed with thyrotoxicosis during the 20-years period and living in the study area were identified retrospectively. Data on the total number of children below 16 years of age living in the area during the study period was collected from the National Board of Statistics, Sweden. Data regarding clinical and biochemical characteristics and the outcome of the treatment were collected from medical records.

Results: 113 patients were identified. The annual incidence was 2.2/100,000 children during the whole study period. The incidence was higher during the last ten studied years as compared to the first ten studied years (2.8 vs. 1.6/100,000, p = 0.006). The increase in incidence was seen in both girls and boys (p = 0.041 and p = 0.038, respectively). Treatment with antithyroid drugs (ATD) was the first hand choice, but 69% of the patients relapsed within three years after the planned discontinuation of the ATD treatment. Boys relapsed more often than girls (p = 0.013), but we could not identify any other significant predictor for relapse.

Conclusion: Thyrotoxicosis is uncommon in pediatric patients but the incidence seems to be increasing. The outcome of the initial

treatment with ATD is poor with high relapse rates. Boys seems to have an increased risk for relapse compared to girls. More studies are needed to identify an optimal treatment protocol for each individual.

RFC5.4

The Value of Cytological, Histological and US Examination to Determine of Management Children with Nodular Goiter

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Introduction: To date, there are no clear indications for surgical treatment of nodular goiter in children. Current scheme of diagnostic evaluation thyroid nodules in children is not always justified. A number of patients either go to the removal of thyroid remnants when a carcinoma is found in the histological examination and the need for radioiodine therapy, or are at risk of surgery if the results of the final histology show that the disease is benign.

Aim: Optimization of management children with nodular goiter.

Materials and methods: Cytological findings in thyroid fine-needle aspiration biopsy, intraoperative frozen section and histological examination in 125 patients, 6 - 17 years old, operated for nodular thyroid formations from November 2015 to December 2017, were analyzed. The mismatch in the cytological and histological diagnosis was found in 12.8% of patients, most of whom were in the group with the Bethesda II diagnostic category, four (8.1%) of them were diagnosed histological confirmed papillary thyroid cancer, 11 (22.5%) follicular adenoma. In the group of patients with Bethesda IV diagnostic category the percentage of malignant neoplasms reached 30.6%.

As for the intraoperative frozen section - only 5 from 44 cases with the initial diagnosis of a follicular tumor or a colloid goiter, the conclusion was carcinoma (11%). In other intraoperative frozen section did not differ from histological diagnosis. The attitude to this method in children is ambiguous. We hope for its development and improvement with the use of new technologies of material processing and its research.

The US picture in cases of mismatch between cytological and histological findings revealed a tendency to increase the size of the nodal formations. The dimensions of the nodes ranged from 1.5 to 6 cm. on average 3 cm. by the largest measurement are in all cases of the mismatch between the interpretation of NFA and histological diagnosis. The largest sizes - 4 cm. or more were noted in cases of a mismatch between colloid goiter or follicular adenoma and various variants of cancer.

Conclusion: All nodal formations according to the classification of Bethesda 3 and 4 are subject to surgical treatment. Colloid nodes of large size (more than 3.0 cm) are subject to surgical treatment even in the absence of compression and cosmetic defect.

RFC5.5

Evidence for a Founder Effect in Multiple Endocrine Neoplasia 2

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Purpose: Multiple Endocrine Neoplasia type 2 (MEN2) affects patients with *RET* proto-oncogene mutations. This cohort study refer to patients who were diagnosed with familial medullary thyroid carcinoma (MTC) and underwent *RET* genetic testing in Cyprus between years 2002 and 2017.

Methods and Patients: Forty patients underwent *RET* testing by Sanger sequencing of exons 10–11 and 13–16. Genotyping with STR genetic markers flanking the *RET* gene along with Y-chromosome genotyping and haplogroup assignment was also performed.

Results: *RET* mutations were identified in 40 patients from 11 apparently unrelated Cypriot families and two non-familial sporadic cases. Nine probands (69.2%) were heterozygous for p.Cys618Arg, one (7.7%) for p.Cys634Phe, one (7.7%) for the somatic delE632-L633 and two (15.4%) for p.Met918Thr mutations. The mean age at MTC diagnosis of patients carrying p.Cys618Arg was 36.8±14.2 years. The age of pheo diagnosis ranged from 26-43 years and appeared simultaneously with MTC in 5/36 (13.9%) cases. The high frequency of the p.Cys618Arg mutation suggested a possible ancestral mutational event. Haplotype analysis was performed in families with and without p.Cys618Arg. Six microsatellite markers covering the *RET* gene and neighbouring regions, identified one core haplotype associated with all patients carrying p.Cys618Arg.

Conclusions: The mutation p.Cys618Arg is by far the most prevalent mutation in Cyprus followed by other reported mutations of variable clinical significance. The provided molecular evidence speculates p.Cys618Arg mutation as an ancestral mutation that has spread in Cyprus due to a possible founder effect.

RFC5.6

DUOX2 Deficiency in Quebec: From Life-Threatening Compressive Goiter in Infancy to Lifelong Euthyroidism

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Background: Congenital hypothyroidism (CH) caused by DUOX2 deficiency has a wide range of clinical presentations and phenotype-genotype correlations are not always straightforward.

Objective: To describe four children from Quebec with biallelic DUOX2 variants and widely variable phenotypes.

Design/Methods: Case series of four children seen for evaluation of thyroid function at the endocrinology service of two university hospitals in the Province of Quebec. Clinical and biochemical data were analyzed and molecular genetic studies were performed.

Results: Patient 1 presented at 13 weeks with a rapidly developing goiter resulting in severe tracheal compression and overt hypothyroidism (TSH 183 mU/L, fT4 4.2 pmol/L) of recent onset. Respiratory distress was successfully managed with levothyroxine replacement. *DUOX2* analysis revealed he had inherited the known p.G1518S mutation from his mother and a novel deletion of 540 base pairs (c.513+53_818del) from his father. Patients 2 and 3 are siblings who are compound heterozygotes for known mutations (p.M866R[pat]/p.F966SfsX29[mat]) in *DUOX2*, yet presented with greatly discordant phenotypes: the sister had overt hypothyroidism at 14 months (TSH 93 mU/L, fT_4 3.96 pmol/L) but only mild hyperthyrotropinemia at 15 years (TSH 7.22 mU/L, fT_4 8.12 pmol/L) while the brother has lifelong euthyroidism; iodine exposure could not account for this discrepancy. Patient 4, the only one with a positive newborn screening (NBS) result (TSH 22 mU/L), is a compound heterozygote for known mutations (p.P303R[pat]/p.F966SfsX29[mat]); he had mild persistent CH, as typically associated with biallelic *DUOX2* variants. All parents were heterozygous and euthyroid.

Conclusion: The clinical expression of biallelic *DUOX2* variants is very heterogeneous. Patient 1 is the first reported case of DUOX2 deficiency with life-threatening compressive goiter in infancy, the prompt recognition and treatment of which allowed to avoid surgical decompression. Genetic modifiers of DUOX2 deficiency that may account for the wide variation in phenotype between and within pedigrees are being studied.

Fat, Metabolism and Obesity

RFC6.1

Allelic Variation in Key Fitness Genes is Linked with Increased Severity of Obesity in Overweight/obese Youth

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Introduction: Childhood obesity is common and is associated with type 2 diabetes mellitus and heart disease [1]. Obesity mainly arises from an imbalance between energy intake and expenditure, although some children appear to carry a genetic predisposition for weight gain. The ability to sustain physical activity and its potential for health benefits is genetically predetermined. Candidate genes for fitness and muscle strength have been shown to substantially influence muscle function and mass in response to exercise[2]. Whether variations in genetic fitness affect a child's propensity to weight gain, in the setting of obesity, has not been investigated.

We aimed to determine whether there is a genetic predisposition in some obese children that limits their muscle's ability to train and utilise substrates effectively, thereby perhaps increasing their risk of worsening obesity.

Methods: Investigations were performed in the Childhood Overweight BioRepository of Australia (COBRA) study, Australia's largest longitudinal overweight and obese paediatric cohort (RCH Ethics 28081)[3]. DNA for genotyping was extracted from peripheral blood mononuclear cells (n=238; Mean BMI z-score 2.45, SD 0.44). SNP analysis was undertaken on a unique fitness gene panel that included; *ACTN3* rs1815739, *CNDP1* rs2887, *HIF1A* rs11549465, *GALNT13* rs10196189, *PPARGC1A* rs8192678, *RPLP1_GEMIN8P1* rs4776471, *CRHBP* rs1715747) using iPlex chemistry on the Sequenom MassARRAY. Correlation analyses were performed between minor allele prevalence of fitness genes and BMI z-scores, body and truncal fat percentage, waist circumference, blood pressure and accelerometer data. Significance was taken as $p<0.05$.

Results: Genotypes associated with athleticism and fitness were less prevalent in our overweight/obese cohort than in reference population studies (e.g. 1000 genomes project). Minor allele frequency, and therefore a more pro-fitness genotype, was associated with lower body weight and decreased waist circumference in female but not male participants. Increased daily physical activity was observed in participants with pro-fitness genotypes for 4 key genes. Sex dependent variation was also observed in blood pressure measurements between genotypes.

Conclusion: More severely obese children are less likely to exhibit a 'pro-fitness genotype' and are less physically active which may confer a greater risk of further weight gain and cardio-metabolic complications.

References

1. Koskinen J, *et al.:* PMID: 28862940, *J Am Heart Assoc* 2017.
2. North KN, *et al.*: PMID: 10192379, *Nat Genet* 1999.
3. Sabin MA, *et al.*: PMID: 20969745, *BMC Med Res Methodol* 2010.

RFC6.2

IGF-I at Four Months Associates to Visceral and Subcutaneous Adipose Tissue at 7 Years of Age

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Objectives and Study: Insulin-like growth factor I (IGF-I) regulates fetal and infant growth and is influenced by nutrition during infancy. Breast fed children have lower IGF-I levels than formula fed infants and the reason is partly explained by lower levels of protein and higher level of polyunsaturated fatty acids (PUFA) in breast milk compared to formula.

Environmental factors, such as nutrition, have long-lasting influences on hormone secretion and on future metabolic health. Intraabdominal adipose tissue (VAT) is known to be associated with metabolic risk factors.

The aim of this study was to investigate IGF-I at 4 months of age and the association to composition of VAT and subcutaneous adipose tissue (SAT) in children at seven years of age.

Method: 81 children (39 boys, 42 girls) who participated in an ongoing Swedish birth cohort, Halland Health and Growth Study (H^2G Study) were included. The children have been followed regularly since birth with anthropometry and blood sampling. At 7 years of age MRI was performed for quantifying VAT and SAT.

Results: IGF-I at 4 months of age correlated to both VAT ($r = 0.35$, $p = 0.002$) and SAT ($r = 0.35$, $p < 0.001$) at 7 years of age. When adjusting for gestational age and gender, IGF-I at 4 months of age together with weight at 4 months and maternal BMI accounted for 37% of the variation of VAT at 7 years of age (β 0.35, $p = 0.001$, β 0.32, $p = 0.005$, β 0.36, $p < 0.001$ respectively). Likewise, IGF-I at 4 months of age, gender and maternal BMI accounted for 32% of the variation of SAT at 7 years of age (β 0.33, $p = 0.004$, β 0.28, $p = 0.02$, β 0.35, $p = 0.001$), when adjusted for weight at 4 months, gestational age and gender.

Conclusion: IGF-I at 4 months of age predicts VAT and SAT at 7 years of age. This indicates that early programming during the first months of life with growth factors, independently of weight, can influence body composition and possibly cardiometabolic risk later in life.

RFC6.3

Effect of the Melanocortin-4 Receptor Agonist, Setmelanotide, on Obesity and Hyperphagia in Individuals Affected by Bardet-Biedl Syndrome

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Background: Bardet-Biedl syndrome (BBS) causes early-onset extreme obesity and hyperphagia that is hypothesized to arise from leptin receptor dysfunction. Setmelanotide, a melanocortin-4 receptor (MC4R) peptide agonist, has been shown to induce weight loss in individuals affected by other rare genetic obesity disorders resulting from leptin-melanocortin pathway dysfunction upstream of MC4R.

Objective: Report preliminary data on body weight, hunger scores, and safety from a Phase 2 proof of concept study of setmelanotide in individuals affected by BBS.

Methods: Individuals 12 years of age and older with a confirmed diagnosis of BBS are eligible for enrollment in this ongoing study. Setmelanotide was administered daily by subcutaneous (SC) injection with dose titration every 2 weeks (maximum 3.0 mg). Adults losing ≥5kg and adolescents losing ≥4kg during the titration period and maintenance period continued treatment for a maximum of 52 weeks. Body weight, hunger or hyperphagia scores, blood pressure (BP) and heart rate (HR) were assessed at each visit. Skin and physical examination along with metabolic, endocrine, hematologic and pharmacokinetic testing were also conducted.

Results: As of 2 April 2018**,** six individuals (aged 12–61 years, 4 females, baseline weight 124.8±10.6 kg; BMI 45.2±1.1 kg/m^2; both mean ± SEM) diagnosed with BBS (including individuals with biallelic mutations in *BBS1*, *BBS2*, *BBS10* and *BBS12* genes) received setmelanotide. Four of six have been treated between 26-45 weeks. Four individuals demonstrated a mean body weight reduction of 17.7% (range 11.7% to 23.1%) after treatment with setmelanotide, while two patients with BBS did not meet criteria for continuing treatment. Five of six individuals reported greater than 50 percent reductions from baseline in either hunger or hyperphagia scores. Metabolic improvement in either lipids, liver transaminases, and/or glycemic indices was observed in 5 of 6 BBS subjects treated. Overall, setmelanotide was well tolerated; adverse events included mild injection site reactions and increased pigmentation of the skin/nevi. No adverse changes in BP or HR were observed with treatment with setmelanotide.

Conclusions: In this updated preliminary data set in individuals affected by BBS who were treated with setmelanotide, marked reductions in body weight and hunger/hyperphagia scores and the safety profile are consistent with other studies in rare genetic obesity disorders. These findings support the continued evaluation of MC4R agonist therapy in BBS and other rare genetic obesity disorders.

RFC6.4

Functionality and Phenotypic Characteristics of Mutations in the Human Leptin Receptor

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Objective: Merge and standardize the scarce data on molecular and phenotypic findings of mutations in the human leptin receptor (LEPR) gene causing a rare form of severe early-onset obesity.

Methods: We summarized functional and phenotypic traits of LEPR mutations reported in the literature in a structured and comprehensive manner. Additional data was obtained from 6 subjects of our outpatient clinic not reported so far. Functionality of mutations was assessed by reported *in vitro*-, *in silico*- and own analysis considering the type of mutation and clinical manifestations.

Results: In total 57 subjects with 38 distinct mutations in the LEPR were identified. 13 mutations led to a single amino acid change. 25 deletions, duplications, insertions or nonsense mutations result in truncated LEPR proteins. Most mutations occurred in the Fibronectin(FN)-III and FN-III like subdomain of cytokine receptor homology(CRH) 2, none were located in the intracellular or transmembrane domain. *In silico* analysis were reported for 23 mutations. Functional data from *in vitro* experiments were available for 4 mutations, showing residual function in one. Considering clinical phenotype and character of respective mutations, we suspect residual function in 5 additional mutations. Summarizing clinical data, we found severe early-onset obesity, hyperphagia and hypogonadotropic hypogonadism to be cardinal features of a complete loss of LEPR function. In contrast, symptoms like recurring infections, altered growth, developmental delay and metabolic disorders were variable in manifestation but without obvious genotype-phenotype relationship. Only 2 subjects managed to regulate their weight due to an extremely restrictive and controlled lifestyle. Bariatric surgery was performed in 6 subjects and yield in weight loss below expectations. However, bariatric surgery seemed to support pubertal development and fertility.

Conclusion: Our results represent the first structured and comprehensive analysis of 57 subjects with 38 distinct LEPR gene mutations. Complete losses of LEPR function result in severe early-onset obesity, hyperphagia, and hypogonadotropic hypogonadism. Symptoms like recurring infections and metabolic disorders were variable in manifestation, but without obvious genotype-phenotype relationship. Considering clinical phenotype, available functional data and character of respective mutations we assume residual LEPR activity for 6 mutations.

RFC6.5

High-Throughput Untargeted Plasma Metabolomics Unravels Gender Dimorphic Metabolic Trajectories in Naturally Conceived and ICSI Prepubertal Children

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Background: Accumulating evidence has indicated that assisted reproductive technologies (ART) influence the metabolic physiology of the offspring, with a higher predisposition to metabolic disorders. Long-term metabolomic studies that separately consider males and females conceived with intra-cytoplasmic sperm injection (ICSI) *vs*. naturally conceived (NC) children are needed. Previously, we had reported that ICSI-conceived prepubertal girls exhibit significant alterations in their metabolic profiles. In this study, we expand our metabolomic analyses on the effect of ICSI on the metabolic physiology of prepubertal boys and conduct comparative analyses of both genders in NC and ICSI children.

Methods and Results: Blood plasma biochemical and metabolomic analyses of 14 NC and 14 ICSI-conceived boys were acquired and compared with multivariate statistics. NC and ICSI boys clustered separately, similarly to our earlier studies in girls. The most significant differences in metabolite concentrations were sorbitol and three aromatic amino acids (phenylalanine, tyrosine and tryptophan). Gender-based metabolic profile comparison of the two genders revealed that the primary clustering is gender-based rather than way of conception based. Gender dimorphism of the metabolic profile was evident, highlighting the amino acid and lipid metabolism together with the Cori cycle as the main metabolic pathways that are different between prepubertal boys and girls.

Conclusions: High-throughput untargeted metabolomics in combination with conventional biochemical analyses provide a detailed fingerprint of the metabolic physiology in both genders and the epigenetic metabolic aberrations due to ICSI. Both methods indicate a profound effect of gender on the metabolic profile. A better understanding of the mechanisms underlying metabolic sexual dimorphism and adverse effects of ART would provide

insight to improve the management of metabolic diseases and to implement prevention of the long-term effects of ART before they become clinically manifested.

RFC6.6

Effects of Cherry's Extract on Increased Osteclastogenesis in Obese Children

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The accumulation of adipose tissue, especially visceral fat, represents a risk factor for reduced bone mineral density and spontaneous fractures. Several mechanisms have been proposed to explain the complex relationship between adipose tissue and bone. Obesity is associated with the production of inflammatory cytokines both by adipocytes and immune cells which may stimulate bone resorption and reduce bone strength.

Studies *in vitro* and *in vivo* have reported that cherries have anti-inflammatory and antioxidant activity due to high content of polyphenols, expecially anthocianins.

We aimed to investigate the effects of different concentrations of anthocyanins contained in extracts of three cherry varieties (Giorgia, Bigaretta, Ferrovia) on osteoclasts differentiation.

We obtained peripheral blood monuclear cells (PBMCs) from 10 obese children and 10 normal weight controls (mean age 10.8 ± 2.56 years) to evaluate the percentage of osteoclast precursors CD14+CD16+ and to perform cultures of osteoclasts. These cells were grown for about 25 days in the presence/absence of „extracts" of cherry varieties Giorgia, Bigaretta, Ferrovia at different concentrations of anthocyanins (75, 100 μg/ml). Multinucleated mature osteoclasts were identified by histochemical TRAP staining. Gene expression was evaluated by real-time PCR in PBMCs from obese children treated for 24 h with Giorgia, Bigaretta, Ferrovia at 100 μg/ml anthocyanins. The bone mineralization status of the patients was assessed by quantitative ultrasonography (QUS), by measuring BTT-Z score and Ad-Sos-Z-score. A reduction of bone mineral density was found in obese subjects compared to controls ($P < 0.01$). A high percentage of CD14+CD16+ osteoclast precursors was measured in patients compared to controls. It was associated to the spontaneous formation of osteoclasts in PBMC cultures, in the absence of exogenous growth factors, unlike what occured in cultures of controls. This spontaneous osteoclastogenesis seems to be associated with the presence of pro-osteoclastogenic cytokines released from the same cells in culture, such as RANKL and TNFa. Consistently, the treatment with extracts from Giorgia, Bigaretta, Ferrovia determined a dose-dependent reduction in the formation of multinucleated TRAP+ osteoclasts as well as the reduction of the expression of RANKL and TNFa in PBMCs.

Conclusions: These results suggest that the anthocyanins present in the cherry extracts reduce the production of inflammatory cytokines in cultures and therefore the formation of osteoclasts. It can therefore be assumed that if introduced into the diet of obese children these compounds can have health-promoting effects and in particular can improve bone quality.

Fetal, Neonatal Endocrinology and Metabolism

RFC7.1

Next Generation Sequencing Results in 142 Patients with Congenital Hyperinsulinism

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Congenital *hyperinsulinism* (CHI) is a life-threatening disorder characterized by hypoglycemia due to dysregulated secretion of insulin from pancreatic β-cells. Genetic diagnosis is essential for patient management. NGS technologies give the ability to generate large amounts of sequence data in a relatively short amount of time.

We report next generation sequencing (NGS) results in 142 patients (66 boys, 76 girls) with CHI seen at Endocrine Research Centre (Moscow, Russia). The diagnosis of CHI was based on clinical picture (persistent hypoglycemia with onset during neonatal period or early infancy) and confirmed biochemically by the presence of detectable serum insulin during hypoglycemia. NGS was made on Ion Torrent platform and included analysis of the following genes: *GCG, GLUD1, WFS1, HNF1A, GCK, INS, HNF1B, ABCC8, HNF4A, RFX6, PTF1A, NEUROD1, AKT2, ZFP57, INSR, EIF2AK3, PPARG, PAX4, PDX1, GLIS3, KCNJ11, SLC16A1, FOXP3, BLK, CEL, KLF11, SCHAD, GCGR.*

In summary 77 patients (54.2 %) were found to carry pathogenic mutations in the CHI related genes. It was estimated that 65 (45.8 %) probands had one or more mutations in *ABCC8/KCNJ11* genes, 10 patients – in *GLUD1* (7.0 %) and 2 patients in *SCHAD* (1.4 %).

A total of 73 different mutations in 77 patients were found, including 52 *ABCC8* mutations (previously reported 23/52), 11 *KCNJ11* mutations (previously reported 7/11), 8 mutations related to *GLUD1* (previously reported 8/8) and 2 heterozygous mutations in *SCHAD* (not reported before).

There were some frequent mutations found in several patients: a combination of monoallelic c.1096G>A:p.G366R in *KCNJ11* and c.1038C>G:p.Y344X in *ABCC8* was found in 4 children, heterozygous c.G1332T:p.Q444H in *ABCC8* occurred in 3 patients

and heterozygous c.G4516A:p.E1506K in *ABCC8* appeared in 3 patients as well.

Therefore, the use of NGS technologies helped to identify genetic cause of CHI in more than half patients.

RFC7.2

Outcomes of a Quality Improvement Project Integrating Continuous Glucose Monitoring Systems Into the Routine Management of Neonatal Hypoglycaemia

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Introduction: Empirical research studies suggest that continuous glucose monitoring systems (CGMS) are safe and could optimize neonatal hypoglycaemia management. However, they need to be tested within resource-limited, time-constrained clinical practice. CGMS was piloted in our Level 3 Neonatal Intensive Care Unit (NICU) in June 2017. Five key barriers to its effective implementation were identified: 1) Lack of NICU staff confidence in device usage 2) Infant discomfort during device removal 3) Calibration errors 4) Wireless connection disruptions during nursing cares 5) Bruising after device removal.

We designed a quality improvement project that aimed to reduce the number of problems per patient associated with CGMS use in our NICU from 5 to 0 over a one-month period.

Methods: This study was conducted from June-July 2017. Eligible for inclusion were term neonates 1.5kg who were admitted for hypoglycaemia (<2.6mmol/L) within the first 48 hours of life. A New Generation Enlite™ Sensor (Medtronic, Northridge, California) was inserted into five consecutive babies admitted with hypoglycaemia and removed when normoglycaemia was achieved. The sensor transmitted interstitial glucose readings to a Minimed® REAL-Time Transmitter and displayed glucose values every 5 minutes on a MiniMed® 530G System (both Medtronic, Northridge, California). Five „Plan-Do-Study-Act" (PDSA) cycles tested the change intervention.

Results: The first two cycles tested CGMS acceptability and practicality of the device using qualitative feedback from nursing staff and families and quantitative data from the Neonatal Infant Pain Scale (NIPS). Subsequent cycles focused on optimizing the insertion process, trouble-shooting calibration errors, and on promoting NICU staff confidence in device usage. Key recommendations included manually inserting the device on smaller babies, using Duoderm® to reduce subcutaneous bruising, timely insertion of calibration readings to avoid sensor errors, adaption of nursing cares to avoid signal loss, and using near-peer teaching techniques to educate medical and nursing staff on CGMS usage. Bland-Altman analysis comparing point-of-care and sensor glucose readings showed no significant proportional bias

Discussion: PDSA cycles revealed aspects of CGMS use that need to be adapted for its successful implementation in real-life clinical practice. Further studies should assess the potential of CGMS as a decision-making tool in hypoglycaemia management.

RFC7.3

Central Venous Cathether-Associated Thrombosis in Children with Congenital Hyperinsulinism

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Introduction: Congenital hyperinsulinism (CHI) is the most common cause of hypoglycaemia in infancy caused by dysregulated insulin secretion. The management of severe hypoglycaemia often requires the administration of high dextrose-containing fluids through a central venous catheter (CVC). However, CVCs carry the risk of complications including thrombosis. We sought to determine the incidence of CVC-associated thrombosis in patients with CHI and examine associated risk factors.

Methods: Patients with CHI admitted at a specialist treatment centre requiring CVC placement from 2014 to 2017 (n=26) were retrospectively reviewed for the incidence of thrombosis and potential risk factors. Non-parametric tests were used for differences between groups with and without thrombosis.

Results: 5 of 26 (19%) patients with CHI requiring CVC placement for the management of hypoglycaemia developed thrombosis in the CVC, confirmed by ultrasound scanning, giving an incidence of 4.9 thromboses per 1000 CVC days. Thrombosis was identified at a median (range) time of 12 (2-17) days after CVC insertion at age 13 (6-139) days. Mutations in *ABCC8* were detected in two patients who were treated surgically; one was paternally-inherited (focal CHI), and the other was homozygous (diffuse CHI). The remaining three patients with no known mutations were managed with diazoxide. Males were more frequent in those with thrombosis (100% vs. 71%, p=0.29), but there was no difference in the frequency of mutations (40 vs 38%, p=0.94), and the incidence of focal CHI (20 vs 24%, p=0.85) compared to those without thrombosis. Similarly, there was no difference in the maximum concentration (%) of dextrose [20 (12.5-50) vs 20 (10-50), p=0.70] or glucagon infusion (mcg/kg/hour) [15 (3-20) vs 10 (4-25), p=0.54] between the groups with and without thrombosis. The duration (days per patient) of high concentration dextrose (>15%) through CVCs was also similar [12.5 (7-27) vs 15 (2-107), p=0.73], while the duration of CVC placement (days per patient) was marginally less in the group with thrombosis [13 (2-41) v 22 (2-213), p=0.17], indicating earlier CVC withdrawal following thrombosis.

Conclusion: Thrombosis was identified in a clinically relevant proportion of patients with CHI and CVC (19%). No definite association was identified with putative extrinsic risk factors. Intrinsic factors specific to CHI, such as hyperinsulinism, may increase the risk of thombosis development in CHI patients. Our data supports the use of prophylactic anticoagulant therapy in severe CHI.

RFC7.4

Expression of MIR-576-5p in Umbilical Cord as a Novel Biomarker for the Identification of Catch-Up Growth in Small-For-Gestational-Age Infants

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Background: Early catch-up growth, between birth and age two years, in infants born small-for-gestational-age (SGA) is a risk factor for the development of cardiometabolic diseases in adulthood. The basis and mechanisms underpinning catch-up growth in SGA newborns are unknown.

Objectives: We aimed to investigate the catch-up predictive ability of cord blood miRNAs in SGA infants.

Methods: MicroRNA PCR Human Panels were used to study the miRNA profile in umbilical cord tissue of 5 SGA infants with catch-up (SGA-CU), 5 SGA infants without catch-up (SGA-non-CU) and 5 control infants (appropriate-for-gestational-age, AGA). The miRNA with differential expression between the study groups were validated in a cohort of 64 infants (24 SGA-CU, 18 SGA-nonCU and 22 AGA) and correlated with anthropometric and metabolic parameters (weight and height gain, body composition and fat distribution) at 1 and 6 years of age.

Results: The miR-501-3p, miR-576-5p, miR-770-5p and miR-876-3p associated with increased weight, height, weight catch-up and height catch-up at 1 year of age (all $p<0.05$); and the miR-374b-3p, miR-548c-5p, miR-576-5p y miR-99a-5p associated with increased weight, height, waist circumference and renal fat (all $p<0.05$) at 6 years of age. Multivariate analysis showed that miR-576-5p was predictor of weight catch-up ($\beta= -0.474$, $p=0.001$; $R^2=19.1$) and height catch-up ($\beta= 0.459$, $p=0.01$; $R^2=0.652$) at 1 year of age; and waist circumference ($\beta= 0.459$, $p=0.01$; $R^2=0.652$) and renal fat ($\beta= 0.455$, $p=0.03$; $R^2=0.207$) at 6 years of age. *In Silico* studies showed that miR-576-5p participates in the regulation of inflammatory, growth and proliferation signaling pathways.

Conclusion: miR-576-5p could be a novel biomarker for the early identification of catch-up growth in SGA infants. miR-576-5p may also contribute to the regulation of postnatal growth and influence the risk for cardiometabolic diseases associated with postnatal growth.

RFC7.5

Alteration of Renal Corticosteroid Signaling Pathways in Preterm Infants: Neonatal Adaptation and Developmental Programming of Hypertension

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Introduction: Prematurity, a worldwide health issue, is often associated with renal tubular immaturity leading to major salt loss, whose mechanisms remain poorly understood. Moreover, these premature infants are prone to develop hypertension early in adulthood.

Objective: To study the ontogenesis of renal mineralocorticoid and glucocorticoid signaling pathways in preterm infants and to evaluate their respective role during neonatal adaptation and in the emergence of hypertension in adulthood.

Materials and Methods: We have developed a model of prematurity induced by intra-peritoneal injection of O111:B4 lipopolysaccharides at 18 days of gestation in Swiss CD1 mice. Offspring of injected mice, when lipopolysaccharides did not trigger preterm birth, were used as a control to exclude the intrinsic LPS effects. Newborns were sacrificed at various developmental stages (P0, P7 and M6). Blood pressure and heart rate were measured in males at M6 and their plasma steroid profiles were determined using liquid chromatography-tandem mass spectrometry. Renal mRNA and protein expression of major players of corticosteroid signaling pathways were examined using RT-qPCR and western-blot analyses. A second (F2) and third (F3) generations, established by mating prematurely born adult female with wild type males, were also analyzed.

Results: As anticipated, premature newborn mice presented with maladaptation, as revealed by high neonatal mortality (35%), and a lower birth weight compared to controls (1.29±0.21 *vs* 1.46±0.15g, $P=0.0027$). Former preterm males developed hypertension at M6 (123.1±1.43 *vs* 114.5±0.79mmHg, $P<0.0001$). We found a very robust activation of renal corticosteroid target genes transcription at birth in premature mice (*αENaC* (+45%), *Sgk1* (+132%), *Gilz* (+85%)), which was not related to modified expressions of the mineralocorticoid receptor (MR) and glucocorticoid receptor (GR). Such alterations of gene expression were not persistent in adulthood. Interestingly, a significant increased blood pressure was found in the F2 and F3 males, descendants of the preterm group, concomitantly with alteration of renal Sgk1 and Gilz mRNA and protein expressions, despite absence of modifications in MR and GR expression and similar aldosterone and corticosterone plasma levels than descendants from the control group. These results are highly suggestive of trans-generational epigenetic inheritance, mechanisms of which are presently under investigation.

Conclusion: We provide evidence for tissue-specific alterations of the renal corticosteroid signaling pathways induced by prematurity, with a trans-generational transmission. These studies should allow better understanding of prematurity-related defects, leading hopefully to better management of premature infants from birth to adulthood.

RFC7.6

Assessment of Pituitary Stalk Anatomy by T2 DRIVE Without Gadolinium in Pituitary Diseases

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Objectives: To evaluate the potential diagnostic role and sensitivity of T2-weighted DRIVE sequence in pituitary stalk (PS) identification and measurements in patients with hypothalamic-pituitary disorders. The degree of agreement and reliability between standard pre- and post-contrast T1-weighted images and T2-DRIVE will be tested in a large group of patients with pituitary dysfunction.

Design: We searched for pituitary MRI reports using „T2-DRIVE" in our Institutional database between 2006 and 2015. Among 135 eligible patients, 102showed eutopic posterior pituitary(PP)gland and 33showed „ectopic"PP(EPP).

Methods: In patients with eutopic PP, two readers measured the PS size in the sagittal plane, drawing a line perpendicular to the axis of the major stem at three levels: proximal, midpoint, and distal on pre- and post-contrast T1-weighted and on T2-DRIVE images. The pituitary stalk was assessed on pre-contrast T1 and T2-DRIVE sequences in those with EPP. Cohen's kappa coefficient was then used to evaluate the chance-correct concordance for the case between two different sequences that are expressed in the form of categorical data.

Results: The agreement between the measurements of the two readers showed that the ICC in the T2-DRIVE sequence was 0.96 at the proximal level of the PS, 0.99 at the midpoint level and 0.97 at the distal level. In pre-contrast T1-weighted sequence, the ICC was 0.89 (proximal part), 0.85 (midpoint), and 0.76 (distal part). Finally, on the post-contrast T1, the ICC was 0.88 at the proximal, 0.87 at the midpoint and 0.79 at the distal PS levels. A significant difference between the ICC on the T2-DRIVE and the pre-and post-contrast T1-weighted sequences was demonstrated. The percentage of PS identified by T2-DRIVE in EPP patients was 72.7% compared to 30.3% of T1 pre-contrast sequences. A significant association was found between the visibility of PS on T2-DRIVE and the height of AP.

Conclusion: T2-DRIVE sequence is precise and reliable for the evaluation of PS size and the recognition of PS abnormalities; the use of gadolinium does not add significant information.T2-DRIVE images allow for a better diagnosis of pituitary gland and PS disorders. A sagittal T2-DRIVE sequence without gadolinium takes less than 3 minutes to acquire, and its inclusion into routine sellar MRI protocols is recommended as a valid alternative to post-contrast imaging which - also in view of safety issues - may be avoided in subjects with pituitary disorders without evident sellar/suprasellar mass lesions.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology

RFC8.1

Male Fertility Genes Located in Y-Chromosomal Regions Display Differential mRNA Profiles in Response to GnRH Treatment of Cryptorchidism-Dependent Infertility

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Background: Undescended testes in patients with defective mini-puberty contain germ cells that fail to differentiate normally into Ad spermatogonia and ultimately leads to infertility. Six months treatment with the gonadotropin-releasing hormone GnRH increases luteinizing hormone and testosterone secretion and rescues fertility in the majority of pathological cryptorchid testes. Several Y chromosomal genes in the male-specific Y region (MSY) are essential for spermatogenesis, testis development and function, and were associated with azoospermia, infertility and cryptorchidism.

Aim of the study: In this study, we analyzed the expression of MSY genes in testes with Ad spermatogonia (low infertility risk patients) as compared to testes lacking Ad spermatogonia (high infertility risk) before and after curative GnRH treatment.

Patients and Methods: We selected 15 patients with isolated cryptorchidism, based on histological results, and divided them into 2 groups. Seven belonged to the Ad– (lacking Ad spermatogonia) and 8 to the Ad+ (presenting Ad spermatogonia) group. The patients had a median age of 18.5 months (range 8–59 months) and were age matched. Data from Ad– bilateral cryptorchid boys treated with GnRH (10 μg intranasally on alternate day) following the first orchidopexy (surgery) (4 patients) were retrieved from an ongoing randomized study. Initial biopsies revealed no Ad spermatogonia, indicating defective mini-puberty (Ad– group). The second testis was managed by orchidopexy and biopsied 6 months after the initial surgery. Thus, results from 21 biopsies were compared. RNA sequencing data were used to analyze manually selected marker genes. Only genes with at least one read per million, in at least two samples, were included. P values and fold-changes were calculated for the treatment factor and differentially expressed genes were defined as those displaying a false discovery rate (FDR) <0.05 and an absolute change in expression of at least two-fold.

Results: We found 21 genes that are significantly differentially expressed between Ad- and Ad+ samples (FDR<0.05). Furthermore, we identified 23 differentially expressed genes when we compared GnRH treated and untreated Ad- patient samples, all of which showed significant differences (FDR<0.05). For clarity, this analysis focusses on protein-coding genes in the MSY region, excluding the Y-chromosomal pseudoautosomal and recombining regions.

Conclusions: Our findings implicate Y-chromosome genes known to be important for spermatogenesis in the curative hormonal treatment of cryptorchidism-induced infertility. Of note, our observation support data of the global conservation of the epigenetic pattern associated with the sequences of the same origin (X-transposed, X-degenerate and ampliconic)

RFC8.2

High Mobility Group Box 1 (HMGB1) is Increased in Adolescents with Polycystic Ovarian Syndrome (PCOS) and Decreases After Treatment with Myo-Inositol in Combination with A-Lipoic Acid (MYO+ALA)

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PCOS treatment in adolescence should aim at improving ovarian function, based on the pathophysiology of this condition. We previously described in cystic fibrosis and then in the PCOS an increase in HMGB1, secondary to reduced cystic fibrosis transmembrane conductance regulator (CFTR) expression in the ovary, associated with insulin resistance and inflammation that both characterize PCOS. Inositols and ALA derivatives are considered a good therapeutic option for their possible positive effects on insulin sensitivity, androgen reduction and ovulation rhythm. The aim of this study was to verify changes in HMGB1 serum concentrations in adolescents with PCOS treated with MYO+ALA, in addition metabolic and other endocrine values were evaluated also.

Twenty-five adolescents (CA:16.46±0.57 years; BMISDS:1.07±0.24; hirsute N.19; with amenorrhea: N.6; with oligomenorrhea: N.11; regular cycles: N.8) affected by PCOS (Rotterdam criteria) and 15 controls matched for age and BMI (CA: 18.18 10; ± 0.84years; BMISDS: 0.4 ± 0.36) all with a gynecological age of at least 2 years were enrolled. In all subjects glycemia, insulin, hepatic and renal function, TSH, PRL, LH, FSH, E2, progesterone, 17-OHP, delta-4-androstenedione, total testosterone, triglycerides, total and fractional cholesterol, IGF-I, and uric acid were assayed. HOMA-IR and the TG/HDL-C ratio were calculated. Waist circumference (WC) and the WC/height ratio were measured. Ovarian and uterine volumes, number of follicles/ovary, uterus body/neck ratio, and uterus volume were evaluated by pelvic ultrasound. Patients were treated with MYO+ALA for 3 months twice a day and for further 3 months, once a day. HMGB1 was assayed using a specific ELISA kit (SHINO-TEST). Statistical analysis was performed using SPSS v23.0.

HMGB1 was increased in PCOS compared with controls (18.63 ± 5.12 vs 4.51 ± 1.10 ng/ml; p <0.005). HMGB1, in PCOS, correlated with E2 (r= -0.40; p= 0.04), total testosterone (r= -0.41; p= 0.05), IGF-I (r= -0.48; p= 0.04), and marginally with TG/HDL (r= -0.43; p= 0.057). After 6 months therapy, HMGB1 decreased to 3.14 ± 0.74 ng/ml, similar to concentrations measured in controls. Treatment reduced also, although not significantly, the HOMA-IR index, FSH and 17-OHP. No other changes were detected.

Circulating HMGB1 is increased in PCOS adolescents, correlates with some parameters of ovarian function and IGF-I. MYO+ALA treatment was effective over a 6 month period in normalizing HMGB1, likely reducing inflammation and improving insulin sensitivity.

RFC8.3

Pharmacological Treatment of Adolescent Polycystic Ovary Syndrome (PCOS) According to the 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS

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The treatment of Polycystic Ovary Syndrome (PCOS) during adolescence is controversial.

The aim of the international evidence-based guideline was to promote accurate diagnosis, optimal consistent care, prevention of complications and to improve patient experience and health outcomes.

Extensive international health professional and patient engagement informed the priorities and core outcomes for the guideline. Internationally nominated panels including women with PCOS and a multidisciplinary team of health care professionals (across 44 societies-71 countries), researchers and an evidence synthesis team developed the guideline funded and led by Australia.

The evidence-based guideline development followed international best practice involving 60 systematic and narrative reviews and applying full Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework to reflect quality of the evidence and considered feasibility, acceptability, cost, implementation and the strength of recommendations.

Principles of treatment:

- Consideration of the individual's personal characteristics, preferences and values is important in recommending pharmacotherapy.
- Combined oral contraceptive pill (COCP), metformin and other medications are generally off label for PCOS. However off label use is evidence-based and is allowed in many countries. Where is it allowed, health professionals should inform pa-

tients and discuss the evidence, possible concerns and treatment side effects.
- Antiandrogens must be used with effective contraception.
- Holistic approaches are required and pharmacotherapy in PCOS should be considered alongside education, lifestyle (behavioural, diet and exercise) and other options including cosmetic therapy and counselling.

In Adolescents, evidence based recommendations for PCOS pharmacological treatment include:

1) COCP
- COCP alone should be considered in adolescents with a clear PCOS diagnosis or those who are deemed "at risk" of PCOS for management of clinical hyperandrogenism and/or irregular menstrual cycles.
- Specific types or doses of progestins, estrogens or combinations of COCP cannot currently be recommended with inadequate evidence in women and adolescents with PCOS and practice should be informed by general population guidelines.
- COCP in combination with metformin could be considered in adolescents with PCOS and BMI >25kg/m^2.
- In combination with COCP, antiandrogens should only be considered in PCOS to treat hirsutism, after 6 months or more of COCP and cosmetic therapy have failed.

2) Metformin in addition to lifestyle, could be considered in adolescents with a clear PCOS diagnosis or with symptoms of PCOS before diagnosis is made.

3) Inositol should be considered an experimental therapy for women with PCOS.

These guidelines are subject to extensive translation including a personalised patient app and certified online health professional training programs.

RFC8.4

Establishing Age, Sex, and Method Related Reference Ranges for Anogenital Distance - A Marker of *In Utero* Androgen Action

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Background: Anogenital distance (AGD) is an indicator of androgen action *in utero*. Reduced AGD has been found in males with hypospadias, cryptorchidism, low semen quality and infertility. Its usefulness as a clinical marker in patients with Disorders of Sex Development (DSD) is currently being investigated. However, detailed age, sex and method related reference ranges do not exist. Whether individual (body-size-adjusted) AGD is stable postnatally also remains to be elucidated.

Objective: 1) To create age, sex and method-related reference ranges for both 'short' (anus-scrotum/fourchette (AGDas/f) and 'long' (anus-penis/clitoris (AGDap/c) measurement techniques for AGD. 2) To evaluate individual longitudinal changes of AGD in young children.

Method: The International AGD Database contains a total of 7703 AGD examinations performed on 3623 healthy children aged 0-26 months. Reference ranges for AGDas/f (TIDES and Cambridge method) and AGDap/c (Cambridge) were generated using the Lambda-Mu-Sigma (LMS) method. Individual dynamics of AGD was evaluated by longitudinal observations (146 individuals, 488 observations) of AGD and adjusting for body size (length, weight, BMI and BSA).

Results: We present age-, sex- and method related reference ranges for AGD. E.g. the short AGD in boys (AGDas, TIDES method) increased from birth (24.3 ± 3.9 mm (mean ±2 SD)) to 4 months of age (36.3 ± 5.8 mm) after which it was relatively stable until 20 months. In boys, individual short AGD (AGDas, TIDES method) was stable when adjusting AGD (mm) per body length (cm), BMI (kg/m^2) or body surface area (m^2) from birth to 14 months of age (mean coefficients of variation (CV) of 7.9%, 8.2% and 9.6%, respectively). Similarly, in girls, short AGD (AGDas, TIDES method) was stable from birth to 14 months when adjusting AGD (mm) per body length (cm) and BMI (kg/m^2) (mean CVs of 8.3% for both).

Conclusion: We provide age, sex and method related reference ranges for AGD. Intra-individual AGD adjusted for body size remained stable during infancy which supports AGD as a prenatally determined marker. Reference ranges could be used for future epidemiological research and may have a clinical application when evaluating prenatal androgen action in DSD patients.

RFC8.5

Latest Progress in Tissue Engineered Urethral Regeneration. From Rabbit to Dog, A Step from Human Clinical Trial for Surgical Treatment of VSD (Variation of Sex Development)

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Introduction: Treatment of patients with VSD (Variation of Sex Development), in particular severe hypospadias, is associated with high rate of post-operative complications using current surgical procedures. This leads to a high rate of re-operation in an already emotionally complicated situation. We improved the tissue engineered acellular tubular collagen scaffolds that showed promising results in the rabbit model to implant it to a dog model. This FDA approved new version accomplishes the ethical criteria to establish human clinical trial.

Methods: The two layered collagen based tube used initially in the rabbit model was replaced by a single layered FDA approved

bovine collagen tube with better mechanical properties and enhanced functional outcome. This was achieved, by varying the collagen density and fibre distribution. Our previous study in rabbits showed regeneration in a 2 cm long acellular graft. In the present study, 4cm tubular urethral grafts were implanted in 9 weight matched stray dogs. An endoscopic examination of the urethra and a contrast voiding cysto-urethrography was done at time of euthanasia. The constructs were all acellular, potentially off-the-shelf.

Results: The initial 2 dogs from the pilot study had no macroscopic nor functional complications on the contrast voiding cysto-urethrography, were euthanized at 2 months post-surgery and the cystoscopic evaluation showed endoluminal regeneration in the total lenght of the graft. Histology and immuno-histochemistry analysis showed regeneration of the implanted site. 7 dogs are currently doing well after operation. No signs of stenosis nor fistula observed after one-year post implantation. They are kept for long term analysis to evaluate the occurrence of late complications as observed after human surgery with current procedures.

Conclusion: This off the shelf graft easy to handle for the surgeons, with high regenerative capacity, safe and cost effective is ideal for urethroplasty. We have shown success using an acellular platform for urethroplasties of 4cm. The data generated from this study was used for submission for human clinical trial application. These procedures are planned to start at the end of 2018.

Further studies, using the same general concept, are necessary to show similar results in vaginal reconstruction.

RFC8.6

Metabolic Profile of Young Adult Transgender Persons Who Started Gender Affirming Treatment in Their Adolescence

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Purpose: Transgender adolescents are treated with gonadotropin-releasing hormone analogues (GnRHa), followed by the addition of gender-affirming hormones. Since during puberty the body reaches maturation, concerns have been risen that the treatment may have negative outcome later in life. The aim of this study is to determine whether treatment with GnRHa and subsequent addition of hormones results in a more atherogenic profile than peers at the age of 22.

Methods: This retrospective study included 71 young adult transwomen (birth-assigned boys) and 121 young adult transmen (birth-assigned girls) diagnosed with gender dysphoria (DSM-IV TR) in their teens. Treatment included solely GnRHa from the age of 12, the addition of hormones from the age of 16, and gonadectomy from the age of 18 with cessation of GnRHa. At the start of GnRHa treatment, at the start adding hormones, and at the age of 22 body mass index (BMI) was measured and a fasting state blood sample was taken to examine insulin sensitivity (HOMA-IR) and lipids. Standard deviation scores (SDS) were calculated to compare values with reference data from male peers (cismen) and female peers (ciswomen) which were retrieved from literature. Informed consent was signed.

Results: Duration of GnRHa monotherapy was 2.1 years (median, inter quartile range (IQR) 1.0-2.8) in transwomen and 1.0 years (median, IQR 0.5-2.9) in transmen. Combination of GnRHa and hormones lasted 3.1 years (median, IQR 2.5-3.6) in transwomen and 2.4 years (median, IQR 2.0-3.1) in transmen. Transwomen at 22 had, in comparison with ciswomen, SDS of +0.2 (95% confidence interval (CI) -0.1;+0.5) for BMI, -0.4 (95% CI -1.9;+1.1) for HOMA-IR, -0.4 (95% CI -0.7;-0.1) for total cholesterol, +0.8 (95% CI +0.5;+1.2) for HDL-C, -1.0 (95% CI -1.3;-0.6) for LDL-C, and +0.2 (95% CI -0.3;+0.7) for triglycerides. In comparison with cismen, SDS in transmen were +0.3 (95% CI +0.2;+0.5) for BMI, -0.6 (95% CI -1.0;-0.2) for HOMA-IR, +0.1 (95% CI -0.2;+0.4) for total cholesterol, +0.3 (95% CI +0.1;+0.4) for HDL-C, -0.1 (95% CI -0.4;+0.2) for LDL-C, and +0.1 (95% CI -0.2;+0.4) for triglycerides.

Conclusion: At the age of 22, the metabolic profile of transwomen is even or less atherogenic than in female peers. Transmen had a higher BMI, and a lower insulin resistence than cismen with a comparable lipid profile.

Pituitary, Neuroendocrinology and Puberty 1

RFC9.1

Clinical and Genetic Features of Central Precocious Puberty Associated with Complex Phenotypes

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Background: Idiopathic central precocious puberty (CPP) is mostly described as an isolated entity. A few studies have shown its association with clinical syndromes and rare cases of chromosomal abnormalities.

Objective: To clinically characterize patients with CPP, pointing out prevalent associated conditions and phenotypes.

Patients and methods: One hundred and forty-five patients with idiopathic CPP were retrospectively evaluated. All patients had clinical follow up at the outpatient Endocrinology Division from the Sao Paulo University hospital. Patients were assessed by at least 3 experienced pediatric endocrinologists. A comprehensive phenotypic characterization was performed, including metabolic

and hormonal studies. All patients had normal brain magnetic resonance imaging and were excluded for pathogenic variants in CPP-genes (*KISS1*, *KISS1R*, *MKRN3* and *DLK1)*. Whole-exome sequencing and/or genomic microarrays were performed in a subset of the cases.

Results: Twenty-six patients (17%) (23 girls, 3 boys; 17 sporadic, 9 familial) were identified as presenting with CPP and at least 2 additional features and/or conditions, characterizing complex phenotypes. In this group of patients with complex phenotypes, mean age at puberty onset was 6.3 yr (±1.9) for girls and 7.9 yr (±0.1) for boys. At first visit, mean chronological age was 8.3 yr (±2.6), mean height SDS was 0.4 (±1.1), mean target height was -0.7 (±0.9), mean BMI SDS 1.2 (±1.1), and mean bone age advancement was 1.8 yr (±1.4). All patients had pubertal baseline LH level, pubertal GnRH-stimulated LH level, or both. There was a wide phenotypic spectrum. The most prevalent clinical features described were as follows: overweight or obesity at first visit (n=15), born small for gestational age (n=10), learning difficulties/intellectual disability/autistic spectrum (n=7), short stature (n=7), motor and/or speech delay (n=6), high palate (n=6), acanthosis nigricans (n=5), and hyperinsulinemia (n=5). Less prevalent manifestations were non-specific dysmorphic facial features, impaired fasting glucose/early onset type 2 diabetes and congenital anomalies. Two patients were previously molecularly diagnosed with rare syndromes with a high CPP prevalence: a boy with a maternal uniparental disomy of chromosome 14 (Temple syndrome) and a girl with a 7q11.23 microdeletion syndrome (Williams syndrome). Moreover, three girls with disproportional stature were diagnosed with deletions in *SHOX* gene region.

Conclusion: CPP might be associated with additional clinical features and conditions, characterizing complex phenotypes with distinct genetic abnormalities.

RFC9.2

Novel Variant in *GNRHR* Gene Regulatory Region in a Pedigree with Maternally Inherited Precocious Puberty

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Background: Gonadotropin-releasing hormone (GNRH) and its receptor (GNRHR) are central regulators of puberty. Loss-of-function mutations of the GNRH-GNRHR signaling pathway are associated with congenital hypogonadotropic hypogonadism, but no mutations were reported so far in patients with central precocious puberty (CPP). Animal data demonstrate the importance of microRNAs in pubertal timing regulation. Among others, miR200b regulates *Gnrh1* gene expression in GnRH neurons and *Lhb* gene expression in gonadotrophs through transcriptional regulation of the transcription factor Zeb1.

Objectives: To identify genetic causes of maternally inherited CPP.

Population and methods: Whole genome sequencing of 8 family trios affected with CPP, demonstrating maternal inheritance pattern, was performed. A family trio analysis approach was utilized as a first tier analysis to generate a set of potential causative genetic variants inherited in the autosomal dominant pattern. The minor allele frequency threshold for known variants was set at 0.2%, all variants exceeding this value were excluded from further analysis. Genetic variants with coverage >10x were retained and analyzed with Variant Studio 3.0 software. Identified candidate variant and its family segregation were verified by Sanger sequencing. By targeted approach, coding and regulatory regions and copy number variants (CNV) of 398 genes reported to be associated with age at menarche by genome-wide association studies were analyzed for rare variants. In silico tool miRIAD was used to predict miRNA seed regions.

Results: The average coverage of each genome was 38x and around 3.8M SNVs and InDels, 5k SVs and 600 CNVs were detected on average per single sample. In a single pedigree, a variant in 3'untranslated region of *GNRHR* gene segregating with CPP, NM_000406.2:c.*1509G>A, was identified. The variant was not reported in the gnomAD database; furthermore, it is in the predicted seed region of miR200b. The proband carrier was diagnosed with CPP at the age of 6,5 years with breast stage 2-3, advanced bone age, normal weight, height at 97th percentile, increased basal and peak luteinizing hormone (LH). Her mother had menarche at 9 years.

Conclusions: With this preliminary result, we hypothesize deranged regulation of *GNRHR* mRNA translation by miR200b influences pubertal timing in the affected pedigree. Further investigation is planned to test the presented hypothesis. If confirmed, our result would be not only the first evidence of implication of GNRHR in familial CPP but also an evidence of a novel biologic mechanism of regulation of pubertal timing at the level of gonadotrophs.

RFC9.3

What Is the Best Parameter to Decide the Initial Dose of Depot Leuprolide Acetate in Girls with Idiopathic Central Precocious Puberty?

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Introduction: Formulations and doses of GnRH analogues used to treat idiopathic central precocious puberty (iCPP) may vary with clinician preference or local approvals. Aim of this study is to define factors that affect initial depot leuprolide acetate (LA) dose which suppress hypothalamo-pituitary-gonad (HPG) axis in girls with iCPP.

Methods: A total of 220 girls receiving LA for iCPP were included. LA is started in the dose of 3.75 mg/28 days, and suppression is examined using GnRH test at the 3rd month of treatment. Dose of LA is increased to 7.5 mg/28 days in those who fail the test (peak LH>2 IU/L). Higher dose is similarly tested for suppression of HPG 3 months later. We retrospectively compared clinical and hormonal characteristics of the two populations whose HPG axis was suppressed with low vs high dose of LA. ROC curves were used to determine thresholds for factors (age, body weight[BW], BMI, BMI-SDS, basal LH and estradiol, peak stimulated LH) with an impact on the suppressing dose of LA. We analyzed whether thresholds differentiate the two populations with low or high dose LA, using univariate logistic regression. Pubertal stages were grouped into early (Tanner 2&3) vs advanced (Tanner 4 &5), and impact of pubertal stages were also analyzed. Significant factors in univariate analysis were reevaluated in multiple logistic regression.

Results: Peak stimulated LH in 88.6% of the patients was <2 IU/L under treatment with 3.75mg LA. Age did not differ between the two different dose populations. The best threshold values that differentiate the two doses were 36.2kg for BW (AUC:0.934), 20.7kg/m^2 for BMI (AUC: 0.964), +1.64 for BMI-SDS (AUC:0.914), 1.5 mIU/mL for basal LH (AUC:0.71), 41pg/ml for basal estradiol (AUC:0.898), 17.6 mIU/mL for peak stimulated LH (AUC:0.710)(p<0.001). Univariate analysis indicated BW, BMI and BMI-SDS as well as advanced stage of puberty were associated with higher dose of LA (p <0.001, <0.001, <0.001, 0.02, respectively). Basal LH, estradiol and stimulated LH peak did not differentiate necessity for low or high dose. Multiple logistic regression showed that BW, BMI, and BMI-SDS above the thresholds indicated requirement of high dose LA(p<0.001).

Conclusion: Low dose monthly injections of LA is an effective treatment in majority of girls with iCPP, however higher initial dose may be preferred in patients with BW≥36.2kg or BMI≥20.7kg/m^2 for effective suppression of HPG axis.

RFC9.4

REplacement of MAle Mini-Puberty in Neonates and Children with Micropenis and Cryptorchidism Due to Hypogonadotropic Hypogonadism. Results of the "REMAP" Study ISRCTN13007297

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Background: Hormonal replacement in boys with congenital Hypogonadotrophic Hypogonadism (HH) as well as hormonal repair of bilateral cryptorchidism and micropenis remain a challenge in pediatric endocrinology.

Methods: In the «REMAP» study ISRCTN13007297 eight neonates and infants, all with bilateral cryptorchidism in intra-abdominal position and micropenis (≤2 cm), with absence of neonatal male-mini puberty were treated for 3 months with daily subcutaneous injections of the recombinant LH 75 plus FSH 150 IU preparation (Pergoveris®) from 2009-2018. One had CHARGE syndrome diagnosed before choanal atresia. Three had non-syndromic and one syndromic Kallmann syndrome diagnosed in the neonatal period. Two had septo-optic dysplasia with panhypopituitarism and one aplastic pituitary all diagnosed in the neonatal ICU before symptomatic hypoglycemia and/or cholestatic jaundice.

Results: Median LH and FSH, from undetectable reached high normal levels 6.4 IU/L and FSH supranormal levels 86 IU/L. Inhibine b and AMH from subnormal, reached high normal levels: median 241 pg/ml and 1034 pmol/L respectively. Testosterone levels increased from undetectable to a median of 2.20 ng/ml. In all cases testes descended in scrotal position by the end of the 1st in two, 2nd in three and 3rd month in three patients with a volume ranging between 1.5 and 2.5 ml. Penile length increased to a median of 4.3 cm In one case with septo-optic dysplasia one of the two testes needed surgical stabilization as 6 months after completion of treatment it regressed in low inguinal position. The same boy needed a supplementary treatment with 3 monthly I.M. injections of 50 mg testosterone enanthate increase penile length from 3.5 to 5 cm (50th percentile for age). In all cases with a follow-up up to 8 yrs testes have slightly regressed to 0.5–1.5 ml but are still in scrotal position. During therapy, all infants seemed to have initiated catch-up growth. All testes had a normal ultrasonography after treatment completion. None presented any adverse events or reactions local or systemic.

Conclusions: In our series, the total dose administered to each patient was 6,750 IU of LH and 13,500 IU of FSH, analogous to that of Bougneres et al. JCEM 2008;93:2202-5, which is the work of reference. The proposed regimen mimics neonatal male mini puberty successfully repairing micropenis and cryptorchidism in HH. This strategy corrects genital hypotrophy, restores testicular endocrine function, and may improve the response to future treatments intended to restore fertility.

RFC9.5

Non-Isolated Central Precocious Puberty: Prevalence of Brain Lesions and Other Associated Disorders

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Background: Non-idiopathic central precocious puberty (CPP) is caused by acquired or congenital hypothalamic lesions visible on magnetic resonance imaging (MRI), or associated with

various complex genetic and/or syndromic disorders without visible lesions on MRI. We investigated the different types and prevalences of non-isolated CPP phenotypes in a large group of consecutive patients with CPP.

Methods: This observational cohort study included all patients identified as having non-isolated CPP in the database of a single academic pediatric care center over a period of 11.5 years. Patients were classified on the basis of MRI findings as having CNS hypothalamic lesions or complex syndromic phenotypes without structural lesions of the hypothalamus.

Results: In total, 63 consecutive children (42 girls and 21 boys) with non-isolated CPP were identified. A broad spectrum of diseases were detected, and the hypothalamic lesions visible on MRI (n = 28; 45% of cases) included hamartomas (n = 17) either isolated or with an associated syndromic phenotype, optic gliomas (n = 8) with or without neurofibromatosis type 1 (NF1), and malformative lesions (n = 3) with interhypothalamic adhesions (IHA) (n = 2), isolated or associated with syndromic CNS midline abnormalities (optic nerve hypoplasia, ectopic posterior pituitary), or arachnoid cyst (n = 1). Patients with non-structural hypothalamic lesions (n = 35; 55% of cases) included individuals with narcolepsy (n = 9), RASopathies (n = 4), encephalopathy or autism spectrum disorders (n = 11) and other chromosomal or molecular disorders (n = 11), such as known syndromes associated with CPP (William-Beuren, Russell-Silver, Temple, Kabuki), or other abnormalities involving chromosomes 2, 9, 11, 13, 21 and X.

Conclusion: Our findings suggest that a large proportion (55%) of patients with non-isolated CPP may display complex disorders without structural hypothalamic lesions on MRI. Our findings provide no direct evidence concerning the etiology of this association, but have important clinical implications for management, as they highlight the need for appropriate careful management with a view to identifying and treating CPP early in patients with such disorders, which may improve long-term outcomes. Future studies should explore the pathophysiological mechanisms underlying CPP in these disorders.

RFC9.6

Can Neuroimaging Predict Endocrine Morbidity in Congenital Hypothalamo-Pituitary (H-P) Disorders?

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Background: Few studies have described the phenotypic spectrum of Septo-Optic Dysplasia (SOD). The aim of this study was to evaluate the range of H-P structural abnormalities and the endocrine morbidity of children with SOD and related disorders.

Methods: Retrospective longitudinal single centre study of children with SOD (n:171), Multiple Pituitary Hormone Deficiency (MPHD) (n:53) and Optic Nerve Hypoplasia (ONH) (n:35).

Results: Of SOD patients, 39/171 (23%) did not develop hypopituitarism over a median (25^{th},75^{th} centiles) follow-up of 6.20 (3.41, 8.06) years, although 73% had a small anterior pituitary (SAP). Half of patients with ONH had SAP, but preserved pituitary function at 10.22 (5.96, 12.98) years of follow-up. Compared to SOD, MPHD were significantly more likely to manifest anterior pituitary deficiencies and to develop these earlier [Hazard Ratio (HR) 0.28 to 0.63], with a higher prevalence of Ectopic Posterior Pituitary (EPP) (80% vs 41.6%; p<0.0001) and Pituitary Stalk Interruption Syndrome (PSIS) (46.9% vs 29.5%; p=0.03). Diabetes Insipidus (DI) (22% vs 5.4%; p<0.006) and Posterior Pituitary Absence (PPA) (21.6% vs 6%; p<0.02) were more frequent in SOD. MPHD developed the first deficit earlier [HR 0.616 (0.44, 0.86); p=0.0044]. The time to first deficiency was significantly associated with the number of pituitary deficits that subsequently developed [HR 1.59 (1.36, 1.85)] and with the presence of EPP [HR 2.11 (1.41, 3.15)] and PPA [HR 2.54 (1.53, 4.21)], in both groups. In SOD only, there was an association between Pituitary Stalk Absence (PSA) and ACTH, GH and TSH deficiencies, as shown by the interaction HR of 3.02 (1.16, 7.84), 2.7 (1.10, 6.61) and 3.04 (1.23, 7.56), respectively. Among DI patients, 6/26 (23%) SOD and 3/5 (60%) MPHD had a normal PP and 3/26 (11.5%) SOD and 1/5 (20.0%) MPHD had EPP. Among patients without DI, 18/128 (14.1%) SOD and 2/45 (4.4%) MPHD had PPA. Unusual MRI abnormalities (pituitary enlargement or pituitary stalk thickening) were documented in SOD only.

Conclusions: SOD patients present with a wide spectrum of radiological H-P abnormalities and with heterogeneous endocrine phenotypes, whilst MPHD tend to develop multiple anterior pituitary deficits at early stages of life with a higher prevalence of EPP and PSIS. PSA is associated with the development of specific anterior pituitary deficits in SOD only. SAP and PPA have low predictive value for the development of anterior and posterior pituitary deficits. MRI findings can predict the evolution of endocrine deficits only to some extent, hence life-long surveillance is essential in all groups.

Late Breaking

RFC10.1

Patients with GH Insensitivity and IGF-1 Resistance Harbour Copy Number Variants Causing a Silver-Russell-Like Phenotype

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Introduction: Our Centre is an international referral centre for genetic analysis of children with short stature (SS) and features of GH/IGF-1 resistance. Following candidate gene and whole exome sequencing, diagnoses for ~50% patients remained elusive. Copy number variation (CNV) has not previously been investigated in GH/IGF-1 resistance and we hypothesised that CNVs contribute to the phenotype in our undiagnosed cohort.

Experimental design and methodology: CGH was performed with oligonucleotide array using ~60,000 probes in 60 patients (38M, mean age 7.0yrs, range 1.1-16.5) mean height SDS -3.87 (range -1.58 to -7.44).

Results: We identified CNVs in 10/60 (17%) patients (Table 1), mean height SDS -3.7 (range -1.6 to -5.7). Interestingly, patients 1-8 had features of Silver Russell Syndrome (SRS). Due to clinical suspicion of SRS, patients 1, 5 and 7 had undergone SRS testing (11p15LOM and UPD(7)mat) which were negative.

Classification 3= Variant uncertain pathogenicity, 4= Likely pathogenic, 5= Predicted pathogenic. NH-CSS, Netchine-Harbison SRS Clinical Scoring System (3/6 plus recognised genetic change or 4/6 clinical features alone recommended for SRS diagnosis).

Conclusion: Our patient cohort was enriched for low frequency CNVs. 8/10 of these patients had features of SRS. Consistent with previous reports, the SRS phenotype in our patients with CNVs appears milder than classic cases due to 11p15LOM or UPD(7) mat. Our study is the first to report CNVs in patients with GH/IGF-1 resistance and contributes to the emerging SRS-like phenotype. Our findings emphasise the importance of CNV testing in SS patients, especially those with SRS features.

Table 1. Copy Number Variants identified in our patients (for Abstract no RFC10.1)

Patient	Age (years)	Height SDS	Clinical details	CNV	CNV Class	NH-CSS criteria
1	12.8	–3.6	Triangular face, high arched palate, feeding difficulties	1q21 del	4	2/6
2	10.1	–1.6	Feeding difficulties, dyslexia.	1q21 del	4	2/6
3	9.1	–3.7	Clinodactly, feeding difficulties.	1q21 del	4	3/6
4	11.3	–5.1	Triangular face, long lashes	12q14 del	5	2/6
5	1.9	–5.7	Low set ears, triangular face, delayed motor development	7q21 del, 7q31 del, 7q31 del	4, 3, 5	2/6
6	14.4	–2.7	No dysmorphic features	7q21 dup, Xp22 dup	3, 3	2/6
7	2.8	–4.9	Triangular face, frontal bossing, feeding difficulties	15q11 del	4	3/6
8	2.7	–2.0	Adrenal insufficiency	7q36 dup	3	2/6
9	17	–4.0	Learning difficulties, delayed puberty	5q12 del	3	1/6
10	2.5	–3.6	Short limbs	3p22 del, 15q13 dup	3, 4	1/6

Classification 3 = Variant uncertain pathogenicity, 4 = Likely pathogenic, 5 = Predicted pathogenic. NH-CSS, Netchine-Harbison SRS Clinical Scoring System (3/6 plus recognised genetic change or 4/6 clinical features alone recommended for SRS diagnosis).

RFC10.2

Non-Inferiority Clinical Trial on Gonadotropinversus Pulsatile Gonadotropin-Releasing Hormone Infusion Therapy in Male Adolescent Patient With Congenital Hypogonadotropic Hypogonadism

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Context: We investigate the efficacy and safetyof non-inferiority clinical trial for human chorionic gonadotropin/ human menopaousal gonadotropin (HCG/HMG) versus pulsatile gonadotropin-releasing hormone (GnRH) which have not been evaluated in puberty boys with CHH.

Objective: To compare the efficacy and security of two different treatments in male adolescent patient with congenital hypogonadotropic hypogonadism (CHH).

Methods: For this prospective cohort nonrandomized controlled study, a total of 43male adolescent CHH patients were recruited and categorized into HCG/HMG (group 1, n=20) and GnRH (group 2, n=23) groups. All patients were treated for 3-12months. Testicular volume(TV), penile length(PL), blood sex hormones levels, height, body weight, and other related laboratory indices were measured and evaluated. And then, when alpha = 0.05, take the 3 month growth differential (2ml) between group 1 and group 2 as non-inferior validity boundary value (δ) and conduct independent sample t test.

Results: All CHH patients were treated for over 3 months. At the beginnig, the average age of patients, the testicular volume, penile length, penile diameter in group 1 and group 2 were 15.3±1.9 years vs 14.2±1.5 years, 2.5±1.4ml VS 2.7±1.5ml, 4.8±1.3cm VS 4.2±1.4cm and 1.6±0.4cm vs 1.5±0.4cm. The difference of two groups was not statistically significant. After 3 months treatment, the testicular volume, penile length, penile diameter, the growth of testicular volume, the growth of penile length and the growth of penile diameter in group 1 and group 2 were 4.6±2.2ml VS 4.6±2.7ml, 6.1±1.3cm VS 5.1±1.6cm, 2.7±2.7 ml vs 2.0±2.2ml, 1.3±1.0 cm vs1.0±0.8cm and 0.9±0.9cmvs0.4±0.4cm. The difference of two groups was not statistically significant.There was no significant difference in height, body weight, or BMI between the two treatments. There was no significant difference in efficacy comparison in both groups after 6-12 months treatment.There was no significant difference in side effects in both groups.

Conclusions: Adolescents patients with CHH may be effectively treated with HCG/HMG and GnRH. We discoverd that the effect of HCG/HMG was as good as GnRH in treating adolescent boys with CHH.

RFC10.3

Developmental Regulation of Obestatin and Adropin in Prader-Willi Syndrome and Non-Syndromic Obesity: Associations with Weight, BMI-Z, HOMA-IR, and Lipid Profile

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Background: The peptides obestatin and adropin are thought to regulate glucose and lipid metabolism, weight gain, and fluid intake in adults. The roles of obestatin and adropin in the regulation of weight and glucose and lipid metabolism in Prader-Willi syndrome (PWS) and non-syndromic pediatric obesity are poorly understood. This study compares the concentrations of obestatin and adropin in infants and children with PWS and age- and BMI-z matched controls, and explores the associations between these peptides and other energy-regulating hormones.

Methods: The cohort included 21infants and 14 children with PWS and 31 controls of similar age, sex, and BMI-z-score. Fasting plasma obestatin and adropin were measured by ELISA. Fasting plasma ghrelin, leptin, and insulin were assayed by radioimmunoassay, and lipid panel and glucose by a Hitachi 911 autoanalyzer.

Results: Obestatin (median 2691.0 pg/mL) and adropin (3.50 ng/mL) levels were higher in infants with PWS than controls (obestatin, 2101.0 pg/mL, p=0.04; adropin, 2.57 ng/mL, p=0.05); adropin was also higher in older children with PWS (2.69 vs. controls, 1.93 ng/mL, p=0.04). Growth hormone (GH) treatment had no effects on obestatin or adropin in PWS and levels were comparable in insulin resistant and insulin sensitive subjects. The ratio of ghrelin to obestatin declined from infancy to childhood but was higher in older PWS than older controls ($p< 0.01$ and $p<0.0005$, respectively). Adropin correlated with fasting glucose in the PWS group only ($r_S=0.78$, $p<0.01$). Analysis of the lipid profile of children with PWS revealed higher high-density lipoprotein (HDL, 49.10 mg/dL) and lower triglycerides (TG, 55.50 mg/dL) compared to controls (HDL, 32.35 mg/dL, p=0.03; TG, 80.00 mg/dL, p=0.03) but similar low-density lipoprotein (PWS, 78.50 vs. controls, 85.95 mg/dL, p=0.86) and total cholesterol (PWS, 132.00 vs. controls, 123.50 mg/dL, p=0.86). Obestatin was correlated with HDL ($r_S=-0.569$, p=0.034) and TG ($r_S=0.541$, p=0.046) in older controls only.

Conclusions: Higher levels of obestatin and adropin in PWS may have implications for glucose and lipid metabolism and water intake. Changes in the ratio of ghrelin to obestatin suggest changes

in the processing of preproghrelin to ghrelin and obestatin during development and preferential processing of preproghrelin to mature ghrelin in children with PWS.

RFC10.4

Comparative Analysis Between Immunoassay and Tandem Mass Spectrometry for Androgens Before and After Human Recombinant Gonadotrophin in Children with Genital Ambiguity and 46,XY Karyotype

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Liquid chromatography associated with tandem mass spectrometry (LC-MS/MS) is currently considered the gold standard for steroid measurement. The aim of this study was to compare traditional immunoassay and LC-MS/MS methods for androgens measurement before and after human recombinant chorionic gonadotrophin (hrCG) stimulation in children with diagnosis of disorder of sex development (DSD) with 46,XY karyotype and past of normal testosterone secretion. We evaluated 19 patients, five cases of partial androgen insensitivity syndrome (PAIS), four of 5α-reductase type 2 deficiency and 10 of idiopathic 46,XY DSD, all prepubertal and non-gonadectomized, before and seven days after application of 6,500 IU of hrCG (Ovidrel®). Total testosterone, dehydroepiandrosterone (DHEA) and androstenedione were measured by immunoassay and LC-MS/MS. The correlation between the tests was analyzed by the Intraclass Correlation Coefficient (ICC) and Spearman Correlation Coefficient (SCC) tests, and for the concordance analysis, the Passing & Bablok (PB) regression and the Bland & Altman (BA) method. Regarding the ICC and SCC coefficients, respectively, the total testosterone showed an excellent correlation in both (0.958 and 0.964), moderate DHEA in both (0.562 and 0.716) and androstenedione a poor correlation in the ICC (0.363) and moderate in the SCC (0.735). By the PB method, the three androgens presented linear relationship, however the androstenedione presented proportional and systematic errors, the testosterone systematic errors, and the DHEA none of these errors. By the BA method there is a tendency of the immunoassay towards LC-MS/MS to overestimate the values of testosterone and androstenedione and to underestimate those of DHEA. In conclusion, the LC-MS/MS method and immunoassays, despite having good correlation and being linearly related, systematic and/or proportional errors were detected, with the immunoassay overestimating the testosterone and androstenedione values and underestimating those of DHEA in relation to LC-MS/MS.

RFC10.5

Abstract not available.

RFC10.6

Effect of the Current Treatment of X-Linked Hypophosphatemia During Growth on the Development of Osteoarticular Lesions in the Hyp Mouse Model

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Mineralization defects and paradoxical mineralizing enthesopathies are hallmarks of X-linked Hypophosphatemia (XLH), a rare skeletal disease caused by inactivating mutations in the *PHEX* gene (Phosphate-regulating endopeptidase homolog, X-linked). The current medical treatment, which consist in oral phosphorus supplementation and active vitamin D analogues, aimed at counteracting consequences of FGF23 excess and is commonly prescribed from early childhood to the end of growth. Despite childhood treatment of the disease, cartilaginous tissue complications in adults become a dominant feature in the clinical evolution of XLH. Here, we monitored the development of these osteoarticular lesions, characterizing the formation of enthesopathies, calcifications and osteoarthritis through a 12-months (M) Micro-CT longitudinal follow up in the *Hyp* mouse, a murine model of XLH. These lesions were already present at 3 months and significantly increased from 3 to 12 months, highlighting the relevance of this murine model for pre-clinical studies. We then studied the impact of current treatment on the development of these osteoarticular lesions. Hyp mice were treated with oral phosphorus supplementation and calcitriol injections. The treatment followed two different outlines: i) from 3 weeks to 3 months to analyze the treatment effects during growth and ii) from 2 months to 3 months to analyze the treatment effects on adult lesion development. We showed that the current treatment given since the early stage improved osteoarticular lesions, bone

mineralization and micro architecture, and fusion of the growth plate. Future studies should compare the effect of the new therapy based on anti-FGF23 antibody.

Bone, Growth Plate & Mineral Metabolism 2

RFC11.1

Diagnosis and Management of Pseudohypoparathyroidism and Related Disorders: First International Consensus Statement

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Pseudohypoparathyroidism (PHP) and related disorders lead to a wide spectrum of abnormal physical characteristics, neurocognitive and endocrine abnormalities. PHP (including all subtypes), pseudoPHP, acrodysostosis and progressive osseous heteroplasia refer to heterogeneous disorders characterized by physical findings, differently associated in each subtype, including short bones, short stature, stocky build, subcutaneous ectopic ossifications, as well as laboratory abnormalities such as hypocalcemia, hyperphosphatemia, and elevated PTH and TSH levels. Other features have been attributed to these disorders, such as intrauterine growth failure, early-onset obesity, hypogonadism, hypothyroidism, elevated calcitonin levels, growth hormone deficiency and neurocognitive deficiency. The main subtypes of PHP and related disorders are caused by *de novo* or autosomal dominantly inherited inactivating genetic mutations, and/or epigenetic, sporadic or genetic-based alterations within or upstream of *GNAS*, *PRKAR1A*, and *PDE4D* and *PDE3A*. The presentation and severity of PHP and its related disorders vary between affected individuals with considerable clinical and molecular overlap between different types.

A specific diagnosis is often delayed due to lack of recognition of the syndrome(s) and associated features. In addition, caregivers and patients are lacking guidelines for the daily life management of patients. Our aim was to provide evidence based recommendations on clinical diagnosis, molecular confirmation of the genetic or the epigenetic defect and management of most frequent manifestations of these rare diseases.

Therefore a consensus statement supported by several patients associations and scientific societies was prepared for 2 years. After a comprehensive literature search using PubMed, >800 papers published since January 1st, 1990 to December 18th, 2016 have been reviewed. The approach comprised 2 pre-consensus meetings, an expert consensus meeting, and a Delphi-like methodology, adjusted to rare diseases.

Experts agreed that the diagnosis of PHP is based on major criteria including resistance to PTH, ectopic ossifications, brachydactyly and early-onset obesity. The clinical and laboratory diagnosis should be confirmed by a molecular analysis. The management of PHP and related disorders requires a multidisciplinary approach including a transition program from pediatric to adult care. Patients should be screened for specific features, such as PTH resistance, TSH resistance, growth hormone deficiency, hypogonadism, skeletal deformities, oral health, weight, glucose intolerance or diabetes, hypertension, as well as ectopic ossifications and neurocognitive impairment. Overall, a coordinated approach from infancy through adulthood should help us to improve the care of patients affected by these disorders.

RFC11.2

Nationwide Hypophosphatemic Rickets Study

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Aim: Hypophosphatemic rickets (HR) is a rare renal phosphate wasting disorder commonly related to X-linked form, caused by *PHEX* mutations and it treatment and follow-up is challenging due to imperfect treatment options.

Here we presented nationwide data on HR with initial and follow-up data on the patients presented to the pediatric endocrinology clinics before the age of 18 years.

Results: From 24 centers, 158 patients (93 male/65 female) were included in the study data. The patients features at presentation has been given in the table. Genetic analysis (n:75) showed PHEX mutation in 80% and DMP1 in 4%, SLC34A3 in 3%, CLCN5 in 1.3% patients. The mean follow-up period of the patients was 6.7± 2.4 years. First 3 year treatment response could be evaluated for 91 patients and, mild increase in P (from 2.6±0.6 to 2.7±0.6, 2.8±0.7 and 2.8±0.7 mg/dl), decrease in ALP (from 786±522 to 627±449, 561±319 and 546±327 U/L) and, elevation in PTH levels (from 68±48 to 84±77, 79±66 and 93±99 pg/ml) had been detected (from intitial to 1st, 2nd and 3rd year, respectively). The height SDS were -2.38, -2.77, -2.72, -2.47 at intitial, 1st, 2nd and 3rd year of treatment, respectively (p>0.05). In follow-up: 36% of the patients showed complete or partial improvement in leg deformities, and, these patients had worse tubular phosphate resorption (70% vs 77%, p: 0.046), better height SDS and ALP at presentation and following years with similar phosphate levels at presentation with

better levels in 1st (2.9 vs 2.6) and 2nd years (3.0 vs 2.7) of treatment, even the treatment doses of phosphate were similar, however, higher calcitriol doses in 1st and 3rd years in improved group.

Furthermore, 27 patients (17%) developed nephrocalcinosis (NC), the patients showed no difference in biochemical differences in presentation and follow-up, but 3rd year PTH was higher (145 vs 78 pg/ml, p:0.002), however, higher treatment dose of phosphate and calcitriol has been detected in NC group ((p<0.05).

Conclusion: HR treatment and follow-up is challenging and our results showed higher treatment doses leading NC without any change in serum levels, suggesting given higher doses lead higher phoshaturia probably through the stimulation FGF23. However, higher calcitriol doses could improve bone deformities. Safer and more efficacious therapies are needed.

RFC11.3

Increased Levels of Bone Formation and Resorption Markers in Patients with Hypophosphatemic Rickets

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Background: X-linked hypophosphatemia (XLH) are rare inheritable disorders caused by excessive renal phosphate wasting manifesting as rickets in children and osteomalacia in adults. Osteoid accumulates due to the reduced mineralization rate. Based on previous histomorphometric bone biopsy studies it the impression that XLH is a low bone turnover disease. Very little is known about the level of bone markers in XLH and the effects of conventional medical treatment with oral phosphate and alfacalcidol on bone turnover. Sclerostin is a potent inhibitor of bone formation described to be elevated in XLH by Palomo et all, 2014.

Objective and hypotheses: The aim of this cross-sectional study was to evaluate aspects of bone turnover and sclerostin levels in treated and untreated patients with XLH using biochemical markers.

Method: In 27 XLH adults and in three age and sex matched controls per patient; markers of bone resorption (carboxyterminal cross-linked telopeptide of type 1 collagen, CTX), and formation (N-terminal propeptide of type 1 procollagen, P1NP) in addition to sclerostin were measured. Eleven of the 27 XLH patients had received conventional medical treatment at least six months prior to the examination, 16 were currently untreated.

Results: CTX and P1NP were significantly elevated in XLH, median 810 ng/l [IQR 500-1,340] and 90 µg/l [57-136], respectively, compared to controls 0.48 µg/l [0.26-0.71] $p<0.001$, and 49 µg/l [39-65] $p<0.001$. CTX and P1NP were numerically, but not significantly higher in currently treated XLH 1.24 µg/l [0.58-2.19] and 136 µg/l [75-144], respectively, compared to untreated XLH 0.68 µg/l [0.43-1.02], $p=0.18$ and 75 µg/l [53-106], $p=0.10$. Sclerostin was significantly elevated in XLH, median 0.81 ng/ml [0.60-1.18] vs. controls 0.54 ng/ml [0.45-0.69] $p<0.001$. There was a trend towards higher sclerostin in untreated 0.83 [0.70-1.03] compared to treated XLH 0.77 ng/ml [0.58-1.18] $p=0.06$.

Conclusion: Both bone resorption and formation markers were significantly elevated in XLH compared to controls indicating a high bone turnover state in XLH. Sclerostin was higher in XLH compared to controls with a tendency towards a lower sclerostin in untreated compared to treated XLH. Thus, even though bone formation was inhibited in XLH as indicated by the elevated sclerostin levels, the overall bone turnover was significantly elevated in XLH tending to be more pronounced in the currently treated. Histomorphometric bone biopsy studies during different treatment regimens are required to further elucidate the effects of treatment on the bone pathology

RFC11.4

A new form of Anhidrotic Ectodermal Dysplasia with Immunodeficiency caused by abolished Store-Operated Ca^{2+} Entry

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Calcium signaling is fundamental to many cellular processes. An important pathway for increasing intracellular Ca2+ levels is store-operated Ca2+ entry (SOCE) regulated by stromal interaction molecule (STIM1-2), and Ca2+ channels formed by ORAI1-3 proteins. Mutations in the ORAI1 and STIM1 genes that abolish SOCE cause a combined immunodeficiency (CID) syndrome that is accompanied by autoimmunity and nonimmunologic symptoms. We present patients with Anhidrotic Ectodermal Dysplasia with Immunodeficiency (EDA-ID) caused by novel homozygous p.V181SfsX8, p.L194P, and p.G98R mutations in the ORAI1 gene

that suppressed ORAI1 protein expression and SOCE in the patients' lymphocytes and fibroblasts. A unifying feature of patients with null mutations in ORAI1 is EDA. Anhidrosis was present in patients P1-P4 and confirmed by pilocarpin iontophoresis. Patients had dry and exfoliate skin. They showed signs of heat intolerance and thermoregulatory instability characterized by several attacks of facial flushing accompanied by tachycardia, tachypnea, and hypertension. A skin biopsy showed the presence of eccrine sweat glands in the dermis demonstrating that anhidrosis is not due to a defect in sweat gland development. Recently, we reported that sweat glands require SOCE for opening of the Ca2+-activated chloride channel TMEM16A and thus chloride secretion and sweat production, pointing that anhidrosis in ORAI1-deficient patients could be functional. ORAI1-deficient patients had severe enamel defects diagnosed as hypocalcified amelogenesis imperfecta type III. In contrast, patients with EDA-ID caused by NF-kB signaling defects also have a tooth defect, which is characterized by hypodontia and conical teeth and thus is morphologically easily distinguishable from the enamel defects in ORAI1-deficient patients. ORAI1-deficient patients showed thin and brittle hair. To date, the diagnosis of EDA-ID is limited to patients with defects in NF-kB signaling who are prone to infections with mycobacteria, P.jirovecii, Candida albicans, and, most frequently, pyogenic bacteria caused by hypogammaglobulinemia and failure to mount a specific antibody response to polysaccharide antigens. In contrast, ORAI1-deficient patients are susceptible to an overlapping spectrum of pathogens, but they are also prone to viral infections, including CMV, EBV, RSV, and rotavirus. In addition, AIHA and autoimmune thrombocytopenia are also common in SOCE deficient patients but not NF-kB; instead, patients with NF-kB defects can have inflammatory bowel disease (NF-kB essential modulator colitis). Here we propose that mutations in ORAI1 that abolish SOCE constitute a new form of EDA-ID and are an important differential diagnosis of EDA-ID caused by defects in NF-kB signaling.

RFC11.5

The Determinants of Skeletal Fragility in Children with Type 1 Diabetes Mellitus

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Background: The pathophysiology of the increased fracture risk in Type 1 Diabetes Mellitus (T1DM) remains unclear.

Objectives: Perform multimodality assessment to determine the effects of T1DM on bone health and fractures.

Methods: Thirty-two children with T1DM at a median (range) age of 13.7 years (10.4,16.7), and median HbA1c 65mmol/mol (27,100) were recruited. Serum bone alkaline phosphatase (BAP) and c-terminal telopeptide type 1 collagen (CTX) as well as DXA total body (TB) and lumbar spine (LS) bone mineral content (BMC) adjusted for bone area were converted to SDS. 3T MRI of the proximal tibia was performed to assess bone microarchitecture, by measuring bone volume/total volume (appBV/TV), trabecular number (appTbN), trabecular separation (appTbSp) and trabecular thickness (appTbTh). MR spectroscopy at lumbar spine was performed to assess bone marrow adiposity, by measuring marrow fat fraction (%). MRI data were compared to 26 age- and sex-matched healthy controls, with median age of 13.8 (10.2,17.8).

Results: Fractures were encountered in 10/32 cases after diagnosis of T1DM and 5/26 controls. In T1DM, median BAP SDS and CTX SDS were -0.6 (-2.5,+2.1) and -1.1 (-2.5,+0.5), respectively whilst median TB and LS BMC SDS were -0.1 (-1.1,+0.9) and -0.3 (-1.0,+1.8), respectively. Children with T1DM had lower appBV/TV with a median of 0.55 (0.47, 0.63) (vs controls 0.59 (0.47, 0.63); p=0.024), lower appTbN 1.67 (1.56, 1.93) (vs controls 1.82 (1.56, 1.99); p=0.004), and higher appTbSp 0.27 (0.21, 0.32) (vs controls 0.24 (0.2, 0.33); p=0.001). The median bone marrow fat fraction in cases and controls were 23% (11, 66) and 20% (8, 61), respectively (p=0.25).

Median BAP SDS was lower in poorly controlled T1DM (HbA1c>75mmol/mol) at -0.79 (-2.5,-0.54) compared to 0.5 (-0.64,+2.10) in those with good glycaemic control HbA1c<58mmol/mol) (p=0.009). Serum CTX was inversely related to the age at diagnosis (r, -0.4, p=0.012). The median HbA1c of T1DM with fracture was 72mmol/mol (49,100) compared to 62mmol/mol (27,87) in those without fracture [p=0.007]. Median TB BMC SDS of T1DM with fracture was -0.5 (-1.1,0.0) compared to 0.0 (-0.5,+0.9) in the non-fracture group [p<0.0001]. There was no significant difference in bone microarchitecture findings between the fracture and non-fracture group.

Conclusion

Children with T1D display a low bone turnover state associated with reduced bone mineralisation and poorer bone microarchitecture. Fractures were more likely in those with poorer glycaemic control and bone mineral status.

RFC11.6

Reference Values of Automated Bone Age and Bone Health Index for Mexican Children and Adolescents

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Background: BoneXpert is a software for automated measurement of bone age (BA) and radiogrammetry (bone health index). The precision error of the software for BA measure is smaller than the human rating error and the accuracy relative to the human routine ratings is 0.80 years. Differences in skeletal maturation between ethnicities have been reported, so it is important to have specific references for the own population.

Table 1. Automated BA minus age (for Abstract no RFC11.6)

Age (y)	Boys			Girls		
	Mean	Std. Dev.	n	Mean	Std. Dev.	n
5	–0.15	0.56	15	–0.60	0.92	20
6	–0.76	0.70	23	0.31	0.76	19
7	–0.77	0.91	53	–0.23	1.12	15
8	–0.30	1.38	46	–0.67	1.09	17
9	–0.38	1.61	41	0.36	1.17	30
10	0.03	1.62	28	0.06	1.19	25
11	0.18	1.03	26	–0.11	1.40	26
12	–0.13	1.32	30	1.10	1.30	22
13	0.37	1.37	20	0.77	1.18	24
14	0.65	1.36	23	0.87	0.61	31
15	0.91	1.26	41	0.66	0.93	26
16	0.61	1.01	26	0.38	0.65	30
17	0.44	0.76	20	–0.42	0.53	18
18	–0.31	0.79	14	–1.22	0.30	4

Objective: To present the automated BA reference curves and bone health index for Mexican children and adolescents.

Methods: We conducted a cross-sectional study. We included 722 children Mexico City´s metropolitn area (5 to 18 years old). A hand AP radiography was taken and analyzed using BoneXpert software to determine automated BA and bone health index. We constructed the reference values curves for BA and bone health index.

Results: We observed a BA similar to Greulich and Pyle scale up to age 10 and then approximately 0.9 years ahead at the end of puberty (Table 1). On the other hand, an increase in the bone health index was observed according to the increase in skeletal maturation; however, the values at the end of puberty are lower than that reported in other populations (mean 5.5±0.46 in boys and mean 5.3± in girls).

Conclusions: Mexican children have an acceleration in BA that causes an advance of about 1 year at the end of puberty. This could have an effect on the lowest final adult height observed in the Mexican population in comparison with other populations. Additionally, the bone health index in Mexican children is lower than other populations at the end of puberty. Future studies are required to evaluate the clinical implications of this observation.

Diabetes and Insulin 2

RFC12.1

Use of Acid-Suppressivemedications During Infancy and Early Childhood and its Association with Type 1 Diabetes

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Background: Type 1 diabetes is a multifactorial, immune mediated disease whose incidence has been increasing worldwide. These changes in prevalence cannot be explained by genetic susceptibility alone and several lifestyle changes have been linked to the rising incidence including obesity, diet and mode of delivery. Many of these environmental factors influence the composition of the gut microbiome which interacts with the immune system as well as affects gut permeability, thus facilitating exposure to potentially diabetogenic antigens and possibly playing a role in initiating autoimmunity against islet cells. Acid suppressive medications have been linked to intestinal dysbiosis, however there is no data analyzing the role of acid suppressant use and development of type 1 diabetes.

Methods: This retrospective study was conducted using the "Explorys" database, an open private cloud platform that electronically integrates non-identified patient data used by major health systems comprising of almost 50 million patients. We queried the database for children who received acid suppressive medications (proton pump inhibitors or H2- receptor blockers) between 0 to 4 years of age. Patients who received acid suppressants served as cases and patients who did not receive the medications served as controls. Then we compared the number of patients who were diagnosed with Type 1 diabetes between 5 and 24 years of age in both the groups. We used Type 1 diabetes and included 8 other sub-diagnosis based on SNOMED (Systematized Nomenclature of Medicine - Clinical Terms) classification of diseases. We excluded patients with a diagnosis of neonatal diabetes. Both groups were controlled for obesity and vitamin D deficiency. Data was analyzed using SPSS software.

Results: The database comprises data of almost 10.3 million patients between ages 5 to 24. 40840 of these patients had a diagnosis of type 1 diabetes in the Explorys database. With the large sample size, we assumed the subjects to have equal risk of developing type 1 diabetes in both the exposed and unexposed groups. Exposure to acid suppressive medications before the age of 4 was not significantly associated with a future risk of developing type 1 diabetes (OR =1.09; CI –0.99 to 1.2, p value=0.09).

Conclusion: Treatment with acid suppressive medications such as proton pump inhibitors and H2- receptors blockers during infancy and early childhood is not significantly associated with higher odds of developing type 1 diabetes.

RFC12.2

Bone Mineral Density Is Increased in 276 Danish Children and Adolescents with Type-1-Diabetes

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Objectives: Bone health is affected in Type-1-Diabetis (T1D) causing higher risk of hip fractures, prolonged fracture healing and altered bone mineral density (BMD). In T1D adults BMD is found to be decreased. In this study we have measured the BMD in children and adolescents from the Copenhagen Pediatric T1D Cohort.

Methods: 276 children and adolescents (131 girls) were included from the diabetes outpatient clinic at Herlev University Hospital. All patients underwent a physical examination, had blood tests drawn, and BMD Z-scores assessed by Dual Energy X-ray Absorptiometry (DXA). Standard deviation scores (SDS) on height, weight and BMI were used from a Danish study of more than 12.000 healthy children and adolescents. Glycemic control was evaluated by HbA1c (mmol/mol). T-tests were used to test for differences between gender, and linear regression analyses were used to estimate factors influencing the BMD.

Results: Mean age of participants was 13.6 (± 3.7) and mean diabetes duration was 4.9 (±3.5) years. Mean HbA1c was 62.6 (± 14.3). Mean total daily insulin dose was 0.85 IE/kg (± 0.29) and 175 (63.4) % were treated with continuous subcutaneous insulin infusion.

T1D patients had significantly higher weight and BMI SDS compared to the background population (+0.34 and +0.39 respectively) and had a higher BMD Z-score (+0.74). Separated into sex, only girls remained heavier and with a higher BMI compared to the background population and girls had a higher HbA1c compared to boys (64.8 vs 60.6). Both genders had higher BMD Z-score (+0.64 and +0.85). When comparing patients with optimal HbA1c (<= 58) with poorly controlled (HbA1c >= 75) we found no difference in weight or BMI, but a significantly lower BMD Z-score in the poorly controlled (P = 0.02). Both groups did however have higher BMD Z-score compared to the background population. Linear regression analysis demonstrated significant negative effect of HbA1c and positive influence of BMI on BMD Z-score.

Conclusion: Our study reveals that children and adolescents with T1D have a higher BMD compared to the general population. Though a higher HbA1c correlates to lower BMD the increased BMI found in girls with T1D may in part explain the overall increase, however BMI in boys were equal to the background population and they still had higher BMD. Further research is needed to fully elucidate the relationship between BMD and diabetes in children and adolescents.

RFC12.3

Barriers and Sources of Support for the Performance of Physical Activity in Pediatric Type 1 Diabetes

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Background: The advantages of physical activity are particularly emphasized in children with type-1-diabetes and 60 minutes of regular daily activity is recommended. However, reports suggest that children with type-1-diabetes perform less than the recommended daily activity and are less active than their non-diabetic peers. This study aimed to: 1) Identify barriers and sources of support for exercise performance in children and adolescents with type-1-diabetes. 2) Identify strengths and limitations in the exercise-directed education provided by our diabetes team.

Methods: Patients with type-1-diabetes 2-20 years of age, followed at the pediatric diabetes clinic, Ruth Rappaport Children's Hospital were recruited while attending a routine visit. After signing consent, participants completed a set of questionnaires assessing demographic and health data, physical activity and barriers to its performance, family and social support, diabetes related exercise education and its implementation. The clinics' medical staff, including physicians, nurses and dietitians filled a questionnaire assessing the exercise-directed education provided in clinic.

Results: One-hundred and one patients with type-1-diabetes were included in this study. Mean age was 13.2±4.2 years. Median weekly time of reported exercise was 4 hours (range 0-22), with no significant difference between males and females. The two most prevalent perceived barriers were risk of hypoglycemia and low fitness (reported by 75%, and 51% respectively). Family support scores were generally favorable, mean score 4.1±0.7(1-5 scale). However, scores for variables reflecting active exercise-participation were in the lower half for over 50% of participants. On the other hand, social support scores were the highest for exercising together and correlated with the amount of activity performed (cc=0.360,p<0.001). The majority of patients (97%) reported that guidance for physical activity was provided in clinic, to their satisfaction. Yet, only 75% reported adjusting food, insulin or activity in order to control glucose during exercise, and less than 50% were familiar with the glucose lowering effect of exercise. All staff members reported conducting routine exercise-directed teaching in clinic, with variations in frequency. The effects of different types of exercise, guidance regarding planning exercise and the diabetes-specific equipment required were topics less consistently included in teaching.

Conclusions: In order to increase the amount of safely performed exercise in pediatric type-1-diabetes, efforts should focus on: 1) encouraging active family and social involvement 2) providing structured periodic teaching by diabetes team members and assessing its implementation.

RFC12.4

Use of Telemonitoring Via a Mobile Device App Reduces HbA1c in Type 1 Diabetic Children and Adolescents

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Background and aims: Type 1 diabetes mellitus (T1DM) belongs to the most common chronic diseases affecting children and adolescents. Technological advances have improved metabolic control over the past decades, thereby decreasing the risk of long-term complications. However, only a minority of patients meets the treatment goals of maintaining a glycated hemoglobin (HbA1c) level below 7.5% (58mmol/mol). *Webdia* is an application for mobile devices developed by the father of a diabetic child, in collaboration with our pediatric diabetology team. A simple interface allows children to calculate insulin doses and pictures representing selected meals help them estimating the carbohydrates on their plate. In addition, all glucose values entered into the program become instantly available to the child's parents and healthcare professionals, thereby allowing remote monitoring.

Research design and methods: 55 children aged 10–18 years were included into this randomized double-crossover one-center study. Intervention consisted of using *Webdia* during 3 months and getting feedback and monthly suggestions for the adaptation of the insulin regimen by the healthcare professionals. The control arm consisted of usual care. Primary outcome was modification of HbA1c. Secondary outcomes were frequency of self-reported hypoglycemia and quality of life (QoL).

Results: 55 patients were included. 33 completed the study, 9 dropped out and 13 were excluded because they used the app < four times / week. Risk factors for insufficient use of *Webdia* were older age (mean 15.1 +/- 2.4 vs. 13.3 +/- 2.3 years in patients who completed the study, p=0.024) and longer duration of T1DM (mean 86 +/- 52 vs. 52 +/- 35 months, p=0.014). The program was well accepted by the users (46.4% rated the program as good and 39.3% as excellent). The intervention lead to a reduction of HbA1c by 0.54%, as compared to the control group (p=0.048) in patients with HbA1c values > 8.0% (63.9mmol/mol) at inclusion, without increasing the prevalence of hypoglycemia (8.52 +/- 9.45 hypoglycemia during last two weeks of intervention, vs. 7.62 +/- 6.37 during last two weeks of observation, p=0.680). QoL scores were not modified by *Webdia* use.

Conclusions: The use of *Webdia*, in combination with remote regular review of glucose values and adaptation of the insulin regimen resulted in a significant reduction of HbA1c in patients with initial values > 8.0% (63.9mmol/mol), without increasing the prevalence of hypoglycemia. Low compliance among adolescents suggests that the app may need to be adapted to this age group.

RFC12.5

Insulin Gene Promoter Methylation Status in Greek Children and Adolescents with Type 1 Diabetes

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Introduction: Insulin (INS) gene is reported to be the most important gene involved in Type 1 Diabetes (T1D); its expression is inversely correlated with methylation at CpG sites. Hypermethylated primers are associated with decreased expression. The present study **aims** to investigate possible differences in DNA methylation pattern between T1D youngsters and healthy controls.

Patients and Methods: Twenty T1D participants and 20 age-/gender-matched youngsters without T1D were enrolled. DNA was extracted from white blood cells, then treated with sodium bisulphate which converts unmethylated cytosines into uracyls, whereas methylated cytosines remain unchanged under the same conditions. DNA was then amplified by PCR using primers: *(F) primer: 5' TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGTA TTTTGGAATTTTGAGTTTATT 3' and (R) primer:5' GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGAACAAAAATCTAAAAACAACAA 3'.* Amplicons were analyzed by electrophoresis (1% agarose gel stained with ethidium bromide), visualized by ultraviolet transillumination, and then Next Generation Sequencing was applied to

Table 1. (for Abstract no RFC12.5)

10 CpGs in INS gene	DNA methylation (%)		
	T1D (n = 20)	Control group (n = 20)	p
Overall mean methylation percentage			
Mean methylation	84.13 ± 3.6	82.28± 2.8	0.0848
Range	77–92	76–87	
CpG sites			
2-4553	96.32±2.2	93.28±4.5	0.02
1-4541	94.00±5	90.78±7.9	0.15
3-4664	91.02±6.3	89.58±8.4	0.65
4-4692	63.16±8.9	62.30±9.8	0.86
5-4718	85.78±6.6	84.35±9.9	0.82
6-4763	56.65±9.8	52.82±1	0.25
7-4796	90.01±3.6	86.53±6	0.06
8-4829	80.28±6.2	77.72±8.4	0.32
9-4879	91.51±5.2	89.05±9.2	0.67
10-4960	96.37±2.7	97.91±1.3	0.10

Results are expressed as Mean ± Standard Deviation.

identify differences in DNA methylation status. The methylation profile was analyzed at 10 CpG sites of the INS gene. Comparisons between groups were performed with student's t-test or its non-parametric analogue, Mann Whitney U test, as appropriate.

Results: The results are described in table. The overall mean methylation percentage in the T1D patients did not differ compared to healthy controls. A statistically significant difference in INS gene between the two groups concerning the methylation at position 2-4553 ($p = 0.046$) was detected, while a trend ($p = 0.06$) at position 7-4796 was observed.

Conclusions: These preliminary data suggest a tendency for increased methylation in INS gene promoter already existing in childhood T1D. Alterations within INS gene promoter sites could serve as a biomarker for early detection of predisposed to T1D children. Further investigation needs to confirm these findings.

RFC12.6

AMGLIDIA, a Suspension of Glibenclamide for Patients with Neonatal Diabetes, Long Term Data on Efficiency and Tolerance

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Background: Glibenclamide has proven to be efficient for patients with neonatal diabetes owing to potassium channel mutations. We developed a suspension of glibenclamide (EMA CHMP Authorization February 2018) fitting recommendations of drug administration to allow a precise dosage. We reported it to be practical, efficient and well tolerated after 3 months of use.

Objective: To determine long term efficiency and tolerance of a new suspension of glibenclamide AMGLIDIA.

Method: Patients where switched from crushed tablets to suspension and prospectively followed-up. Efficiency and tolerance were recorded (Dosage, number of preprandial hyperglycaemia, number of hypoglycaemia, adverse events, HbA1C). Adverse events were recorded.

Results: 5 patients (3 boys) with neonatal diabetes owned to KCNJ11 mutation were treated and prospectively followed-up. Suspension was introduced as a very young age and some months after sulfonylureas introduction. Indeed, median age at suspension introduction was 1.5 years of age (0.47 to 1.7 years of age). Treatment duration with AMGLIDIA suspension ranged from 20 to 34 months. Median dosage at introduction 0.1 mg/kg/d (0.06 to 0.26 mg/kg/d) and didn't change significantly throughout the follow-up as median dosage was 0.08 mg/kg/d (0.03 to 0.27 mg/kg/d). Metabolic control remained excellent throughout the follow-up: HbA1C at initiation: 6.7% (5.1 to 7.9%), HbA1C at last visit: 5.5% (5.5 to 6.5%). During the month before last visit, 7 hyperglycaemia > 250 mg/dl was recorded in one patient and 5 hypoglycaemias (2 in on and 3 in another one). Safety record was excellent: 1 asymptomatic hypoglycaemia below 54 mg/dl was recorded another hypoglycaemia with neurological symptoms in the context of acute viral gastroenteritis. No other adverse event was recorded.

Conclusion: Glibenclamide suspension AMGLIDA allows an excellent long term metabolic control and is very well tolerated. (ClinicalTrial.gov NCT02375828)

Pituitary, Neuroendocrinology and Puberty 2

RFC13.1

Risk of Long-Term Endocrine Sequelae in Survivors of Progressing Childhood Optic Pathway Glioma (OPG) Treated by Upfront Chemotherapy. Preliminary Analyses of 102 Subjects from the French Multicentric BB-SFOP Registry

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Objective: Therapeutic approach favors chemotherapy as the first-line-treatment in progressing OPG. There are few data on long term endocrine outcomes of aggressive OPG treated by upfront chemotherapy. Our main objective was to describe the long-term endocrine sequelae in these patients and to identify potential early predictors of the endocrine involvement.

Subjects and methods: Children diagnosed with OPG at an age younger than 16 years from the French multicentric BBSFOP registry were included. They were treated with upfront chemotherapy according to the BB-SFOP protocol in France between June 1990 and December 2004, and subsequent treatment (second-line chemotherapy, surgery, radiotherapy) was used depending on tumor progression. They underwent a late evaluation with clinical and biological assessment between January 2011 and March 2016.

Results: One hundred and two patients were included in our study. The mean age at tumor diagnosis was 3.3 ±0.3 years. The mean time of follow-up was 13.9 ± 3.7 years. A history of precocious puberty was present in 36% of the subjects. At least one endocrine deficiency was present in 93% of the subjects (GHD 74%, TSH deficiency 57%, ACTH deficiency 36%, hypogonadotropism 33%, gonadic deficiency 30%, diabetes insipidus 15%; inappropriate AVP secretion 7%). 37% of males and 39% of females were overweight or obese. Mean adult height, reached in 51 subjects, was -1.2±1.3 SDS in males, and -0.7±1.4 SDS in females. Chemotherapy only was protective from pituitary deficiencies (odds ratio 0.19 to 0.37, $p < 0.05$). NF1 was protective from TSH and ACTH deficiencies (odds ratio 0.25 to 0.35, $p < 0.05$). Tumor volume on diagnostic MRI was not predictive of pituitary deficiencies. Gonadic deficiency was significantly more frequent in males than females (46,5% vs. 12.2%, $p < 0.05$), and associated with chemotherapy only (OR 3.2, $p < 0.05$) and NF1 (OR 4,8, $p < 0.05$). Overweight/Obesity was associated with ACTH deficiency (OR 5, $p < 0.05$).

Conclusion: Obesity and late endocrine dysfunction were frequent in subjects treated by upfront chemotherapy for aggressive OPG during childhood. However, chemotherapy only, when possible, was protective from pituitary involvement.

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RFC13.2

Growth Outcomes and Near Adult Height of Children with Congenital GH Deficiency (GHD) Due to Abnormal Pituitary Development: Data from a Prospective, Multinational Observational Study

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Background: Children with structural hypothalamic-pituitary anomalies, e.g. ectopic posterior pituitary (EPP) with/without pituitary stalk interruption syndrome, septo-optic dysplasia (SOD), and isolated anterior pituitary aplasia/hypoplasia (AP/HP) usually have more severe GHD and better auxological outcomes with GH therapy than those with normal hypothalamic-pituitary magnetic resonance imaging findings. However, adult height data is limited.

Objective: To characterize growth and near-adult height (NAH) outcomes in GH-treated patients with EPP, SOD, AP/HP or "Other"-GHD, using Genetics and Neuroendocrinology of Short Stature International Study (GeNeSIS) data.

Methods: Patients were grouped by investigator-provided diagnoses: 1) EPP (including interrupted pituitary stalk); 2) SOD; 3) AP/HP; and 4) Other-GHD (non-acquired/non-pituitary abnormality associated). Statistical significance was assessed by non-overlap of 95% confidence limits (CI). Height standard deviation score (SDS) was calculated using US age/sex-adjusted CDC data. NAH was defined by ≥1 of closed epiphyses, height velocity <2 cm/year, bone age >14 years (girls)/>16 years (boys).

Results: Patients with EPP were younger at baseline than AP/HP or Other-GHD, but older than SOD, with significantly shorter stature than SOD or Other-GHD (Table). 1st-year height velocity SDS and Δheight SDS were greatest for EPP, significantly different from AP/HP and Other-GHD (Table). Height SDS gain from baseline to NAH was greatest for EPP, with significant difference from Other-GHD, albeit after longer GH treatment duration (Table).

Conclusion: Patients with structural hypothalamic-pituitary abnormalities had more severe GHD and greater height deficit than those without such abnormalities. They appeared to have better outcomes of GH treatment, with EPP having the best 1st-year and NAH gain, but age at GH start and treatment duration varied.

RFC13.3

Circulating MKRN3, Kisspeptin and IGF-1 Levels in Girls During The Clinical Onset of Puberty

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Introduction: MKRN3, kisspeptin and IGF-1 maybe involved into the initiation of puberty. The aim of our research is to evaluate the differences of serum IGF-1,MKRN3 and kisspeptin in girls with central precocious puberty, rapidly progressive puberty, premature thelarche and controls, and further assess the value of IGF-1 in puberty initiation.

Methods: The patients enrolled in the study were divided into four groups: central precocious puberty(CPP), rapid progressive puberty(RPP), premature thelarche(PT)and normal controls. One-way analysis of variance was used when data was normal distribution, Mann-Whitney *U* test and Kruskal-Wallis *H* test were used

Table 1. (for Abstract no FC13.2)

	EPP	SOD	AP/HP	Other-GHD
Baseline/1st-year				
N	185	76	291	6095
Proportion with MPHD	52%	75%	30%	8%
Baseline age (years)	6.2 (5.6, 6.9)	4.5 (3.6, 5.4)*	8.9 (8.4, 9.5)*	10.2 (10.1, 10.3)*
Height SDS	−3.0 (−3.2, −2.8)	−2.4 (−2.7, −2.1)*	−2.8 (−3.0, −2.7)	−2.4 (−2.4, −2.4)*
Maximum GH peak (ng/mL)	3.9 (3.1, 4.8)	2.9 (2.3, 3.5)	5.0 (4.6, 5.4)	8.2 (8.0, 8.4)*
1st-year height velocity SDS	4.4 (3.8, 4.9)	3.4 (2.7, 4.0)	3.3 (3.0, 3.7)*	2.5 (2.4, 2.5)*
1st-year Δheight SDS	1.2 (1.1, 1.3)	1.1 (0.9, 1.2)	0.9 (0.8, 0.9)*	0.6 (0.6, 0.6)*
NAH				
N	95	39	119	2386
NAH SDS	−0.6 (−0.8, −0.3)	−0.7 (−1.2, −0.3)	−0.6 (−0.9, −0.4)	−1.0 (−1.1, −1.0)*
NAH SDS gain	2.5 (2.2, 2.7)	1.9 (1.4, 2.4)	2.1 (1.9, 2.4)	1.4 (1.3, 1.4)*
GH duration (years)	9.2 (8.3, 10.0)	11.2 (9.7, 12.6)	7.9 (7.0, 8.9)	5.6 (5.5, 5.7)*

* Significant difference to EPP.
MPHD, multiple pituitary hormone deficiencies.

when data was for skewed distribution.Spearman rank correlation was given to assess the correlation. The ROC curve was used to determine the diagnostic value of IGF-1 in identifying the initiation of HPGA. $P<0.05$ was considered statistically significant.

Results: There were statistically differences in the levels of kisspeptin and IGF-1 among the four groups of CPP, RPP, PT and controls($P=0.003<0.05$,$P=0.000<0.05$), positive correlation was existed between kisspeptin level and bone age, basal LH levels, basal FSH levels, peak LH levels, and the ratio of peak LH and FSH levels($P<0.05$), and positive correlation was also existed between IGF-1 levels and estradiol, basal LH levels, basal FSH levels, peak LH levels, and the ratio of peak LH and FSH levels($P<0.05$).The area under the curve of ROC of IGF-1 was 0.873. There were no difference in the levels of MKRN3 among the four groups of CPP, RPP, PT and controls($P=0.244>0.05$), over 10 years of age, the MKRN3 levels in the Hypothalamic-pituitary-gonadal axis(HPGA) initiated group was lower than the HPGA non-initiated group, the difference was statistically significant($P=0.006<0.005$),The overall MKRN3 levels was not correlated with gonadotropin levels($P>0.05$), the negative correlation between estradiol and basal LH level appeared only after 10 years ($r=-0.464$, $P=0.034<0.05$, $r=-0.473$, $P=0.017<0.05$).

Conclusions: MKRN3, kisspeptin and IGF-1 play a regulatory role in the process of puberty initiation, MKRN3 has a large individual variability. Among them, MKRN3 exhibits as an inhibitory factor on GnRH, kisspeptin and IGF-1 manifests the opposite. The expression of MKRN3 is down-regulated after the initiation of HPGA, but the levels of kisspeptin and IGF-1 are up-regulated. In addition, IGF-1 has certain diagnostic value in the differential diagnosis of puberty initiation.

RFC13.4

Gain in Predicted Adult Height Using the Combination of an LHRH Analogue and an Aromatase Inhibitor in Early Maturing Girls with Compromised Growth for 2 Yrs Or Until the Age of 11 Is Maintained and Further Improved by Aromatase Inhibitor Monotherapy. Results on Final Height of the "GAIL" Study ISRCTN11469487

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Background: Third generation aromatase inhibitors (AI) have never been used as monotherapy to increase predicted adult height (PAH) in girls. Our previously published GAIL study [J Endocrinol Invest. 2016 Apr;39(4):439-46] has shown that the combination of anastrozole to an LHRH analogue for 24 months is safe and effective in ameliorating PAH in girls with early puberty +1.21 SDS (+7.51 cm) compared to inhibition of puberty alone +0.31 SDS (+1.92 cm), p=0.001.

Objective and Hypotheses: We assessed the adult (i.e. age 16.5 yrs) or near adult height (i.e. at bone age 14 yrs) (NAH) of the girls who participated in the GAIL study compared to the PAH after 24 months of combined treatment and additionally the efficacy of anastrozole monotherapy after completion of the combined treatment in further improving NAH.

Methods: We measured the 40 girls who participated in the GAIL study and were divided in two groups Group A (20 girls on anastrozole+ leuprorelin) and Group B (20 girls on leuprorelin alone). Group A was further randomized into two subgroups. Group A1 (10 girls), after completion of the combined therapy, received anastrozole 1 mg/day as monotherapy until bone age of 14 yrs with a 6-month follow-up. Group A2 (10 girls) had stopped the combined therapy at 24 months or 11 yrs of age and were recalled for NAH evaluation.

Results: NAH exceeded the PAH at the completion of the initial phase of the GAIL study in all three groups but the result was statistically significant only in Group A1: NAH-PAH = Group A1: +3.85 cm (+0,62 SDS) p=0.001, Group A2:+1,6 cm (+0,26 SDS) p=0.26, Group B: +1,7 cm (+0,3 SDS) p = 0.09. Gain in Group A1 was significantly greater to that of Group A2 (p=0.046) and Group B (p=0.035).

Conclusion: Early maturing girls with compromised growth treated with the combination of anastrozole and LHRH analogue for up to 2 years or until the age of 11 yrs maintain the gain in the PAH after completion of combination therapy. Anastrozole monotherapy thereafter and until bone age 14 yrs further improves NAH by +2.25 cm (+0.36 SDS). In total, it seems that the addition of an AI to the treatment by an LHRH analogue followed by monotherapy with the AI may add 8.06 cm (+1.28 SDS) to the NAH.

RFC13.5

Pubertal Voice Break: Temporal Relation of Secondary Sexual Characteristics in Healthy Boys

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Introduction: The clinical hallmark of male puberty is testicular enlargement ≥4mL. While this initial sign largely depends on central reactivation of the hypothalamic-pituitary-gonadal (HPG) axis along with peripheral follicle-stimulating hormone (FSH) action, the attainment of voice-break, activation of sweat- and sebaceous- glands, acne as well as axillary hair development require testosterone action.

Objective: To investigate the temporal relation of emerging secondary sexual characteristics and correlation with testosterone levels during pubertal transition in healthy boys

Methods: 731 healthy Danish boys from the COPENHAGEN Puberty Study [cross-sectional: n=637; longitudinal: n=94, medi-

an (range) number of examinations: 10 (2-13)] underwent blood sampling including measurement of reproductive hormones as well as clinical examinations of secondary sexual characteristics. (Mean) BMI z-scores were calculated using the WHO reference. Mean age (95% CI) at pubertal event was assessed by probit analysis (proc lifereg; SAS Institute) integrating censored observations. Data on testicular volume and pubic hair stages as well as reproductive hormones have previously been published (Sørensen, JCEM 2010).

Results: In our cohort, voice-break occurred at 13.6 (95% CI: 13.5-13.8) yrs, activation of sweat glands 12.4 (12.2-12.6) yrs, axillary hair development 13.6 (13. 5-13.8) yrs and acne 14.9 (14.6-15.2) yrs. Testicular enlargement ≥4mL occurred at 11.6 (11.5-11.8) yrs and pubic hair at 12.2 (12.1-12.4) yrs. All events, except acne, were significantly ($p<0.001$) negatively associated with mean zBMI score with effect sizes ranging from -0.4 yrs (-0.5 to -0.2) yrs (axillary hair development)up to -0.5 (-0.5 to -0.3) yrs (activation of sweat glands) per zBMI. Serum Testosterone (T) levels in the examination prior to the examination in which voice-break was detected were 8.34 (0.1-26.8) nmol/L and the time from the examination with detectable T (>0.115nmol/L) to voice break was 1.6 (-1.2 to 3.8) yrs. At time of voice break, testis size (largest testis) was 11.8 (4-20) mL and genital stage was Tanner 3 (2-5).

Conclusions: We provide a comprehensive temporal analysis of pubertal events in a large contemporary cohort of healthy boys. Reference ranges can be directly implemented in a clinical setting. Threshold of T levels for voice-break to occur varied substantially between individuals.

RFC13.6

Close Correlation Between Salivary and Blood Steroids in Normal Boys: Salivary Testosterone Best Characterizes Male Puberty

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Aims: The golden standard to characterize pubertal maturation is the analysis of steroid hormones in the blood. The aim of the investigation was to assess whether the analysis of salivary steroids is similarly able to characterize male pubertal development.

Methods: The investigation included 165 normal boys (mean age 12.7 ± 2.8 years, mean body mass index 19.6 ± 4.2 kg/m^2). Pubic hair stages were stratified by Tanner and testicular volume by using the Prader orchidometer. Steroids (17-hydroxyprogesterone, dehydroepiandrosterone/ dehydroepiandrosterone-sulfate, androstenedione, testosterone) were measured in saliva by ELISA procedures and as serum total steroids by ECLIA assay.

Results: Correlations between salivary and serum concentrations of steroids were significant independent of pubertal development. Salivary and serum steroids correlated ($p<0.001$) with pubertal development (pubic hair stages, testis volume). Considering all salivary steroids for binomial logistic regression analysis, testosterone correlated best with testicular volume ($p<0.001$) and pubic hair stages ($p<0.001$). Inclusion of more steroids into the analysis did not improve the predictability of pubertal development.

Conclusion: Serum and saliva steroid levels reflect pubertal maturation equally well, notably salivary testosterone can be used as a non-invasive surrogate for serum testosterone to monitor male pubertal development.

Multisystem Endocrine Disorders

RFC14.1

Psychometric and Psycho-social Profile of Children and Adolescent Survivors of Pediatric Cancer

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Objective: The aim of this study was to compare the psychometric and psychosocial profile of children and adolescents survivors of pediatric cancer to that of healthy controls.

Methods: Children and adolescents survivors of pediatric cancer, aged 7-17 years, who attended the Hematology-Oncology Unit of the First Department of Pediatrics, and healthy controls who visited the Centre for Adolescent Medicine and UNESCO Chair on Adolescent Health Care of the First Department of Pediatrics, from September 2016 until June 2017, were eligible for study entry. Participants were evaluated with the Self-Reporting Children's Depression Inventory (CDI) and the Wechsler Intelligence Scale for Children (WISC-III). The validated LAMDA software for screening for learning difficulties was administered on a laptop in all study participants.

Results: A total of 60 children and adolescents, 30 survivors of pediatric cancer (survivor group) and 30 age-matched (P=0.933) controls (control group) participated in the study. The survivor group demonstrated increased self-assessment of interpersonal problems (mean ± SD 3.6 ± 1.0) compared to the control group (mean ± SD 2.9 ± 1.1) and this difference was statistically significant (P=0.015).

Evaluation with the WISC-III showed elevated levels of general (mean ± SD 108.1 ± 15.8) and practical intelligence (mean ± SD 54.9 ± 8.0) of the control group compared to the survivor group (mean

± SD 97.9 ± 18.1 and 48.9 ± 9.7 respectively) and these differences were statistically significant (P=0.031 and P=0.016 respectively). In particular, statistically significant differences were found in coding (P=0.022), image scheduling (P=0.009) and number memory (P=0.005) between the two groups, with the control group demonstrating higher levels than the survivor group. Regarding the LAMDA test, the survivor group had significantly lower scores than the control group in supplementation of images (processing speed) (mean ± SD, survivors 2.8 ± 1.3 vs. controls 3.4 ± 0.9; P=0.034), verbal proportions (accuracy) (mean ± SD, survivors 2.8 ± 1.1 vs. controls 3.4 ± 0.8; P=0.011) and range of letters (accuracy) (mean ± SD, survivors 2.8 ± 1.0 vs. controls 3.3 ± 1.0; P=0.036).

Conclusion: Children and adolescents with a history of pediatric cancer require psychometric, cognitive and psychosocial assessment at the end of treatment to detect any deficits and ensure timely intervention. Larger studies are needed to fully elucidate young cancer survivors' psychometric, cognitive and psychosocial profile.

RFC14.2

British Society for Paediatric Endocrinology and Diabetes Peer Review of Specialised Paediatric Endocrinology Services in the UK – Evaluation of the Outcomes

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Introduction: The BSPED Peer review programme was initiated in 2011 to provide a regular cycle of independent impartial professional assessment, against quality standards for Specialised Paediatric Endocrine Services (SPES) in the UK.[1] We present here an evaluation of the outcomes from the first review cycle completed in 2017.

Methods: We examined pre-review self-assessments (4-6 weeks before a site visit by the Peer Review team) and post-review questionnaires (at least 6 months after a review) completed by the SPES lead, and final Peer Review assessment reports completed by the BSPED Peer Reviewers from each SPES. The assessment reports showed whether standards were met or unmet.

Results: All 22 SPES (England 18, Scotland 2, Wales 1, Northern Ireland 1) accepted the invitation to be reviewed. The total population served (median 2.6 million; range 1-8 million) and number of annual consultations (median 1872; range 779-6738) per SPES varied considerably. The 22 SPES met a median 43 (range 30-49) of the 54 criteria in the UK standards[1]. Adherence to the standards was suboptimal for the ‚availability of specialist psychology support' (n=11), ‚telephone access to a paediatric endocrine specialist 24 hours a day' (n=8), ‚appropriate facilities for adolescents' (n=8) and ‚transition clinics' (n=3).

From the post-review questionnaire, 21 SPES found the review process useful in identifying developments and implementing quality improvements. However one SPES reported no impact from the peer review owing to lack of support from the hospital's senior management team. This SPES served a total population of 2.5 million, met 33 of the 54 criteria and had a dedicated cohesive team working above their remunerated sessions. Although a major recommendation from the review conducted in 2013 was to secure funding for an additional paediatric endocrinologist to meet the criteria of one paediatric endocrinologist per 1 million population, this has not been achieved.

Conclusions: This BSPED Peer Review programme has contributed to promoting the quality of SPES and the care they provide for children and young people with endocrine disorders within the UK National Health Service. To enable appropriate action plans from the final report and recommendations, it is vital that these are presented to the medical and health care professionals of the SPES, but also to the hospital management and planning teams. Evidence and experience from this first cycle of SPES peer reviews will help refine future standards and reviews.

References

1 BSPED. UK Standards for Paediatric Endocrinology, 2010. https://www.bsped.org.uk/media/1370/bspedpaediatricendocrinestandards-vs130710.pdf

RFC14.3

Dysregulated Glucose Homeostasis in Congenital Central Hypoventilation Syndrome

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Background: Congenital Central Hypoventilation Syndrome (CCHS) is a rare disorder of respiratory control resulting from heterozygous polyalanine repeat expansions within the Paired-Like Homeobox 2B (*PHOX2B*) gene. A hypoglycaemic seizure in a 4-year-old girl with CCHS, lead to a more detailed examination of glycaemic control in a cohort of children with CCHS.

Objective: To describe glucose homeostasis in children with CCHS.

Methods: An observational cohort study of glucose homeostasis in seven children (3 months to 12 years) with genetically confirmed CCHS was conducted. Glycaemic profiles were evaluated using a combination of continuous glucose monitoring (CGM), fasting studies and response to an oral glucose tolerance test (OGTT). CGM was also used to compare the effect of Diazoxide and dietary intervention in the patient who presented with a hypoglycaemic seizure.

Results: Hypoglycaemia was not elicited by fasting in any of the patients. Increased postprandial glycaemic variability was evident in all patients using CGM, with 7/7 demonstrating initial hyperglycaemia (plasma glucose concentration >7.8mmol/L 1-2 hours post-prandially), followed by asymptomatic hypoglycaemia (plasma glucose concentration ≤2.8mmol/L) in 2/7. OGTT demonstrated asymptomatic hypoglycaemia occurring at 120 mins in both patients selected on the basis of CGM-detected hypoglycaemia. A low Glycaemic Index (GI) dietary intervention and Diazoxide treatment both reduced the proportion of CGM readings <4mmol/L, however Diazoxide also increased the proportion of readings in the hyperglycaemic range.

Conclusion: Glucose variability associated with autonomic dysfunction may be unrecognised in CCHS, particularly in children with more severe phenotypes. This report highlights the occurrence of hyperglycaemia as well as hypoglycaemia in CCHS. Given the challenges of recognising hypoglycaemia based on clinical symptomatology, the use of CGM may facilitate its identification allowing appropriate management. The observed normoglycaemia during fasting combined with increased post-prandial BGL variability is more consistent with dumping syndrome than persistent hyperinsulinism. Dietary modifications therefore may be more effective than Diazoxide in managing hypoglycaemia. The long-term consequences of dysregulated glucose homeostasis in this group are unknown.

RFC14.4

A Novel Germline *DICER1* Mutation in a Girl with Multinodular Goiter and Ovarian Sertoli-Leydig Cell Tumor

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Background: DICER1 is an endoribonuclease that acts post-transcriptionally by processing mRNA into siRNA and microRNA, thus leading to mRNA downregulation. DICER1 syndrome is usually caused by germline variants and is characterized by a variety of benign or malignant tumors: pleuropulmonary blastoma, ovarian Sertoli-Leydig cell tumor, cystic nephroma, pituitary blastoma and multinodular goitre. Patients with germline aberrations in the *DICER1* gene may carry additional somatic missense *DICER1* mutations within the associated tumors, located in the metal ion-binding residues of the RNase IIIb domain.

Patient: A 10 yo girl was evaluated for thyroid enlargement. Thyroid sonography revealed three nodules in the right lobe (diameter: 1.9, 2.3, and 3 cm, respectively). Thyroid function tests were normal and thyroid autoantibodies negative. Thyroidectomy was carried out and the lesions proved hyperplastic nonmalignant. She entered puberty at age 11 years and at age 12 years, both breast and pubic hair were Tanner stage IV. Ten months later, during follow-up, breast had regressed to Tanner stage I, hirsutism was present and her voice had notably deepened. Hormonal evaluation showed Testosterone 478ng/dL, DHEAS 2480ng/mL, 17OH-progesterone 11ng/mL, Δ4 androstenedione 7.9ng/mL, LH 10.7mIU/mL, FSH 3.2mIU/mL, Cortisol 3μg/dL and ACTH 12.2pg/mL. Ovarian sonography revealed an enlarged right ovary (12cc) while the left ovary was normal (3cc). Pituitary MRI was normal. Right salpingo-oophorectomy was carried out and biopsy revealed an ovarian Sertoli-Leydig cell tumor. Ten days postoperatively androgens had returned to normal levels.

Methods: Genetic analysis of the *DICER1* gene in peripheral leukocytes and ovarian and thyroid tissues as well as immunohistochemistry of the tumors were carried out.

Results: A novel germline nonsense *DICER1* mutation (p.W1481*, c.4443G>A) was detected, inherited from her father (in whom sonography revealed multinodular goiter). Further studies in the ovarian and thyroid tissues showed two different somatic missense mutations of the same codon. The ovarian tissue carried the missense mutation p.E1813D (c.5439G>T) in heterozygous state whereas, the thyroid tissue carried the missense variant p.E1813Q (c. 5437G>C) in heterozygosity. Immunohistochemistry revealed that within these tumors, the DICER1 protein expression was significantly decreased compared to normal tissue.

Conclusion: We report a novel *DICER1* mutation (p.W1481*, c.4443G>A) and confirm that patients with germline *DICER1* mutations can develop somatic mutations within the RNase IIIb domain. Our findings show that impaired DICER1 function affects the thyroid and ovarian tissue homeostasis and offer further proof that *DICER1* is a tumorigenic driver during childhood.

RFC14.5

Natural Course of MEN Type 2B Syndrome; A Dutch Single-Center Cohort

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Background: Multiple endocrine neoplasia type 2B (MEN 2B) is a rare endocrine disease associated with early and aggressive medullary thyroid carcinoma (MTC), pheochromocytoma and several non-endocrine manifestations. MEN 2B is often diagnosed late, when symptomatic thyroid disease is present. Recognition of early, often non-endocrine, manifestations is elemental and may lead to early intervention through early diagnosis. However, early recognition is complicated by both the broad clinical spectrum of manifestations and rareness of MEN 2B.

Objective: The aim of this study is to describe disease presentation, subsequent manifestations and outcome in a MEN 2B cohort and to aid in increasing awareness for early symptoms.

Methods: A retrospective single-center cohort study was conducted at the University Medical Center Utrecht, a tertiary referral and national expertise-center for MEN-patients. All MEN 2B patients in follow-up between 1990-2017 were included and medical records were reviewed.

Results: Eight patients (3 males, 5 females) were identified, all had a de novo RET-mutation (Met918Thr). MEN 2B in this cohort most often presented with neonatal gastro-intestinal symptoms (50%), as well as with mucosal neuromas (38%) or delayed motor development (38%); not with symptomatic MTC.

Thyroidectomy cured or prevented thyroid disease in 50% of patients. Patients operated at young age (<1 year) have remained free of disease. Pheochromocytoma was detected in 2; the youngest patient presenting at an age of 16 years. All patients suffered from intestinal problems, most commonly severe and chronic obstipation which severely impacts daily life. Other common non-endocrine manifestations, which might help to raise suspicion of MEN-2B, were oral and ocular neuromas, 'hypertrophic bumpy lips', central diastemas as well as less specific symptoms such as joint hyperlaxity and a marfanoid body habitus.

Conclusion: Awareness among clinicians of symptoms of MEN 2B is important, as early diagnosis of MEN 2B is associated with still curable thyroid disease. Neonatal gastro-intestinal manifestations may offer a window of opportunity for early detection of MEN 2B, as rectal biopsies can show diffuse intestinal ganglioneuromatosis, strongly pointing to a diagnosis of MEN 2B. In addition, other non-endocrine manifestations can be the first detectable sign of MEN 2B. Therefore, these symptoms are important to recognize as they can be the clue for an early diagnosis of MEN 2B.

RFC14.6

Identification of Epithelial Sodium Channel (ENaC) in Endometrial Pipelle Biopsy Samples

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Background: The fluid milieu along the female reproductive tract has a major role in a complex series of events that follow oocyte ovulation. These include oocyte transport in the fallopian tube, the transport and capacitation of sperm, fertilization, transport of the blastocyst and implantation of the embryo in the uterus. These processes are regulated by the activity of ion channels located on the surface of endometrial epithelia. In our previous studies we showed that epithelial sodium channels (ENaC) are widely distributed in the female reproductive tract (1).

Aim: To examine the expression of ENaC in endometrial biopsy samples obtained by pipelle suction for diagnostic purposes.

Subjects: The samples were obtained from four normal control subjects and a pseudohypoaldosteronism type 1 patient with an Arg508X mutation in the SCNN1A gene that codes for the ENaC alpha subunit (2). The patient failed to conceive naturally and despite nine IVF attempts over six years.

Methods: Endometrial samples were obtained by Pipelle suction. The samples were fixed in formalin and then reacted with anti-ENaC antiserum. After reaction with secondary antibodies sample immunofluorescence were visualized by confocal microscopy. The study was approved by the ethics committee at the E. Wolfson Medical Center.

Results: The analysis showed strong ENaC immunofluorescence along the luminal border (apical membrane) of the epithelial cells in pipelle samples from healthy subjects. In contrast, none of the samples from the PHA patient showed ENaC immunofluorescence. The Arg508X mutation interrupts transport of ENaC subunits to cell surface, yet it would not be expected to disrupt ENaC localization in the cytoplasm. In contrast to endometrium where ENaC is localized in the apical membrane of the epithelial cells, in keratinocytes ENaC is expressed in cytoplasmic pools. Thus, we examined ENaC immunofluorescence in plucked hair follicles from normal subjects and the PHA patient. As expected, ENaC immunofluorescence was detected in the cytoplasm of keratinocytes of both normal and PHA samples. **Conclusion**: Our results show that endometrial samples obtained by pipelle biopsy can be used for identification of key proteins by immunofluorescence.

References

Enuka Y, Hanukoglu I, Edelheit O, Vaknine H and Hanukoglu A (2012) Histochem Cell Biol 137 339–353.

Hanukoglu A, Edelheit O, Shriki Y, Gizewska M, Dascal N and Hanukoglu I (2008) J Steroid Biochem Mol Biol 111 268–274.

Growth and Syndromes

RFC15.1

Diagnosis of Silver-Russell Syndrome in Patients with Chromosome 14q32.2 Imprinted Region Disruption: Phenotypic and Molecular Analysis

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Background: Silver-Russell syndrome (SRS) (mainly secondary to 11p15 molecular disruption) and Temple syndrome (TS) (secondary to 14q32.2 molecular disruption) are imprinting disorders with very close phenotypic (prenatal and postnatal growth retardation, early feeding difficulties, early puberty) and molecular anomalies. Our objective was to describe the clinical overlap between SRS and TS and to extensively study the molecular aspects of patients with 14q32.2 molecular disruption.

Patients: We identified 28 patients with disruption of the 14q32.2 imprinted region in our center. We retrospectively analyzed clinical data and performed extensive molecular analysis in these patients including multiloci methylation analysis and exome sequencing.

Results: A majority of patients (60.7%) showed loss of methylation of the *MEG3/DLK1* intergenic differentially methylated region (IG-DMR) by epimutation. Eight (28.6%) patients had maternal uniparental disomy of chromosome 14 and three (10.7%) had a paternal deletion in 14q32.2. Netchine-Harbison SRS clinical scoring system was ≥4/6 and consistent with a clinical diagnosis of SRS in most patients (72.7%). Multiple methylation defects (MLMD) were identified in 58.8% of patients with *MEG3/DLK1* epimutation. No correlation was found with the phenotype of the patients. No mutation, deletions or duplications of the 14q32.2 region were identified in patients with epimutation. Four potentially damaging genetic variants in genes encoding proteins involved in the establishment or maintenance of DNA methylation were found by exome sequencing. Among these patients, one with MLMD affecting six loci aside from 14q32.2, inherited an unreported maternal variation in the *ARID4A* gene.

Conclusions: We provide clinical and molecular data to support that, as raised in the SRS international consensus, 14q32.2 disruption may be considered as an alternative molecular diagnosis of SRS. *MEG3/DLK1*:IG-DMR hypomethylation should be investigated in case of suspected SRS without chromosome 7 or 11p15 region anomalies. These clinical data encourage similar consideration and management for TS and SRS patients with a special attention to their young age at puberty onset and their early BMI increase. In case of *MEG3/DLK1*:IG-DMR hypomethylation identification, an additional molecular analysis must be carried out to identify any paternal deletion within the 14q32.2 region because of the different prognosis and management of these patients. The MLMD frequency being particularly high in this population and the absence of cis-regulatory element defects strongly suggest that these imprinting disturbances may be secondary to the dysfunction of one or several trans-acting factors.

RFC15.2

Molecular and Clinical Analyses of Two UPD(16)Mat Patients Detected by Screening of 94 Silver-Russell Syndrome Patients Without Known Etiology

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Background: Maternal uniparental disomy of chromosome 16 (UPD(16)mat) is defined as the presence of two homologous chromosomes 16 inherited from only the mother. To our knowledge, 49 live-born UPD(16)mat patients without chromosomal abnormalities other than that in chromosome 16 have been reported. UPD(16)mat patients presented with non-specific clinical features such as preterm birth, growth retardation, congenital heart diseases (CHDs) and hypospadias. Silver-Russell syndrome (SRS) is characterized by growth failure and dysmorphic features. Hypomethylation of the *H19/IGF2*:IG-differentially methylated region (DMR) at the 11p15 imprinted region (*H19*-hypo) and maternal uniparental disomy of chromosome 7 (UPD(7)mat) are major genetic causes of SRS. Recently, a patient with UPD(16)mat presenting SRS phenotype was reported. However, the prevalence of UPD(16)mat in SRS patients and the phenotypic difference between UPD(16)mat and SRS have been poorly documented.

Methods: We studied 94 SRS patients without known etiology. Sixty-three out of 94 patients satisfied Netchine-Harbison clinical scoring system (NH-CSS) criteria (SRS-compatible) and the remaining 31 patients met three NH-CSS criteria together with triangular face, fifth finger clinodactyly and/or brachydactyly. To detect UPD(16)mat, we performed methylation analysis for the *ZNF597*:TSS-DMR and subsequently performed microsatellite, single-nucleotide polymorphism array and exome analyses in patients with a hypo-methylated *ZNF597*:TSS-DMR.

Results: We identified two patients (3.2%) with a mixture of maternal iso- and heterodisomy of chromosome 16 in the SRS-compatible group. Both patients exhibited preterm birth, growth failure, and mild intellectual disability. The male patient had ventricular septal defect and hypospadias. Whole exome sequencing detected no gene mutations related to their phenotypes.

Discussion: Our study suggests that UPD(16)mat constitutes a rare but important underlying factor for SRS. We compared the clinical findings between patients with UPD(16)mat in the literature and this report and previously reported patients with *H19*-hypo or UPD(7)mat. The median of gestational ages in UPD(16)mat was earlier than in *H19*-hypo and UPD(7)mat. The frequen-

cy of SGA was significantly lower in UPD(16)mat than in both *H19*-hypo and UPD(7)mat, and that of CHDs was significantly higher in UPD(16)mat than in both *H19*-hypo and UPD(7)mat. Genetic testing of UPD(16)mat should be considered for etiology-unknown SRS cases with preterm birth and CHDs, even if they are not born SGA.

RFC15.3

Multiple Pituitary Hormone Deficiencies and Early Onset Obesity in Two Siblings with a Mutation in the *MAGEL2*-Gene.Evidence for an Important Regulatory Function of the *MAGEL2*-Gene in the Hypothalamic-Pituitary Hormone Pathways

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We have investigated 2 siblings, a sister and a brother, who presented at the age of 2 years, with central hypothyroidism, short stature and early onset obesity. The older sister presented at the age of 6 months with central hypothyroidism and was started on a low dose of thyroid hormone (25 ug l-thyroxine). Her growth continued to be poor and at the age of 2 years and 6 months her height was -3,98 SDS. She was started on growth hormone followed by a rapid catch-up growth and an improvement of body height.

The younger brother presented at the age of 1 year and 4 months with a height of -3,81 SDS and was started on thyroid- and growth hormone. The BMI at start of therapy was 19,8 and 25,6 for the sister and brother, respectively, both numbers well above the 97.%ile. Leptin levels were not measurable and/or repeatedly below the normal range in both children but neither had an increased appetite. Polyuria and polydipsia is present in the boy, but CT-ProVasopressin in relation to serum osmolality was not reduced.

We performed an MRI of the brain in the boy, which showed a small pituitary and a small stalk. The MRI in the girl was done abroad and reported to be normal.

We performed genetic analysis and detected in both children a heterozygous mutation in the *MAGEL2*-gene (c.2909G>A, p.Trp970Ter) which led to a premature stop. Similar nonsense-mutations have been described in Schaaf-Young-syndome, a Prader-Willi-like syndrome and the *MAGEL2*-gene is one of the five protein-coding genes in the Prader-Willi-syndrome region on chromosome 15q11-13. The mutation described here is novel, meaning that is has not been reported before. We could not find this mutation in the parents, suggesting it to be *de novo*.

In conclusion, we found as a cause of multiple pituitary hormone deficiencies a stop-codon mutation in the *MAGEL2* – gene. Both children had developmental delay, but no autistic features yet. The multiple hormone deficiencies are most likely due to a regulatory defect in the hormone secretion of wide variety of hypothalamic-pituitary hormones. The *MAGEL2*- gene seems to play an important role in the organization of central hormone secretion.

RFC15.4

Characteristics, Effectiveness and Safety Data from Clinically Relevant Subgroups of Patients with Severeprimary IGF-I Deficiency (SPIGFD): Results from the European Increlex® Growth Forum Database (EU-IGFD) Registry

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Background: The EU-IGFD registry was established to monitor the safety and effectiveness of recombinant human IGF-I (rhIGF-I) (mecasermin [rDNA origin] injection; Increlex®) for short stature in children with SPIGFD, including those with Laron syndrome (LS).

Objective: To report patient characteristics, effectiveness and safety data in clinically relevant patient subgroups.

Methods: Data were compiled from this ongoing observational study (NCT00903110; 10-May-2017 cut-off) for three treatment-naïve prepubertal (NPP) cohorts: LS (irrespective of treatment-response status); non-LS with treatment response (non-LS-responder; responder=year-1 height SDS change ≥0.3); non-LS with poor treatment response (non-LS-poor-responder). Two cohorts who were not treatment-naïve or who were pubertal (non-NPP) were additionally characterized (LS and non-LS).

Results: Characteristics: Of 246 patients enrolled, 213 were included in the analysis (NPP: 21 LS, 50 non-LS-responder, 38 non-LS-poor-responder; non-NPP: 17 LS, 87 non-LS). Of 33 patients excluded: 29 missing treatment-response status; 4 missing pubertal status and/or missing previous treatment. Cohorts had more males than females (NPP cohorts: LS 12/21 vs. non-LS-responder 30/50 vs. non-LS-poor-responder 27/38; non-NPP cohorts: LS 10/17 vs. non-LS 59/87). At first rhIGF-I intake, mean (SD) ages for NPP cohorts were 6.07 (3.49) vs. 7.00 (3.11) vs. 10.28 (3.53) years, respectively, and for non-NPP cohorts were 12.78 (3.73) vs. 11.43 (3.58) years, respectively. Mean (SD) height SDS in NPP cohorts were –5.62 (1.95) vs. –3.49 (1.15) vs. –3.44 (0.90) and in non-NPP were –4.63 (1.51) vs. –3.61 (1.20). At first rhIGF-I intake, mean (SD) height velocities (HVs) in NPP cohorts: 5.67 (1.10) vs. 4.99 (1.66) vs. 4.19 (1.98), and in non-NPP: 4.43 (1.23) vs. 4.70 (1.84). Effectiveness (year 1): Mean (SD) height SDS changes from baseline in NPP cohorts: 0.70 (0.56) vs. 0.64 (0.26) vs. 0.01 (0.21), and in non-NPP: 0.19 (0.50) vs. 0.24 (0.47). All year-1 HVs (cm/year) improved (mean [SD] for NPP: 8.25 [2.54] vs. 8.06 [1.69] vs. 5.66 [1.36]; non-NPP: 5.50 [2.88] vs. 6.48 [2.37]). Safety: Targeted adverse events (TAEs) occurred in NPP cohorts for 15/21 (71.4%) vs. 24/50 (48.0%) vs. 14/38 (36.8%) patients and in non-NPP for 13/17 (76.5%) vs. 38/86 (44.2%). The TAE reported in the greatest proportion of patients was hypoglycemia, except in non-LS-poor-responders (headache).

Conclusions: NPP responded better to treatment than non-NPP at year 1. Among NPP, patients with LS were younger and shorter than non-LS at first IGF-I intake, but showed a slightly better response at year 1. Safety is consistent with the known profile of mecasermin.

RFC15.5

Effect of Adjusting for Tanner Stage Age on Short and Tall Stature Prevalence in US Youths

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Background: Although differences in pubertal timing alters frequency of indicators of attained stature at the extremes, its magnitude is unknown across ethnic groups of US youths.

Methods: We performed analyses of anthropometry and Tanner staging data of 3206 cross-sectional national sample of youths ages 8–18y (53% male (n=1606), 72% Non-Hispanic White (NHW), 9% Mexican American (MA) and 19% Non-Hispanic Black (NHB). Specialized Tanner-stage-age growth models were used to derive Tanner-age adjusted Z-scores. The prevalence of short (<-1SD) and tall (>=+1SD) status was quantified after adjustment for Tanner stage-age height Z-scores (TSA_{HAZ}). We then examined average growth patterns with age splines across estimated Z-scores by sex and race/ethnicity.

Results: Highly variable patterns of prevalence of shortness and tallness via chronologic-age height Z-score (CA_{HAZ}) was observed in results stratified by Tanner stages, race-ethnicity and sex. Tallness CA_{HAZ} prevalence was high among NHW and NHB males relative to MA (40.0–43.3, vs 20.5%) and in females, the ranking was (39.2% NHB > NHW 29.6 > MA 20.3, each p =0.0167). In both sexes, this pattern was eliminated with TSA_{HAZ}, with MA youth becoming statistically not different from their NHW and NHB peers on both stature indicators.

Conclusions: Differences in timing of puberty between race-ethnic groups affects estimated prevalence of shortness and tallness of attained height. Considerable pubertal maturation effects remain uncaptured with age-conditioned height Z-scores. Adjustment for pubertal development might help isolate crucial determinants of attained stature and other aspects of body composition which may be most responsive to intervention programs in populations of youths.

RFC15.6

Latest Results from PATRO Children, A Multi-Centre, Non-Interventional Study of the Long-Term Safety and Efficacy of Omnitrope® in Children Requiring Growth Hormone Treatment

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Objectives: PATRO Children is a non-interventional, international, longitudinal study of the long-term safety of a recombinant human growth hormone (rhGH; Omnitrope®, Sandoz). In particular, the study will assess the diabetogenic potential of rhGH and the risk of malignancies. The long-term efficacy is a secondary objective of the study.

Methods: The study population includes infants, children and adolescents receiving Omnitrope® therapy according to local prescribing information. All adverse events (AEs) are monitored and recorded for evaluation of rhGH safety. Laboratory values (including glucose metabolism and anti-hGH antibodies) are requested at least once a year. Height standard deviation score (HSDS), height velocity (HV) and HVSDS are calculated using height measurements and country-specific reference tables to evaluate rhGH efficacy.

Results: As of March 2018, 6214 patients were recruited from 299 sites in 14 countries. The mean (standard deviation [SD]) Omnitrope® treatment duration was 36.9 (25.8) months (approx. 3 years), with 1541 (24.8%) patients completing 5 years of treatment. Overall, 84.4%% of patients were rhGH naïve and 15.1% had previously received rhGH treatment. Since September 2006, 2930 (47.2%) patients reported 11408 AEs, with 583 AEs in 415 (6.7%) patients suspected to be related to treatment. Overall, 1261 AEs in 668 (10.7%) patients were regarded as serious; of these, 52 events in 39 (0.6%) patients were suspected to be related to treatment. Drug-related serious AEs included type 1 diabetes mellitus (n=1 SGA patient, rhGH treatment discontinued), impaired glucose tolerance (n=1 SGA patient, rhGH treatment discontinued), craniopharyngioma (n=1 GHD patient, no change to rhGH treatment), germ cell cancer (n=1 GHD patient, rhGH treatment discontinued), neoplasm progression (n=1 GHD patient, rhGH treatment interrupted) and malignant astrocytoma recurrence (n=1 patient with other indication, rhGH treatment interrupted). No clinically relevant positive anti-hGH antibody titers have been found after the start of rhGH therapy in patients tested so far. Efficacy data indicate that rhGH treatment has a positive impact on growth parameters in the majority of pediatric indications. Following 3 years of treatment, the improvement in HSDS from baseline was +1.31 and +1.40 in prepubertal treatment-naïve GHD and SGA patients, respectively. At 3 years, HVSDS improved from baseline by +4.74 and +4.14 in prepubertal naïve GHD and SGA patients, respectively.

Conclusion: The latest data snapshot from the ongoing PATRO Children study suggests that rhGH is well tolerated and efficacious across pediatric indications; these findings will be confirmed by further analyses.

Poster Presentations

Adrenals and HPA Axis P1

P1-P001

Evaluation of Long Term Metabolic Effects After Prenatal Dexamethasone Treatment in the Context of CAH - The Swedish Cohort

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Background: Prenatal dexamethasone (DEX) treatment is in many countries offered to the pregnant woman, at risk of having a child with classic congenital adrenal hyperplasia (CAH), to reduce virilization in an affected female fetus. The treatment is effective in reducing virilization but may give long lasting effects on somatic and cognitive health. Here, we explore the potential effect on metabolism in children and adults not having CAH and exposed to DEX during the first trimester of fetal life.

Objective and hypotheses: We hypothesize that prenatal DEX treatment has negative effects on glucose and lipid metabolism.

Method: All treated subjects (n=40, age range 5,2-26,4) as well as control subjects (n=75, age range 4,5-25,9) gave blood samples after one night fast to assess blood count, renal function, glucose homeostasis and the incidence of dyslipidemia. The glomerular filtration rate was calculated using four different methods. Insulin resistance and beta-cell function was determined with HOMA-beta and HOMA-IR. For significant differences, we performed post hoc tests to further verify the results.

Results: There were no significant differences between the groups regarding age, weight, height, BMI or birth data. The results show no significant effects of prenatal DEX treatment on blood count, renal function, glucose homeostasis and dyslipidemia (all p >0.05). In the MANCOVA there was a significant DEXxSEX interaction for the parameter C-peptide (p=.043), but the result did not remain significant after post-hoc analysis.

Conclusion: There is no major impact of first trimester DEX treatment on metabolism in childhood and in young adulthood. However, the long-term effects during late adulthood remain to be investigated. The eldest DEX treated individual in our cohort was, at time of testing, only 26 years old. Metabolic diseases usually present later in life which makes the need for longer follow-up necessary.

P1-P002

Obesity and Cardio-Metabolic Risk Factors Among Children and Adolescents with Non Classic 21-Hydroxylase Deficiency

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Background: Increased risk of obesity and cardio-metabolic risk factors were reported in patients with classical congenital adrenal hyperplasia but little is known about adiposity among patients with non-classical congenital adrenal hyperplasia (NC-CAH).

Aim: To assess the prevalence of overweight, obesity and cardio-metabolic risk factors among NCCAH patients.

Methods: A cross-sectional retrospective study of 114 NCCAH patients (93 females; mean age at assessment 17.1±6.9 years) diagnosed before age 18. Clinical assessment included anthropometric measurements, body composition (bio-impedance, waist-to-hip ratio) and blood pressure. Laboratory evaluation included fasting glucose, insulin, and lipid profile. Prevalence of overweight/obesity was calculated for the entire cohort. Data of patients in grades 7-12 (n=76) were compared to those of the National Health and Nutrition Survey (grades 7-12).

Results: For the entire cohort rates of overweight and obesity were 21.9% and 11.4% respectively. Prevalence of obesity or obesity+overweight for patients in grades 7-12 was comparable to that in the Israeli population (10.5 vs. 15.1% p=0.24, 34.2 vs. 41.6% p=0.18). No significant difference was found between treated (n=76) and untreated patients (n=38) in any of the metabolic or anthropometric parameters except for lower fat mass in untreated patients: fat in % of body weight - 21.4±8.3 vs. 27.8±6.8, p=0.02. Longer duration of steroid treatment was associated with increased systolic (r=0.26, p<0.05) and diastolic (r=0.31, p<0.01) blood pressure and with higher hip circumference (r=0.54, p<0.0005) but inversely related with BMI-SDS (r= -0.20, p<0.05).

Conclusion: NCCAH diagnosed in childhood (treated or untreated) is not associated with increased risk of overweight, obesity or metabolic derangements.

P1-P003

Cognition in Children with Congenital Adrenal Hyperplasia

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Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is one of the most common autosomal recessive disorders, affecting around 1/10 000 newborns worldwide. Postnatally, patients with classic CAH are treated with life-

long glucocorticoid (GC) replacement therapy, such as hydrocortisone or prednisolone, and in the more severe cases also with mineralocorticoids. A negative impact of GCs on human cognition such as memory deficits have been reported both in disease, such as Cushing´s syndrome characterized by prolonged exposure to elevated GCs, as well as in healthy people using synthetic GC in an experimental design. Therefore, it is possible that long-term glucocorticoid replacement therapy might affect cognitive and affective functions in patients with CAH as well. In addition, neonatal salt-losing crisis may have an additive negative effect on cognitive performance.

Objective: To investigate cognition in children with congenital adrenal hyperplasia (CAH) and the impact of prenatal DEX treatment.

Design, patients and setting: An observational study comparing children with CAH, (n = 45, mean age, 11.8 yr; range 7-17 yr) with population controls (n = 66, mean age 10.7; range 7-17 yr). All CAH children were identified through the national neonatal screening program. Eleven of 45 children with CAH (f= 6, m= 5) were treated prenatally with dexamethasone (DEX).

Measurements: Standardized neuropsychological tests (Wechsler scales and the Stroop interference test) were used to assess cognition.

Results: Children with CAH performed equally well on tests assessing general intellectual ability and executive functions compared to populations controls and better on tests assessing learning and memory (p= 0.046). We could not find differences in cognitive perfomance between children with salt-wasting versus simple-virilising CAH. Prenatally DEX-treated girls with CAH performed significantly poorer on tests assessing verbal intelligence compared to girls with CAH that had not receive prenatal treatment (p = 0.018).

Conclusion: Children with CAH identified through the national neonatal screening program in Sweden for CAH have normal cognitive functions. These findings are in contradiction with a previous report from UK where children with CAH who were not subjected to neonatal screening had impaired executive functions already at an early age. Our results indicate that prenatal DEX therapy may affect verbal intelligence in girls with CAH.

Keywords: cognition; congenital adrenal hyperplasia; glucocorticoids; dexamethasone; prenatal treatment.

P1-P004

Carriers of CYP21A2 Mutations Have Decreased Mortality in Infectious Diseases, Anational Population Registry Study

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Background: Congenital adrenal hyperplasia (CAH) is a relatively common monogenic recessive disorder with an incidence of 1/15 000 in most populations. It has been suggested that *CYP21A2* deficiency is relatively common because it may confer a survival advantage to be a carrier. Carriers of *CYP21A2* mutations typically do not have clinical symptoms but have a defined phenotype. The cortisol response to ACTH stimulation has been shown to be both more prompt and increased compared to healthy, non-carrier, controls. We have previously shown that carriers are less vulnerable to psychological stress.

In this study, we investigated the mortality, and cause of mortality in carriers compared to population controls.

Method: A total of 1143 (561 men, 582 women) obligate carriers of a *CYP21A2* mutation, were identified using the Swedish National CAH Registry encompassing more than 700 CAH patients and the Multigeneration Registry. Controls, matched for year of birth and sex, were identified from the general population, 100 controls per study subject. The mortality and cause of death was identified through the Swedish Cause of Death Registry. The Hazard Ration (HR) was calculated.

Results: The overall mortality was lower in carriers of one of the classic *CYP21A2* mutations compared to the general population, for women (p=0.05), but not for the whole cohort (p=0.12). Infection as the cause of death was significant with HR 0.651 (CI 95%, 0.485-0.874; p=0.0043). In particular, a lower mortality in pneumonia was seen HR 0.220 (CI 95%, 0.055-0.881; p=0.03). There was no difference in mortality due to cancer. The generally observed lower overall mortality among women compared to men was confirmed in our study, both among the carriers and the controls.

Conclusion: Obligate *CYP21A2* carriers had a reduced mortality, and specifically a reduced mortality due to pneumonia. The increased capacity to synthesize cortisol in acute situations could be the explanation for an evolutionary advantage of being a carrier of a *CYP21A2* mutation.

Our results suggest a better ability to cope with the somatic stress of severe infections among heterozygous carriers of severe *CYP21A2* mutations. This may contribute to the apparent survival advantage since infectious diseases represent a common cause of death, especially in a historical perspective and in the history of mankind.

P1-P005

Elevated Concentrations of Adrenal Steroid Precursors with Glucocorticoid Activity Might Prevent Addisonian Crisis in Untreated Patients with Classic Congenital Adrenal Hyperplasia

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Introduction: Congenital adrenal hyperplasia (CAH) is most often caused by 21-hydroxylase deficiency (21OHD: 95%) or by 11-hydroxylase deficiency (11OHD). Classic CAH results in impaired cortisol production and consequently elevated ACTH concentrations leading to chronic adrenal stimulation with strongly elevated adrenal steroid precursors before the enzymatic defect. In contrast to other forms of adrenal insufficiency, some untreated classic CAH patients seem to have less clinical signs of cortisol deficiency.

Hypothesis: Elevated adrenal steroid precursors have agonistic glucocorticoid receptor (GR) activity, thereby compensating for the cortisol deficiency in CAH patients.

Methods: Clinical data of untreated classic CAH patients (age 3-46 years) from Indonesia (n=22) were collected. Adrenal steroids and precursors were measured by LC-MS/MS before and after ACTH stimulation. *In vitro* GR transactivation studies were performed using a dual luciferase assay in HEK293 cells transfected with the GR, that were incubated for 24 hours with increasing concentrations of steroids.

Results: Thirteen untreated classic CAH patients (59%) reported severe stress situations in the past: genital surgery (n=6), vomiting and/or seizures (n=5) or dengue or typhoid fever (n=3). All patients improved without application of glucocorticoid medication. Serum morning cortisol concentrations (before 9.00 am) were low without any increase after ACTH stimulation (median 73 (21OHD) and 180 (11OHD) nmol/L). Adrenal steroid precursors were strongly elevated (in 21OHD: 17-hydroxyprogesterone, 21-deoxycortisol, progesterone and in 11OHD: 11-deoxycortisol, deoxycorticosterone) without increase after ACTH stimulation. *In vitro* exposure of HEK293 cells showed that the GR was activated with similar potency to cortisol by corticosterone and 21-deoxycortisol. 11β-hydroxyprogesterone, 11-deoxycortisol, aldosterone, deoxycorticosterone, progesterone and 17-hydroxyprogesterone also led to GR transactivation, with a 4-100x lower potency than cortisol.

Conclusion: Untreated classic CAH patients may survive in severe stress situations even without application of stress-dosing of glucocorticoids. The elevated concentrations of adrenal steroid precursors, which are able to activate the GR, might compensate for the cortisol deficiency. Further studies have to be performed to study the clinical consequences of these findings.

P1-P006

Altered DNA Methylation in Peripheral T-Cells from Patients with Congenital Adrenal Hyperplasia

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Background: Patients with Congenital Adrenal Hyperplasia (CAH) are at risk of several co-morbidities, such as impaired cognitive functions, short stature and adverse effects on metabolism. The causes of these effects are suboptimal glucocorticoid replacement therapy, adrenal crises and prenatal glucocorticoid exposure. However, there are no data available to this day how these factors are affecting epigenomic programs.

Objective and hypotheses: We investigated DNA methylation in patients with CAH. We hypothesized that the epigenetic programming in patients with CAH is affected.

Method: We used CD4+ T-cell DNA from patients with CAH, and population controls (n=63). The Infinium HumanMethylation450 BeadChip array was used to measure locus specific DNA methylation. Statistical analyses were performed in R.

Results: By comparing DNA methylation between patients with CAH and population controls we identified differential methylation in peripheral T-cells. Changes were associated with CAH *per se*, but we also identified significant correlations between DNA methylation and the subject's phenotype (salt-wasting,simple virilising or unaffected) as well as the *CYP21A2* genotype.

Conclusion: Our findings suggest that DNA methylation is altered in patients with CAH. These changes may be relevant for the health of the individual.

P1-P007

Birth Incidence, Age at Diagnosis, Mortality in Congenital Adrenal Hyperplasia in Korea: A Nationwide Population-Based Study

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Background: Congenital adrenal hyperplasia (CAH) is a disease inherited by autosomal recessive manner and one of the most common congenital metabolic disorders. The incidence of CAH has been reported mainly through neonatal screening tests, mostly for 21-OHD. It is reported that 21-OHD occurs one in 15,000 peo-

ple per year. However, there are few studies on all types of CAH incidence including 21-OHD. CAH is a rare disease, studies on large populations are needed to identify a significant number of cases. In Korea, CAH has been designated as a Rare Intractable Disease (RID) since 2008 and is being managed by implementing financial support in the country. We investigated the birth incidence, age at diagnosis, and mortality of CAH patients using this database.

Objective: In Korea, CAH patients are register in the Rare Intractable Disease (RID) program run by the government. The strength of the RID program is that predefined criteria are used for registering patients, which ensures diagnostic accuracy. We studied CAH patients identified through the Rare Intractable Disease (RID) registration code V115 (E25.0 in ICD-10, E250 in KCD) during the 10-year study period (2006–2015), and data on health care utilization of the patients were collected from the health insurance review and assessment(HIRA) database between 2004 and 2015.

Result: From 2004 to 2015, 506 CAH patients were born in Korea and CAH annual birth incidence was 9.6 / 100,000 live births (10,438: 1). There were 8.6 boys / 100,000 live births, 8.7 girls / 100,000 live births, and male / female sex ratio was 1.05: 1. The age at diagnosis ranged from 0 to 8 years. Within 3 months of age, total 83.8% were diagnosed, with 88.0% in boys and 79.1% in girls. As a result, 15% of all patients were not diagnosed through the neonatal screening test. The number of confirmed deaths was 9, and SMR was 1.8%. Patients diagnosed after 3 months had a statistically significant 4-fold higher risk of death (HR 4.06, CI 1.07-15.70).

Conclusion: As our results show, CAH incidence through neonatal screening test is likely to be underestimated in the real world, which is why our findings differ from existing incidence results. A non-biased evaluation from a national level study with a sample size of more than 50 million people and reliable diagnosis could provide valuable information on the epidemiologic features of CAH patients.

P1-P008

Impact of Puberty on Final Height in Children and Adolescents with Congenital Adrenal Hyperplasia (CAH)

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Introduction: An optimized replacement regimen with glucocorticoids and mineralocorticoids in subjects with congenital adrenal hyperplasia (CAH) aims at preventing life-threatening salt wasting and adrenal crises, virilization and pubertal precocity, and at enabling normal linear growth.

Aims: We investigated puberty and its impact on final height in children and adolescents with CAH

Patients and Methods: In a cohort of post-pubescent male (n=172) and female (n=284) adolescents with CAH, the following parameters, documented in the German CAH registry, were retrospectively analyzed: Age at pubertal onset (Tanner stage B2 / single testicular volumes ≥ 4 ml), final adult height and parental target height, the Δ between height SDS of the subjects during ages 0-4, 5-8, 9-12, 13-16 and >16 years and their corresponding target height SDS. In addition, the relationship of age at pubertal onset and the Δ between height SDS at pubertal onset and final height SDS were investigated. Puberty data were compared to published references from the Danish puberty study; height references were retrieved from the German AGA registry.

Results: Median age at pubertal onset was 9.75 [Q1;Q3:8.43;10.74] years in CAH females (vs. 10.88 years in the reference population), and 10.83 [8.69;12.99] years in CAH males (vs. 11.66 years). Male patient´s median final height was 7 cm below their median target height (172 [166;178] vs. 179 [174;182] cm); and female´s 3 cm below it (161 [156;167] vs. 164 [161;168] cm). While median height-SDS *before* pubertal onset in both sexes was *above* median target height SDS, it continuously dropped *during* puberty on a value *below* it. This pubertal height SDS-*loss* was highest in subjects with *precocious* pubertal onset: 2.5 [1.4;3.3] SDS in boys with pubertal onset ≤ 9 years / 2.1 [1.5;2.5] SDS in girls with onset ≤ 8 years. Boys with *normal* pubertal onset (at ages 10-13) experienced a height SDS-*loss* of 1.0 [0.3;1.8]; girls with *normal* pubertal onset (at ages 9-12) a loss of 0.7 [0.1;1.2]. In boys with *late* puberty (at ages ≥ 14), height SDS-*loss* was 0.4 [0.2;0.9]. By contrast, girls with *late* pubertal onset (at ages ≥12) experienced a height SDS-*gain* of 0.5 [-0.2;0.9].

Conclusion: Current treatment is more effective in delaying pubertal precocity in CAH boys than in girls. Height SDS loss occurs in both sexes during puberty; it is inversely correlated to age at pubertal onset. Adult height within mid-parental expectations is reached more often in CAH females than in males.

P1-P009

The Relationship of Baseline, Incremental and Peak Cortisol Following a Short Synacthen Test – Single-Centre Analysis of Three Years' Data

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Introduction: The Short Synacthen Test (SST) is the most popular diagnostic investigation of adrenal insufficiency (AI) amongst adult and paediatric endocrinologists. AI can present insidiously and symptoms may be non-specific. The number of medical indications for glucocorticoids is growing and SST usage is correspondingly increasing. There is evidence that an early morning plasma cortisol (EMC) of below ~100-150nmol/L is highly predictive of failing the SST and the corollary is seen with an EMC above

~336-400nmol/L. Using an EMC to screen patients for AI has been advocated to reduce the number of invasive, time-consuming and resource-intensive SSTs, although there is a paucity of studies in children. More sensitive and specific modern cortisol assays make deriving local diagnostic thresholds important. We analysed our SST data since the introduction of a new cortisol assay to derive our own screening thresholds for SST and examined the relationship between the basal, incremental and peak plasma cortisol following synacthen stimulation.

Methods: All SST performed at Sheffield Children's Hospital, UK, between September 2014 and 2017 were retrospectively analysed. Cortisol quantification was performed on the Abbott Architect i1000 chemiluminescent immunoassay (CVs <5%). A "pass" for both the high and low-dose SST is currently 450nmol/L. Basal cortisol was used as a surrogate for EMC and correlation coefficients with increment and peak examined. Subgroup analysis was performed using sex and an age-approximate for pubertal status (0-9 and 10-16 years old). Positive and negative predictive values using a basal plasma cortisol of <160nmol/L and >340nmol/L respectively were calculated.

Results: Overall 393 SSTs were included (209M, 184F, 175 „prepubertal", 218 „post-pubertal"). The correlation coefficient for basal and peak cortisol was 0.63, (0.63 female, 0.62 male; 0.65 0-9 years, 0.66 10-16 years of age). There was no relationship in any of the groups between basal and incremental cortisol (overall data correlation coefficient 0.061). Of the cohort 28% had basal cortisols <160nmol/L of which 54% "failed" the SST, PPV=0.54. Correspondingly 13% had basal cortisols >339nmol/L, none of whom "failed" the SST, NPV=1.

Conclusions: There is a reasonably strong relationship between basal and peak cortisol on the SST, but no relationship exists between basal and incremental cortisol. Subgroup analysis did not significantly strengthen the correlations. On the Abbott Architect plasma cortisol assay an EMC of >339nmol/L appears to safely predict passing the SST and <160nmol/L yields a high PPV for failing the SST.

P1-P010

The Circadian Rhythm of Cortisol Binding Globulin Has Little Impact on Cortisol Exposure After Hydrocortisone Dosing

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Background: Optimisation of hydrocortisone replacement therapy remains challenging due to complex pharmacokinetics as circulating cortisol is protein bound mainly to corticosteroid-binding globulin (CBG) that has a circadian rhythm.

Objective: a detailed analysis of the CBG circadian rhythm and its impact on cortisol exposure during hydrocortisone replacement therapy.

Methods: CBG was measured over 24 h in 14 healthy individuals and, employing a modelling and simulation approach using a semi-mechanistic hydrocortisone pharmacokinetic model, we evaluated the impact of hydrocortisone administration at different clock times and the changing CBG concentrations on cortisol exposure.

Results: The circadian rhythm of CBG was well described with two cosine terms added to the baseline of CBG: baseline CBG was 21.8 µg/mL and inter-individual variability CV 11.9%; the amplitude for the 24 and 12 h cosine functions were relatively small (24 h: 5.53%, 12 h: 2.87%) and C_{maxCBG} at 18:00h and C_{minCBG} 02:00h. In simulations, the lowest cortisol exposure (AUC, C_{max}) was observed after administration of hydrocortisone at 23:00-02:00, whereas the highest was observed at 15:00-18:00. The differences between the highest and lowest exposure were minor (<11%).

Conclusions: CBG has a circadian rhythm but the difference in cortisol exposure is <11% between times of highest and lowest CBG concentrations; therefore hydrocortisone dose adjustment based on time of dosing is not required.

P1-P011

Characterizing the Steroidome in Ammniotic Fluid of Mid-Gestation by LC-MS/MS

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The amniotic fluid (AF) milieu is complex and essential to fetal well-being. Here we present a new LC-MS/MS method for the targeted metabolomics analysis of 20 unconjugated and conjugated steroids in 65 AF samples during mid-gestation.

Sample preparation included protein precipitation, centrifugation, solid phase extraction and derivatization. We measured progesterone (Prog), 17α-hydroxyprogesterone (17OHProg), testosterone (T), estrone (E1), estradiol (E2), estriol (E3), estrone sulfate(E1S), 17β-estradiol 3-sulfate (E2S), estriol 3-sulfate(E3S), 17β-estradiol 17-sulfate (E2-17S), 16α-hydroxy dehydroepiandrosterone sulfate (16OHDHEAS), dehydroepiandrosterone sulfate (DHEAS), pregnenolone sulfate (PregS), 17α-hydroxypregnenolone sulfate (17OHPregS), testosterone sulfate (TS), epitestosterone sulfate (eTS), dihydrotestosterone sulfate (DHTS), androsterone sulfate (AnS), epiandrosterone sulfate (epiAnS), and 3,17β-androstenediol 3-sulfate (AnDiolS). Except DHEAS, all other sulfated steroids were quantified by LC-MS/MS in AF for the first time. The compounds with highest concentrations were Prog (16.39-78.55 ng/mL), 17OHProg (0.38-2.04 ng/mL), PregS (2.57-20.25 ng/mL), 17OHPregS (2.08-13.18 ng/mL), epiTS (2.92-17.81 ng/mL), DHEAS (1.54-12.27 ng/mL), 16OHDHEAS (6.87-62.91 ng/mL), AnS (0.90-39.39 ng/mL), E1S (0.38-25.26 ng/mL), E3 (0.59-2.60 ng/mL), E3S (2.16-20.99 ng/mL).

We have produced MS based reference values for 20 steroids in AF of mid-gestation. DHEAS and E3S were both strongly correlated with 16OHDHEAS, thus confirming the classic concept of

the feto-placental unit. Our LC-MS/MS method can be used for prenatal diagnosis of congenital adrenal hyperplasia and low-E3 diseases such as aromatase and ORD deficiencies, X-linked steroid sulfatase deficiency or Smith-Lemli-Opitz Syndrom.

P1-P012

Pediatric Adrenocortical Tumors. A Single Tertiary Center Experience: Clinical, Biological and Pathologic Characteristics Analysis

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Background: Adrenocortical Tumors (ACT) is a rare endocrine malignancy with heterogeneous presentation.

Aim: To evaluate the clinical, biochemical and pathologic characteristics of pediatric ACT in a single tertiary center.

Subjects and Methods: Review of 28 medical records with childhood ACT (chronological age (CA) <18 years (y) treated between 1987-2017. Clinical, biochemical, and histological features (Wieneke index), staging (ST) according to COG system, and therapeutic interventions were evaluated.

Results: Mean CA at diagnosis was 4.6 y (range 0.3-17.3 y, median 2.8 y, F/M ratio 2.5/1). Before diagnosis mean duration of symptoms was 10.9 months. Median follow-up was of 3.64 y (range 0-12 y). Initial clinical signs were hormonal overproduction (virilization, Cushing's syndrome) in 57.1%, abdominal mass/pain in 35.7%, and hypertensive encephalopathy in 7.1%. In clinically predominant virilizing ACTs (n=16) mean±SD Height-SDS (1,03 ±1,29) and ΔBA–CA were significantly higher, while BMI-SDS (0,79±0,8) was significantly lower than in clinically predominant Cushing ACTs (n=10) ($p<0.05$). Limited disease (ST I/II) was observed in 13 (46.4%), while advanced disease (ST III and IV) was observed in 10 (35.7%) and 5 patients (17.8%) respectively. Accordingly to hormonal production 3 groups (Gr) were analyzed: Gr1 (n=14) co-secretion of androgens and cortisol, Gr2 (n=8) isolated androgen secretion, and Gr3 (n= 2) cortisol secretion (4 patients could not be assessed). Very high serum DHEAS levels in Gr1 and Gr2 (X±SD 18603 ±16419 ng/ml) were detected. Serum DHEAS levels were significantly higher in ST IV vs ST I ($p=0.03$). Total adrenalectomy was performed in 26/28 patients. Eight patients (ST III-IV) received adjuvant chemotherapy (AChemo) with cisplatin, etoposide and doxorrubicin. Disease free survival (DFS) and overall survival (OS) was 100% for ST I-II, and 46.7% and 53.3% for Stage III and IV respectively (media follow-up of 8,4 and 8,6y for DFS and OS). A tendency of higher DFS on AChemo (75%,n=8) vs without AChemo (29 %,n=7) was found (OR=0.13, CI 95% 0.01-1.31). Tumor staging correlated positively and significatively with tumor weight and Wieneke criteria ($p<0.01$).

Conclusions: We reported the experience in our cohort of 28 pediatric ACT seen in a single center over 30 years. Height-SDS and BMI-SDS mirror ACT hormonal secretion. Very high serum DHEAS levels might be use as a biological marker of tumor stage. Less advanced disease were associated with best patient outcomes. Long term follow-up is needed to draw valid conclusions of using AChemo.

P1-P013

Role of Mast Cells in the Establishment of the Mineralocorticoid Pathway in the Developing Mouse

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Mast cells are known to control mineralocorticoid synthesis and secretion in human normal adrenal gland and aldosterone-producing adenomas through release of serotonin. We recently detected these immune cells in human fetal adrenal from 18 weeks of gestation in the subcapsular layer, in correlation with the expression of steroidogenic enzymes required for aldosterone biosynthesis. This observation suggests the implication of mast cells in the mineralocorticoid synthesizing pathway during adrenal development.

To test this hypothesis, we investigated the impact of the absence of mast cells on mineralocorticoid enzymes expression and on perinatal aldosterone secretion in mouse models. Using Q-PCR, we studied at different stages of perinatal development (E18, E20, P0, P1, P3) adrenal-kidney complexes obtained from either mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ *versus* wild type (WT) C57BL/6 mice. Aldosterone plasma levels were also quantified in neonates at P0 and P1using tandem mass spectrometry in both models.

RT-QPCR revealed lower *Cyp11b2* mRNA levels in $Kit^{W\text{-}sh/W\text{-}sh}$ than WT animals during fetal and post-natal development. By contrast, *Cyp21a1* and *Hsd3b1* mRNAs levels were similar in both models. Moreover, aldosterone levels were significantly lower in $Kit^{W\text{-}sh/W\text{-}sh}$ compared to wild type mice at P0 and P1. Altogether, these data strongly suggest a role of mast cells in perinatal mineralocorticoid pathway in mice.

In conclusion, we here demonstrated the implication of mast cells in the establishment and control of the mineralocorticoid function in fetal and post-natal development in mice. Further studies are now required to better understand the pathophysiology of the perinatal aldosterone production in mouse models as well as in humans, in order to better manage the salt wasting syndrome disorder in extreme premature infants.

P1-P014

Molecular Characterization of *TNXA/TNXB* Chimeras in *CYP21A2* Gene Deletions: High Frequency of Undiagnosed Ehlers-Danlos Syndrome in Congenital Adrenal Hyperplasia Patients

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The contiguous gene deletion syndrome, CAH-X, was reported in an 8.5% of Congenital Adrenal Hyperplasia (CAH) patients with a *TNXA/TNXB* chimera (Morissette et al 2015). This results in deletions of *CYP21A2* gene, encoding 21-hydroxylase necessary for cortisol biosynthesis, and *TNXB*, encoding the extracellular matrix glycoprotein tenascin-X (TNX). There are three *TNXA/TNXB* chimeras (CH1, CH2, CH3) that differ in the junction site, resulting in *TNXB* haploinsufficiency or dominant negative effect and an Ehlers Danlos Syndrome (EDS) phenotype. Recently, it has been described a biallelic form of CAH-X syndrome.

The aim of this study was to analyze copy number variations and genetic status of *TNXB* gene in 58 CAH patients due to *CYP21A2* deletion to determine the frequency of TNXB alterations in our population.

A total of 58 unrelated CAH patients carriers of *CYP21A2* gene deletion(65 alleles) were screened for *TNXB* defects. All the patients were analyzed for the presence of CH1 by MLPA technique evidenced by a 120 bp deletion in *TNXB* exon 35, and confirmed by exon 35 Sanger sequencing. In addition, all of them were screened for other *TNXB* alterations related to CH2 and CH3 by exon 40, 41 and 43 Sanger sequencing.

Results: The presence of *TNXB* deletion due to CH1 was found in 28/65 (43%) alleles carriers of *CYP21A2* gene deletion. Moreover, when we analyze the presence of other chimeras (CH2 and CH3) 47/65 (75%) alleles were found to carry a contiguos deletion that extended into T*NXB* gene. Of 58 patients evaluated for copy number variations, haploinsufficiency of *TNXB* was found in 39 patients, two patients were homozygous for CH1 (biallelic form) and two patients were compound heterozygous for CH1 and CH2 (biallelic form).

Conclusion: A high frequency of *TNXB* alterations was found in *CYP21A2* deletion carrier alleles in our population. MLPA and Sanger sequencing techniques resulted useful to characterize *TNXB* deletion. Accurate genotype-phenotype correlation remains to be elucidated in this cohort. Nevertheless, based on the high frequency of *TNXB* alterations in *CYP21A2* deletion carrier alleles found in this study, we recommend to evaluate *TNXB* status in these patients, warranting assessment of connective tissue dysplasia including cardiologic alterations in positive cases.

P1-P015

New insights into Low Dose Dexamethasone Suppression Test in paediatric Cushing's Syndrome (CS)

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Background: The Low dose dexamethasone suppression test (LDDST) is an important investigation for suspected Cushing's Syndrome (CS). The traditional definition of normal suppression of serum cortisol to ≤50 nmol/L during the LDDST (0.5 mg 6 hrly x 48 hrs) comes from a time when biochemical autoanalysers did not routinely detect very low values. Previous studies reported 5.1-8.3% of patients with Cushing's Disease (CD) suppressed to <50nmol/L at 48 hrs during LDDST. Many clinicians experienced in the assessment of suspected CS consider that 'normal' individuals should suppress to ≤20 nmol/L during a LDDST and that LDDST values of 20-50 nmol/L represent a range of uncertainty. Current sensitivity and specificity is reported as 90% and 100% for a cut off of ≤50 nmol/L.

Methods: We reviewed a retrospective cohort of paediatric patients referred to our centre with suspected CS between 1982 and 2018.

Results: Of 70 suspected CS patients, 49 had Cushing's Disease (CD), 7 had Primary Pigmented Nodular Adrenocortical Disease (PPNAD) and 14 'control' subjects, in whom the diagnosis of CS was excluded following detailed biochemical evaluation and prolonged clinical/auxological follow-up. The serum cortisol remained >50 nmol/l in 42/49 (86%) CD patients (29 males, median age 13.22 years) during LDDST. In contrast, cortisol during LDDST was >20 nmol/l in 48/49 (98%) CD patients. One patient with cortisol ≤20 nmol/L during LDDST had a high clinical suspicion of CD and investigations including bilateral simultaneous inferior petrosal sinus sampling confirmed this. The sensitivity and specificity of a LDDST cut off value of ≤20 nmol/l is 97.96% (95% confidence interval 89.15%-99.95%) and 100% (76.84%-100%). None of the 7 PPNAD patients (4 male, median age 12.2 years) had cortisol levels of ≤50 nmol/l during LDDST. Cortisol levels in all 14 controls (3 males, median age 12.7 years) suppressed to ≤20 nmol/l during LDDST.

Conclusion: Whilst the numbers are small, changing the LDDST cut off from ≤50 nmol/L to ≤20 nmol/L improves the sensitivity of the test from 85.71% to 97.96% in our paediatric CD patients. This does not adversely affect the specificity which remains 100%. We therefore suggest using serum cortisol of ≤20 nmol/l as a new diagnostic cut off value.

P1-P016

Recurrent Hypoglycemia in a Preschooler Girl with Overgrowth: Isolated ACTH-Deficiency with a Novel TPIT Mutation

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Objective: Congenital isolated ACTH deficiency (IAD) is a rare autosomal recessive disorder that is characterised by low levels of plasma ACTH and cortisol with normal pituitary structure and hormones. Clinical presentation can occur in the neonatal period, as well as later in childhood. Here, we report a patient with IAD due to a novel TPIT mutation.

Case: A $4^{8/12}$ years old girl presented with loss of concioussness and found to be hypoglycemic with a capillary glucose of 25 mg/dL (1.4 mmol/L). The parents were first degree cousins. Patient was born at term with a birth weight of 3800 g (1.6 SDS) and had been hospitalized for 10 days in a neonatal care unit for her mild respiratory problems and the history of unidentified sibling's death. She had several hospitalizations for hypoglycemia and episodes of abdominal pain and vomiting before her diagnosis is established. At her presentation to our clinic, her weight and height were 23.1 kg (1.8 SDS) and 116.5 cm (2.2 SDS), respectively. Weight for height was 0.8 SDS. Her mother and fathers height SDSs were -1.6 and -0.2, respectively. Cardiac and abdominal examination were normal, she was prepubertal. No hyperpigmentation was detected. Bone age was 7.8 years at admission. Laboratory investigations confirmed hypoglycemia, serum glucose 25 mg/dL (1.4 mmol/L), with a low-normal sodium (135 mmol/L) and normal potassium (4.5 mmol/L). Hyperinsulinemia was excluded. The child was hypocortisolemic (<0.1 μg/dl) with an extremely low ACTH level (<5 pg/ml). Insufficient cortisol response was detected in the low-dose ACTH stimulation test. Other anterior pituitary hormones were normal. A diagnosis of IAD was made and hydrocortisone treatment (10 mg/m^2/day) was started. Her hypoglycemic episodes and recurrent infections disappeared after replacement. Magnetic resonance imaging of the pituitary was normal. Whole exome sequencing revealed a novel homozygous c.302 G>A (p.Trp101Ter) mutation in *TBX19* gene. In two years follow-up, her growth velocity was 4.6 cm/year. In the first and second year of her diagnosis height SDS was 1.6 and 1.3, respectively.

Conclusion: We reported a new mutation in the *TBX19* gene in a patient with isolated ACTH deficiency. While overgrowth is a known feature of some types of familial glucocorticoid deficiency, it may be a novel feature for IAD as in our patient.

P1-P017

Biochemical, Genetic and Molecular Characterization of a Novel P399_E401Dup Mutation in P450 Oxidoreductase (POR) Altering Several Enzymatic Activities in a Patient with a 46,XX DSD Phenotype at Birth

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Background: P450 oxidoreductase (POR) mutations can present with disordered sexual development (46,XX virilisation as well as 46,XY under-masculinisation), perturbed steroidogenesis and mild to severe skeletal malformations. As POR is an obligate electron donating cofactor to many P450s, and as this interaction may vary from partner to partner, the phenotypic spectrum of PORD is extremely broad. Therefore, to characterize novel POR mutations, specific testing is required.

Case report: A 46,XX patient, second child of consanguineous Kurdish parents, was born at term with ambiguous genitalia (Prader III) and dysmorphic facial features (frontal bossing, low set ears). Newborn screening for 21-hydroxylase deficiency and ACTH-testing were normal. At age 14 days diagnosis of PORD was made by GC-MS urinary steroid metabolome-analysis showing the pathognomonic pattern of combined impaired activities of 17-hydroxylase and 21-hydroxylase. Genetic analysis revealed a novel homozygous mutation P399_E401Dup in POR.

Methods: The novel POR variant was characterized by bioinformatic and functional tests using recombinant proteins produced in bacteria, combined with small molecule and protein substrates. The ability of POR wild-type (WT) and P399_E401Dup variant to reduce ferricyanide [measures intactness of the FAD-binding domain of POR], MTT [as an indicator of electron transfer from the co-factor FMN bound inside the POR to its redox partners], and cytochrome c as well as the activity towards the drug and steroid metabolizing P450s were analysed. Effects of the mutation on cofactor (FAD/FMN) binding and activity under varying substrate and cofactor conditions were also investigated.

Results: The interaction with substrates was altered in the P399_E401Dup. Compared to WT, P399_E401Dup variant showed 51% activity in the cytochrome c reduction assay; in the MTT reduction assay the P399_E401Dup had only 6.2% of WT activity, showing a clear problem in electron transport mechanism. In the ferricyanide reduction assay, a 50% increase in the Michaelis constant (Km) for the FeCN was observed in addition to a 30% loss in maximal velocity. Overall results indicated a structural change by P399_E401Dup mutation in POR, which affects protein conformation and stability.

Conclusion: POR P399_E401Dup leads to alteration in Km and Vmax for multiple substrates, pointing towards an effect on protein conformation and stability. It also affects steroid production as manifested by alterations in the steroid metabolome of the patient. Previously, a P399_E401Del mutation in a Turkish child was reported, which had reduced activities of CYP17A1, CYP21A2 and CYP19A1. P399_E401 seems a sensitive spot for POR mutations.

P1-P018

Young Lean Women with Evidence of Both Premature Adrenarche and Pubarche Display a Metabolic, Hormonal and Psychologic Profile That Is Similar to That of Their Peers with Polycystic Ovary Syndrome

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Context: The early activation of adrenal *zona reticularis,* denoted by increased circulating levels of adrenal androgens before the age of eight years in girls is called premature adrenarche (PA), while the concomitant appearance of pubic hair is termed premature pubarche (PP). Girls with PA-PP display an unfavorable metabolic, hormonal and psychologic profile, compared to their normal peers and are also at an increased risk of developing polycystic ovary syndrome (PCOS) features peripubertally, especially those born small for gestational age. The natural history of these girls with PA-PP post puberty is unclear.

Aim of the study: To define the metabolic, hormonal, and psychologic profile of young lean women with a history of both PA and PP, born with a normal birth weight. These women were prospectively followed since childhood, did not seek medical assistance and their majority did not fulfill PCOS criteria.

Participants: 21 PA-PP women (age: 21.35±3.36 years, BMI: 23.59±4.40kg/m^2) were compared with 26 controls and 45 women with classic PCOS. Only three women (14%) in the PA-PP group had PCOS by the Rotterdam criteria.

Results: PA-PP women had significantly lower serum total cholesterol (165±20 *vs.*187±28 mg/dl), LDL (87±21 *vs*. 21±12mg/dl) and higher HDL (65±11 *vs*. 56.2±10.9mg/dl) than controls. Insulin resistance index HOMA-IR was similar in PA-PP (2.09±1.42) and PCOS (2.08±0.83), and significantly higher than that of controls (1.13±0.49). Serum delta 4-androstenedione levels (ng/ml)did not differ between PA-PP (3.22±1.44) and PCOS (3.54±1.14) but were significantly higher than controls (0.58±1.42). Similar findings were obtained for DHEAS and 17OHP, however serum testosterone and free androgen index were comparable among all groups. Ovarian volume (cm^3) was similarly increased in PA-PP (11.14±3.34) and PCOS (10.99±4.61) compared to controls (6.74±1.83). Regarding their psychologic profile, PA-PP women had a significantly higher score of state and trait anxiety, as well as of depressive and eating disorder symptoms than controls, with a pattern that was quite similar to that of PCOS.

Conclusions: Young lean women with a history of PA and PP displayed hormonal, metabolic and psychologic profiles similar to those of their peers with classic PCOS. These findings indicate that in women with PA-PP history, a thorough evaluation and long-term monitoring is needed.

P1-P019

The Usefulness of Combined Analysis of Serum and Salivary Maximum Cortisol Response to Low-Dose ACTH Test to Define the Requirement of Hormone Replacement Treatment

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Introduction: The low-dose synacthen test (LDT) is widely used to assess central adrenal insufficiency (CAI); however, the total serum cortisol (C) cut-off value is controversial. A correct diagnosis of CAI is required, but overdiagnosis may lead to unnecessary hormone replacement therapy. Salivary cortisol (SC) reflects the levels of free serum cortisol and is a noninvasive alternative.

Objective: To define a new cut-off value of serum cortisol in pediatric patients evaluated for suspected CAI considering SC of normal responders.

Patients and Methods: 145 pediatric patients (88 males) with suspected of CAI were included in the study. Mean age (SD) was 11.3 years (4.88). All patients underwent LDT with intravenous injection of 1 μg/m2 of tetracosactide (Synacthen). Serum C and SC levels were measured at baseline and after 30 and 60 minutes. The highest value of the tested parameters, at either 30 or 60 minutes, was regarded as the maximum response value. Reference cut-off value ≥18 μg /dl of serum cortisol levels was considered as a sufficient response (CAS).

Results: A significant positive correlation between maximum C and SC response was found (r.0.90, p0.001). Patients were divided according to serum cortisol response into the following groups (Gr): CASGr: n=72, (median (interquartile range) C and SC, 21.3 μg/dl (19.8-35.2) and 1.14 μg/dl (0.77-1.58), respectively, and CAIGr: n= 73 (median (interquartile range) C and SC, 14.5 μg/dl (12.2-16.4) and 0.58 μg/dl (0.36-1.04), respectively. ROC curve analysis established a SC cut off level of <0.61 μg/dl for CAI diagnosis (specificity and sensitivity of 84% and 56.3%, respectively)

Considering the lower quartile SC of CASGr (SC ≥ 0.77 μg/dl), an intermediate (I) Gr (ICAIGr) was established within the CAIGr. ICAIGr: n=28/73 (median (interquartile range) C and CS, 16.35 μg/dl (14.25-16.87) and 1.16 μg/dl (0.88-1.29), respectively.

The remaining 45 patients were considered real (R) CAI, median (interquartile range) C and SC 13.2 µg/dl (11.3-15.3) and 0.41 µg/dl (0.32-0.55), respectively. Significant differences in maximum serum C level responses were found among CASGr, ICAIGr, and RCAIGr ($p< 0.001$).

Conclusion: A maximum serum C response of <16.35 and SC response of <0.77 µg/dl may be appropriate cut-off values to define RCAI. Recognition of an ICAIGr allows avoiding unnecessary hormone replacement therapy; however, rigorous patient follow-up is required. Finally, the combined evaluation of maximum serum C and SC level responses improves the accuracy of CAI diagnosis in children.

Table 1. (for Abstract no P1-P020)

	B2		B4		1 yr post M	
	ND	HD	ND	HD	ND	HD
Age yr.	9.7	9.5*	11.4 **	11.1	13.1	12.7**
Height SDS	0.11	0.21	0.32	0.46*	0.20	0.08
BMI SDS	0.85	1.07*	0.98	1.36**	0.93	1.43**
HOMA-IR	1.6	1.9*	2.1	2.0	2.4	2.6
Adione ng/ml	0.23	0.28**	0.72	0.81*	0.81	0.96*
T ng/ml	0.06	0.07*	0.16	0.18	0.18	0.20
DHEAS µg/dl	51.9	94.5**	71.5	119**	72.1	124**
AMH ng/ml	4.0	3.4*	2.19	1.94	3.0	2.9
FAI	0.28	0.37*	1.22	1.54**	1.57	2.04

P1-P020

High DHEAS (HD) in Girls Determines Earlier Pubertal Maturation and Mild Hyperandrogenism Throughout Pubertal Development

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Background: Premature adrenarche (PA),characterized by high concentrations of DHEAS,has been considered a benign condition until recently,where associations to increased metabolic risk and PCOS have arisen,which may depend on ethnic background and infancy weight gain.

Objective and hypotheses: To determine whether PA in girls determines:i)a different timing of pubertal events, and ii)a different pattern of Ovarian morphology/hormones and adrenal hormones.

Methods: Study set up in the Chilean Growth and Obesity Cohort Study (GOCS, n=1,190,50% female) followed from 2006 (born in 2002-2003), PA was defined by DHEAS (RIA)>75th percentile for sex (F= 42 microg/dl at age 6.8±0.6 yr). Annual clinical examination including Tanner assessment until 1 yr postmenarche and fasting blood sample for glycemia, insulin, lipid profile, adiponectin, IGF-I,LH,FSH,AMH, DHEAS, Adrostendione,17OH prog,T(androgens by LC-MS/MS). Mann-Whitney test was used to compare difference in the medians of high DHEAS group (HD) and normal DHEAS (ND). Logistic regression models to assess the relation between DHEAS and anthropometric, metabolic and gonadal hormones were adjusted by chronologic age at DHEAS sampling and BMI SDS.

Results are summarized in the table as medians (* $p <0.05$ and ** $p < 0.01$). Girls with high DHEAS presented earlier breast and pubic hair (9.3 vs 9.8 yr) development, menarche (11.7 vs. 12 yr) and higher BMI SDS throughout puberty. Time between B2 and menarche was similar as well as ovarian size 1 yr after menarche. HOMA-IR was only higher at B2 however HD group showed persistent mild hyperandrogenism.

Conclusion: in Chilean adolescents, PA is associated with earlier breast, pubic hair and menarche and higher BMI SDS throughout puberty. We believe our findings support that adrenarche is not a benign process and continuous follow-up of this cohort is a unique opportunity to address prospectively the interrelationships of PA, early growth and adiposity as determinants of ovarian function and metabolic risks.

P1-P021

Higher Dehydroepiandrosterone Levels in Prepubertal Children Born Very Preterm

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Objective: To evaluate the impact of gestational age and birthweight on dehydroepiandrosterone and dehydroepiandrosterone-sulfate (DHEA and DHEA-S) in children born very preterm (VPT) appropriate for gestational age (GA) compared to children born at term (T).

Methods: We recorded anthropometric parameters in 72 VPT (< 32 GA) and 41 T (≥ 38 GA) aged 5.0 to 8.5 years. Birthweight standard deviation scores (BW-SDS) were calculated using INTERGROWTH-21st standards and Body Mass Index (BMI) percentile according to WHO references. Fasting insulin and Insulin-like Growth Factor 1

(IGF-1) were measured by automated immunoassay, and DHEA, DHEA-S and cortisol by mass spectrometry (LC-MS/MS).

Results (mean and SD): VPT (n=72, females = 26, GA = 29 ±2 weeks) and T (n=41, females= 23, GA= 38 ±1 week) had similar age (6.6 ±0.9 vs 6.7 ±1.0 years; p= 0.543), abdominal circumference (58.5 ±7.4 vs 58.5 ±7.1 cm; p= 0.982), BMI % (59 ±32 vs 64±29; p=0.476 and BW-SDS (0.4 ±1.03 vs 0.52 ±0.72 SDS; p=0.512). In VPT higher DHEA concentrations (6.70 ±3.97 vs 4.44 ±2.14 nmol/L; p=0.001) and higher DHEA/cortisol ratios (0.034 ± 0.020 vs 0.023±0.013; p= 0.003) were observed compared to T, but not for cortisol (p=0.517) and DHEA-S (p=0.107). When separated by sex, DHEA concentrations and DHEA/cortisol ratio were higher in VPT females than males (6.4 ±3.2 vs 4.2 ±1.7 nmol/L, p= 0.005, and 0.033 ±0.014 vs 0.023 ±0.013, p=0.019, respectively). In VPT males these parameters trended to be higher compared to terms but not statistically different (6.9 ±3.2 vs 4.7 ±1.7 nmol/L; p= 0.058 and 0.035 ±0.023 vs 0.023 ±0.012; p= 0.051). GA was inversely associated to DHEA in both sexes (females, r=-0.375; p<0.001, males r=-0.260; p<0.001). This association persisted after controlling by age at the sampling time. On the other hand, no association were observed between DHEA with BW-SDS, BMI percentile, abdominal circumference, Insulin and IGF1.

Conclusions: Higher DHEA concentrations were observed in children who were born very preterm, especially in females, independently of birthweight, chronological age, BMI and abdominal circumference. Lower gestational age could determine a higher activity of the reticulata which could contribute to an earlier pubertal maturation. FONDECYT 1140447 and 1160836

P1-P022

A Large Consanguineous Family with a Mild and Transient Form of Autosomal Recessive Pseudohypoaldosteronism Type 1 (PHA1) Caused by a Novel Mutation in the SCNN1A Gene: Functional Studies

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Background: PHA1 is a rare inherited disease characterized by resistance to aldosterone action and distinguished in two forms: the autosomal dominant renal form caused by mutations of the *NR3C2* gene (MR) and the autosomal recessive systemic form caused by mutations of the subunit genes *SCNN1A, SCNN1B, SCNN1G* of the epithelial sodium channel (ENaC). The classic phenotype of the autosomal recessive form of PHA1 is usually severe, lifelong, and expressed with multi-organ symptoms, whereas the autosomal dominant form is milder, transient and restricted to the kidneys. A large consanguineous family with a mild and transient form of autosomal recessive PHA1 due to a novel homozygous mutation in the *SCNN1A* gene has been previously described.

Objective: To establish the effect of the p.F226C *SCNN1A* gene mutation on the PHA1 phenotype by functional studies.

Methods: Human αENaC wt, or αF226C or αF226S, together with human β and γ ENaC from synthetic cRNAs, were expressed in *Xenopus laevis* oocytes. F226S was generated to have a conservative substitution of the Cys226 lacking the reactive -SH side chain. ENaC activity was measured as amiloride-sensitive currents (INa) with the addition of trypsin during concurrent recording. The expression of α ENaC wt and mutants was determined by Western blot.

Results: Patients were diagnosed between 5 and 60 days of age presenting with failure to thrive or during the course of a respiratory illness, with hyperkalemia, hyponatremia, elevated renin and aldosterone levels and a positive sweat test. All patients responded well to sodium supplementation with decreasing requirements with age until discontinuation of treatment.

All patients were found to be homozygotes, whereas their parents were heterozygotes for the mutation p.F226C of the *SCNN1A* gene.

ENaC activity was significantly reduced for the F226C (83% reduction, n= 40) and the F226S (94 % reduction, n= 13). Both mutants responded to trypsin by a robust increase in ENaC current, but under trypsin, the magnitude of ENaC current remained lower for the mutants than the wt. However, the trypsin-induced increase in ENaC current relative to baseline was greater for the mutants than the wt.

Western blot revealed that a reduced amount of ENaC protein was expressed under both the full-length and the cleaved αENaC mutants, F226C or F226S, compared to wt.

Conclusions: The p.F226C *SCNN1A* gene mutation leads to a 50% decrease in the intrinsic ENaC activity, probably due to a lower channel open probability.

P1-P023

Associations Between Maternal and Offspring Hair Cortisol Concentrations and Child Behavioral Symptoms in Pairs of Children 18–48 Months Old and Their Mothers with and Without Perinatal Mental Disorders

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Introduction: Maternal perinatal mental disorders (PMDs) are associated with developmental and behavioral problems in the offspring, probably mediated by the programming of the limbic-hy-

pothalamic-pituitary-adrenal (LHPA) axis. Increased or decreased cortisol concentrations during pregnancy and the perinatal period have been associated with alterations in the stress responses of the offspring and with child behavioral problems; however, such associations remain unclear.

Methods: We compared 16 mothers with PMDs and their children (18-48 months) with 30 aged-matched control mothers and their children (92 individuals in total). Participants of both groups were evaluated with a clinical interview, the Depression Anxiety Stress Scale (DASS-42) and the Child Behavior Checklist 1½-5 (CBCL 1½-5) questionnaires. We measured mother and child hair cortisol concentrations, which is a reliable biomarker of chronic stress exposure.

Results: Children of the PMD group had increased symptoms of attention deficit hyperactivity disorder (p=0.035) compared to the control group. The PMD mothers had lower hair cortisol concentrations (11,8 ± 8,2mg/dl) than the control mothers (13.9 ± 9 mg/dl), however, the difference was not statistically significant (p=0,471). Similarly, children of the PMD group had lower hair cortisol concentrations (12 ± 9,7mg/dl) than the controls (15.9 ± 17.4 mg/dl), but this difference was not significant (p=0.455). A positive linear association between maternal and child hair cortisol concentrations was found in the total sample of mother-child pairs (r=0,63, p<0.001), as well as in the control group separately (r=0,63, p<0.001). This association, however, was not significant in the PMD group (r=0,57, p=0.05).

In the PMD group, child „anxiety / depression" symptoms were associated with child hair cortisol concentrations (r=0.57, p=0.042). In the same group (PMDs) symptoms of „aggressive behavior" and „oppositional/defiant problems" of children were significantly associated with both their hair cortisol concentrations (r=0.67, p=0.013; r=0.58, p=0.037) and with their mothers' hair cortisol concentrations (r=0.61, p=0.028; r=0.58, p=0.039, respectively).

Conclusions: These findings suggest that a chronic dysregulation of maternal and child HPA axis in the PMD pairs may underlie the associations between chronic maternal stress and child behavioral and emotional problems and stress responses.

P1-P024

Gonadotropin-Dependent Pubertal Disorders Are Common in Patients with Virilizing Adrenocortical Tumors in Childhood

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Background: In pediatric patients with adrenocortical tumors (ACT), morbidity and mortality rates have been extensively evaluated. However, there are almost no data on the late consequences of early exposure to high androgen levels on pubertal development and on final height (FH) in these patients.

Objective: To investigate the impact of early exposure to androgen excess on gonadotropin-dependent pubertal development and on final height (FH) of patients with childhood ACT.

Design: Retrospective cohort study of 63 pediatric patients (69.8% female) with virilizing ACT followed in a single institution from September 1975 until September 2017.

Methods: Data between patients with normal puberty (n=26) and pubertal disorders – central precocious puberty (CPP, n=7) and early fast puberty (EFP, n=3) – were compared.

Results: At diagnosis of ACT, median age was 25.8 months and duration of signs, 6 months; stature SDS was 0.5 (-3.6–3.9) and bone age advancement was 14.7 months (-27.9–85.4). To date, 58.7% of the patients developed gonadotropin-dependent puberty: 26 had normal puberty, 7 CPP, and 3 EFP. GnRH analogues effectively treated CPP/EFP. Tall stature and older age at diagnosis of ACT were associated with risk of CPP [RR 4.17 (95% CI 1.17–14.80)] and pubertal disorders [RR 3.0 (95% CI 1.04–8.65)], respectively. Recurrence/metastasis were associated with CPP [RR 4.17 (95% CI 1.17–14.80)] and pubertal disorders [RR 3.0 (95% CI 1.12–8.02)]. Among the 19 patients that reached FH, stature SDS dropped from 1.4 to -0.02 since diagnosis of ACT (p=0.01). Seventeen of them achieved normal FH. There was no difference in FH SDS between patients with normal puberty and pubertal disorders (p=0.75).

Conclusions: this study clearly shows that gonadotropin-dependent pubertal disorders are more common than previously expected in patients with childhood virilizing ACTs. Additionally, it confirms that FH is usually not impaired, reiterating the good prognosis for FH in these patients. Our study reinforces the importance of close and prolonged endocrinology follow-up after surgery, not only to detect ACT-related complications, but also to promptly identify and treat consequences of early exposure to androgen excess.

Adrenals and HPA Axis P2

P2-P001

Contribution of Direct Measurements of Steroids by Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) in Non-Classical Adrenal Hyperplasia (NCCAH)

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Background: To diagnose non classical congenital adrenal hyperplasia (NCCAH) and adrenal insufficiency (AI), current guidelines recommend ACTH test. Cutoffs for 17 hydroxyprogesterone (17OHP) and cortisol are derived from immunoassays values.

Thanks to a recently developed and validated mass spectrometry approach (LC-MS/MS) we routinely quantify simultaneously 16 circulating steroids and we are able to speculate on new cut off values and uses.

Objective and hypotheses: We prospectively analyzed in children addressed to our endocrine unit for premature pubic hair, all steroids assayed by LC-MS/MS, basal and stimulated by ACTH tests. We searched for additional basal variables discriminant enough to the make the diagnosis.

Patients and Methods: 83 patients were referred in our unit in 2017, because of premature pubic hair. Mean age was 7.3 +/- 2.3 yrs, sex ratio was 19 males and 64 females. Patients with stimulated 17 OHP values above 9 ng/ml and their parents gave their consent for molecular testing of *CYP21A2* according to our local ethics committee. Hence 69 had a premature pubarche (PP), 9 a NCCAH and 5 male patients were excluded because of central puberty. Bone age was more advanced in the NCCAH group compared to the PP group 2.9 yrs *versus* 1.3 yrs.

Results: Mean basal 17 OHP ranged from 0.053 to 1.1 ng/ml in PP patients and from 3.62 to 87.94 ng/ml in NCCAH patients ($p<0.0001$). Mean basal 21-Deoxycortisol (21DF) was 0.03 ng/ml in PP patients and 3.42 ng/ml in NCCAH patients ($p<0.0001$). Basal Testosterone was 0.08 ng/ml in PP patients versus 0.2 ng/ml in NCCAH ($p<0.0001$). Basal Androstenedione was 0.28 ng/ml in PP patients and 0.94 ng/ml in NCCAH patients ($p<0.0001$) and 11 Beta-OH-Androstenedione was 0.57 ng/ml in PP patients *versus* 2.17 ng/ml in NCCAH patients ($p <0.0001$). ACTH tests revealed 6 AI among the 9 NCCAH patients. Stimulated 17 OHP was 0.27-9.06 ng/ml in the PP group *versus* 22.73-92.57 ng/ml in NCCAH patients. Using multivariate data analysis (Partial Least Squares regression (PLS/PLS-DA)), we propose a score with a high contribution of basal levels of 17OHP, 21DF, testosterone, Androstenedione and 11 Beta-OH-Androstenedione, with a sensitivity/specificity of 100 % towards the diagnosis of NCCAH.

Conclusion: We propose in addition to the gold standard ACTH test, a new score using different steroids at basal levels to ascertain the diagnosis of NCCAH with an excellent sensitivity.

P2-P002

GnRH-Analogue Treatment in Children with Congenital Adrenal Hyperplasia (CAH): Data from a Multicenter CAH Registry

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Background: Final height in patients with congenital adrenal hyperplasia (CAH) is generally assumed to be lower than the population norm. Besides CAH subtype and age at diagnosis, timing of pubertal development is considered to have a significant impact on final height. In most CAH patients, puberty starts within normal ranges, although at a somewhat earlier mean age compared to reference populations. CAH-complicating gonadotropin-dependent precocious puberty has been reported in few cases, especially in conditions of late CAH diagnosis and treatment initiation, and often requires additional treatment with GnRH-analogues.

Patients and Methods: We retrospectively assessed frequency, clinical parameters and height outcome of GnRH-analogue treated CAH-patients from the German CAH registry (DGKED-QS), comprising longitudinal data of a total of >1500 CAH-patients.

Results: 64 CAH patients (28 female) received GnRH-analogue treatment. The majority of them (n=53, 82.8 %) were born before nationwide introduction of 17-OHP newborn screening in Germany in 2000, and mean age at CAH-diagnosis among these patients decreased significantly over time (<1990: 5.31 yrs, 1990-1999: 4.38 yrs,>2000: 1.05 yrs). Compared to the frequency distribution in the total DGKED-QS/CAH-cohort with >66 % salt wasting CAH, only 42.1 % of the patients treated with GnRH-analogues were classified to have salt-wasting CAH. Mean age at first database entry of GnRH-analogue treatment was 8.81 yrs in girls and 9.24 yrs in boys. In addition, a significant proportion of treated children had no documented clinical signs of gonadarche (e.g. testicular volume <4 ml in about one quarter of boys) at the time of treatment initiation, indicating that the rationale for GnRH-analogue treatment was primarily based on auxological reasons in these individuals. Mean height-SDS at the beginning of GnRH-analogue treatment was +1.18 in girls and +0.62 in boys, while bone age was significantly accelerated in both genders (girls: +3.29 yrs, boys: + 3.35 yrs). At the last documented visit before transition, height-SDS

had decreased to -1.13 (-0.15, target height- corrected) in girls and -2.15 (-1.43, TH-corrected) in boys.

Conclusion: GnRH-analogue treatment in CAH patients is rare, especially in the newborn screening era. A significant decrease of GnRH-analogue use over the last three decades is paralleled by decreasing mean age at CAH diagnosis, supporting the concept that chronic hyperandrogenemia (or its cessation) can trigger central precocious puberty. The auxological data of our retrospective cohort analysis seems to indicate that GnRH-analogue treatment may have a beneficial effect on final height in this subgroup of CAH patients.

P2-P003

Glucocorticoid Replacement Regimens in the Treatment of 21-Hydroxylase Deficiency Congenital Adrenal Hyperplasia: A Systematic Cochrane Review

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Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive condition which leads to glucocorticoid deficiency. During childhood, the main aims of treatment are to prevent adrenal crisis and to achieve normal stature, optimal adult height and to undergo normal puberty. In adults, the aims of treatment are to prevent adrenal crisis, ensure normal fertility and to avoid long-term consequences of glucocorticoid use. Current treatment regimens for CAH with glucocorticoids cannot optimally replicate normal physiological cortisol level. Overtreatment or undertreatment of CAH is often reported in individuals who may be treated with different steroid treatment regimens. There is no current standard treatment for CAH and physicians often customise treatment for each individual using various regimens. It remains unclear which treatment regimen is most effective

Objectives: This Cochrane review aims to determine the efficacy and safety of different glucocorticoid replacement regimens in the treatment of CAH due to 21-hydroxylase deficiency in children and adults.

Methods: We included any RCT or quasi-RCT comparing different glucocorticoid replacement regimens in the treatment of CAH due to 21-hydroxylase deficiency in children and adults. The authors independently searched and extracted data. Data from different interventions were analysed separately. GRADE was used to assess the quality of the evidence.

Results: The initial search identified 297 records which identified 20 publications for further examination. After screening full texts of 20 selected papers, we included five RCTs with 101 people with CAH due to 21-hydroxylase deficiency. The number of participants in each trial varied from 6 to 44 with participants' ages ranging from 1.2 to 21 years. They received different glucocorticoid replacement regimens such as frequency in the day or different forms of glucocorticoids and were followed up for between six and 12 months. Although 17OHP and androstenedione are frequently used to monitor treatment, there is a high amount of variability in the measurements which hampers usefulness of these tests. Overall, we judged trials to be moderate to high risk of bias; lack of methodological detail led to ‚unclear' risk of bias judgements across many of the domains.

Conclusions: There are limited trials to date which compare the efficacy and safety of different glucocorticoid replacement regimens in the treatment of CAH in children and adults. This review addressed a diverse range treatment regimens with many trials at high or unclear risk of bias. There is insufficient evidence to indicate which glucocorticoid replacement regimen results in better outcomes.

P2-P004

Hydrocortisone (HC) Dose in Children with Congenital Adrenal Hyperplasia (CAH)

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Background: Recommendations for initial and maintenance dose of HC in CAH differ widely. However, treatment of CAH in young children is complicated by the lack of a suitable low-dose HC preparations.

Methods: The German Society for Paediatric Endocrinology and Diabetology (DGKED) initiated a registry for patients with classical CAH (German CAH registry). Anonymized data are transferred for central analysis, including a validation step and a benchmarking report, twice yearly. Until March 2018, the DGKED-CAH database included 26818 patient visits from 1480 patients (654 males). 43 centres from Germany and 3 centres from Austria contributed longitudinal data. Parameters were selected based on current treatment guidelines. A custom-made electronic health record software is used at participating centres for standardized documentation and anonymous transfer of patient records. Linear regression model were implemented with SAS 9.4.

Results: Daily hydrocortisone (HC) dose per m^2 body surface area (BSA) was 20.03 ±0.35 mg (mean ±SE) for patients younger than 3 months of age (n=309), 15.10 ±0.3 mg/m^2 for the age-group 4-12 months (n=442), 14.31 ±0.24 for patients 1-5 years (n=707) and 14.54 ± 0.20 for patients 6-18 years (n=969). Overall, there was no significant gender difference regarding dose. In patients on fludrocortisone (presumable salt-losing CAH), HC dose was lower in the age-group 0-3 months (19.6 versus 24.4 mg/m^2, $p < 0.05$) and in the age-group 1-5 years (14.1 versus 15.1 mg/m^2, $p < 0.05$), while in patients older than 6 years a higher HC dose was

recorded in patients on fludrocortisone (15.1 versus 13.5 mg/m², p < 0.0001). ANOVA regression modeling revealed a significant interaction between age-group and fludrocortisone use, as well as between gender and fludrocortisone use (both p<0.001).

On average, the largest HC dose was administered in the morning. Median absolute doses morning– midday – evening were 2.0 [Q1-Q3: 2.0-2.5] – 1 [1.0-1.4] – 1.0 [1.0-1.5] mg for children < 3 months of age, and 2.5 [2.0-3.0] - 1.1 [1.0-1.8] – 1.3 [1.0-2.0] in the age-group 4-12 months. For children 1-5 years of age, the respective median doses were 4.2 [3.0 - 5.3], 2.2 [1.7 - 2.6] and 2.3 [1.8-2.9] mg.

Conclusion: This large, multicentre database provides comprehensive information on prescribed hydrocortisone substitution doses in children with CAH. Low absolute doses required in children younger than 6 years of age are difficult to achieve, considering that currently only a 10 mg tablet formulation is available in Austria and Germany.

P2-P005

Perioperative Care of CAH – Incongruencies of Practices Among Canadian Specialists

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Introduction: In pediatric years, the most common cause of primary adrenal insufficiency is congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency. Current Endocrine Society guidelines advocate for the use of perioperative supraphysiologic (often referred to as 'stress dose') glucocorticoids for children with primary adrenal insufficiency undergoing general anesthesia or surgery. We perceived a difference in practice patterns amongst pediatric subspecialists which prompted an assessment of perioperative glucocorticoids administration in Canadian centres. To better understand the state of practice patterns of perioperative glucocorticoid administration in children with CAH, we performed a cross sectional survey of Canadian subspecialists.

Methods: Following ethical approval, an electronic survey was sent to Canadian subspecialists using Canadian Pediatric Anesthesia Society (CPAS) and Canadian Pediatric Endocrine Group (CPEG) member email lists (approximately 300 and 85 recipients, respectively) to assess reported practice patterns and responses to select clinical scenarios.

Results: A total of 86 responses were received; 49 anesthesiologists and 37 pediatric endocrinologists. Among anesthesiologists, less than half reported they would provide stress dose steroids for patients undergoing cystoscopy while a clear majority of pediatric endocrinologists reported they would recommend stress dose administration (45% vs 92% respectively, p<0.0001). Over half of endocrinologists (57%) reported to recommend stress dosing regardless of CAH severity or type of procedure being performed. Twenty-one percent of anesthesiologist reported they would not provide stress dose steroids for patients undergoing laparotomy. Pediatric endocrinologists reported they were more likely to refer to guidelines for management of stress dose steroids (84% vs 51%, p<0.001), with many reporting to use institution specific guidelines. Themes emerged in written responses suggesting anesthetists were of the opinion that current guideline recommendations led to overtreatment with glucocorticoids, while endocrinologists believed general-anesthesia itself warrants stress-dose steroids.

Discussion: Current guidelines suggest the use of perioperative supraphysiologic steroids for all patients with primary adrenal insufficiency, with a graded dose depending on degree of surgical stress, in order to pre-emptively prevent clinical deterioration in unforeseen circumstances. Our data has identified a clear difference in self-reported approach to perioperative stress dose steroids between Canadian anesthesiologists and pediatric endocrinologists. It is unclear whether this incongruency is present in other countries or extends to adult practices.

Conclusions: Further dialogue among both pediatric and adult, and endocrine and anesthesia specialists is required to address this apparent discrepancy in practice patterns. Future well-designed research is paramount to provide evidence-based practice recommendations for perioperative management of patients with adrenal insufficiency.

P2-P006

Analysis of Phenotypes and Genotypes in 84 Patients with 21-Hydroxylase Deficiency

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Background and Aims: Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders characterized by impaired cortisol synthesis. 21-hydroxylase deficiency (21-OHD) caused by mutations in CYP21A2 gene is the most common form of CAH. This study aims to analyze the phenotype-genotype correlation and the characteristics of gene mutation frequency of 21-OHD patients in China, helping to provide evidence for clinical practice and genetic counseling of 21-OHD patients.

Method: The clinical features, laboratory tests and gene mutational analysis of 84 cases of 21-OHD in department of Pediatrics of Sun Yat-sen Memorial Hospital, Sun Yat-Sen University from 2012 to 2018 were analyzed retrospectively. The correlation between phenotypes and genotypes of these patients were analyzed.

Results: (1) 59 of 84 patients (70.2%) who were classified as salt-wasting (SW) forms presented adrenal crisis or other signs of salt loss at the age of 7 days to 2 months. The other 21 patients did not present any signs of salt loss. (2) Mutations of CYP21A2 gene on two alleles were found in all 84 patients (168 alleles). The mutation types included different point mutations (145/168, 86.3%), large gene deletions (15/168, 8.9%) and clusters of point mutations (8/168, 4.8%). 20 different point mutation were found in these patients, and the most frequent point mutations in order were I2G, p.I173N, p.R357W and p.Q319*, accounting for 69.8%

of alleles. (3) In 46 of 59 patients of SW forms (78.0%), predicted phenotypes according to genotypes were consistent with their actual salt-wasting phenotypes.

Conclusion: Patients of 21-OHD might often present adrenal crisis or other signs of salt loss in 2 month after birth. Point mutations were the most comment types of CYP21A2 gene mutations. In this study, the most frequent point mutations in order were I2G, p.I173N, p.R357W and p.Q319*, and in 78.0% patients of SW forms, predicted phenotypes according to genotypes were consistent with their actual phenotypes, indicating that estimate of phenotypes according to genotypes had certain clinical significance for 21-OHD patients.

P2-P007

Miscarriages in Families with a Child with Classic Congenital Adrenal Hyperplasia and 21-Hydroxylase Deficiency (CAH)

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Background: The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency (CAH). In women with classic CAH, the fertility rate is lower than in the general female population, and an increased rate of miscarriages has been reported. There are no data on the incidence rate of miscarriages in families with an offspring that have classic CAH.

Methods: The families came from different parts of Germany and attended the annual meeting of the German CAH support group for parents and patients which was held in Hamburg in September 2014. The data was collected pseudonymously by a questionnaire which was completed by the families at home. The families also accepted the responsibility to address this question to the families of their married siblings. In all, the data of 50 families with at least one child with CAH, and the data of 164 parental siblings were available for evaluation. Miscarriage rates were calculated in relation to the reported pregnancies.

Results: Twenty-two miscarriages were reported from 19 families. At least one miscarriage occurred in 38 % of the families, three families experienced two miscarriages and 16 families had one miscarriage each. The mean miscarriage rate was 15.8 %. The heterozygous mothers had a total of 90 siblings (41 m, 49 f), while 74 siblings (33 m, 41 f) were reported from the heterozygous fathers. The miscarriage rate was 10.1 % in the families of the mothers' siblings, and 11.4 % in the families of the fathers' siblings. The genotype was known in all parents that have an offspring with CAH, but not defined in 82 % of the maternal siblings, and in 86 % of the paternal siblings. No child with classic CAH has been diagnosed in any of the sibling´s families to date.

Conclusion: Our data show that the miscarriage rate in German families with a child with classic CAH is not elevated.

P2-P008

Testing Antiandrogens and Aromatase Inhibitors to Achieve Normal Growth in Children with Classical Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis

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Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency is an autosomal recessive disease in which adrenal synthesis of glucocorticoids and mineralocorticoids is impaired and steroid biosynthesis is directed toward the formation of excessive androgens. Persistently high androgens will accelerate bone maturation and reduce final adult height.

Objectives: To assess the efficacy of androgen antagonist Flutamide and aromatase inhibitor Tastolactone when added to the standard treatment of CAH (Hydrocortisone and fludrocortisone) in normalizing growth rate and rate of bone maturation and to test the effect in lowering cortisol clearance that intended lower daily Hydrocortisone doses and further improving the final height.

Methods: In April 2016 we searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE/PubMed, Embase, and CINAHL, in each search we considered searching for original review, references and the update. We also explored other internet sources and we hand searched abstracts from the meetings and conferences (updated search on October 2017).

Types of outcome measures: Primary outcomes: rate of bone maturation, rate of growth velocity and cortisol level (blood and urine). Secondary outcomes: adrenal androgen levels and ACTH level.

Main Result: We included six studies involving 102 participants of children with classical congenital adrenal hyperplasia. Four RCTs and two cohort studies compared adding Flutamide and Tastolactone or letrozole to hydrocortisone and fludrocortisone in comparison to the standard treatment, studies are pooled with subgroup analysis. Growth rate and bone rate of maturation were significantly decreased in the experimental group with 95% CI: [-2.39, 0.49] for the growth rate and significantly lower 95% CI: [-1.38, -0.29] for the bone rate of maturation. Two studies were testing the direct effect of this regimen on decreasing cortisol clearance. Total body cortisol excretion was significantly low when patients received the four-drugs ($P \leq 0.001$) and ($P < 0.01$), 95% CI: [-28.14, 2.31] than patients who were on the standard treatment. Final analysis indicated favorable results and high precision supporting this new treatment combination.

Conclusion: Although the result of this review and analysis was in favor of the efficacy of this potentially new treatment in normal-

izing growth rate and rate of bone maturation to improve final height in children with classical CAH, the safety of androgen antagonist in different dosage regimens also need to be investigated with more trials. A large scale RCTs is recommended.

P2-P009

Phenotype-Genotype Correlations of *CYP21A2* Mutations in Patients with Congenital Adrenal Hyperplasia in Turkey

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Background: Mutations in the 21-hydroxylase gene (CYP21A2) accounts for 90–95% of all congenital adrenal hyperplasia (CAH) cases. There is a strong relationship between genotype and disease severity.

Objective: The aim of the study was to investigate the most frequent known mutations in CYP21A2 and to describe the genotype-phenotype correlation in Turkish children with CAH due to 21-hydroxylase deficiency.

Methods: Based on clinical and hormonal criteria, patients were classified according to phenotype as salt-wasting (SW), simple-virilising (SV) or nonclassical (NC). Genetic analysis was performed using a reverse-hybridisation strip-based assay (the CAH StripAssay®) that explored the presence of the 11 CYP21A2 mutations most prevalent in European populations: P30L, I2 splice (IVS2), Del 8 bp E3 (G110del8nt), I172N, Cluster E6 (I236N, V237E, M239K), V281L, L307 frameshift (F306+T), Q318X, R356W, P453S and R483P.

Results: Of the 46 patients included in the study, the disease-causing CYP21A2 gene mutations were found in 25 (54%) across all three forms of CAH. The most frequent mutations were point mutations (84%), followed by splice site mutations (24%) and deletions (4%). In the SW group, three patients were homozygous and one heterozygous for I2 splice, one was homozygous for P30L+I2splice+del 8bp+E3 del, one was homozygous for I2splice+Q318X and one was heterozygous for I2splice+V281L. In the SV group, one patient was homozygous for I172N and one was heterozygous for I172N+Q318X. In the NC group, seven patients were heterozygous for Q318X, seven were heterozygous for V281L, one was heterozygous for V281L+P453S and one was heterozygous for I172N.

Conclusion: Hormonal assays can diagnose CAH, but they are unable to discriminate heterozygotes from normal individuals or detect disease severity. This study showed a good correlation between genotype and phenotype in patients with 21-hydroxylase deficiency. The results suggest that well-known mutations can predict disease severity.

P2-P010

Hypoglycemic Crisis and Salt Loss in Children with Classic Congenital Adrenal Hyperplasia

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Objective: Acute adrenal crisis is one of the main concerns in children with classic congenital adrenal hyperplasia (CAH). The aim of this study was to evaluate hypoglycemic and salt-wasting episodes in children with an established diagnosis of classic 21-hydroxylase deficiency (21-OHD) after start of treatment.

Methods: A retrospective observational study was conducted for 85 patients with classic CAH (68 salt-wasting and 17 simple virilizing), aged 1 to 16 years. Clinical records, biochemical profile and therapeutic management of adrenal crisis were reviewed. Episodes were classified according to clinical presentation and outcome.

Results: 33% of recruited patients reported at least one episode of hypoglycemia and/or salt loss. Of the 43 total episodes, we found 22 cases of hypoglycemia (51%), 9 of salt wasting (21%) and 12 combined (28%). 79% of episodes were mild/moderate. Six patients experienced seizures and three patients died as a result of adrenal crisis. The most frequently observed underlying causes were infections, prolonged fasting and treatment errors. Only in 77% of cases the families of patients have taken the correct therapeutic measures. The overall frequency of episodes/year for 100 patients was equal to 6.3%.

Conclusions: The prevention and proper therapeutic management of the crisis is of crucial relevance. It is feasible only through active and continuous training of the patients' families by medical team. Further research on the interactions that exist between the cortisol deficiency, adrenaline and glucose metabolic dysregulation would be useful to identify the strategy for the prevention of the acute adrenal crisis. New experimental drugs could reduce frequency of mild/moderate episodes related to the non-physiological cortisol circadian rhythm replicated by conventional therapies.

P2-P011

Neonatal Screening for Congenital Adrenal Hyperplasia in Turkey: A Pilot Study with 38,935 Infants

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Background: Congenital adrenal hyperplasia (CAH) is the most common form of primary adrenal insufficiency in children. 21-hydroxylase enzyme deficiency (21-OHD) occurs in 90 to 95%

of all cases of CAH. Despite it being a treatable condition, if unrecognized, CAH may present with life-threatening cardiovascular collapse. Mortality in the first years is reported to be higher than in the general population. Neonatal screening for CAH is effective in detecting the salt-wasting form and thereby reducing mortality.

Aim: This study describes the incidence of CAH in Turkey and analyses the results obtained from a pilot study of public CAH screening program of Turkish Directorate of Public Health comprising four cities of Turkey.

Method: Newborn babies ≥32 gestational weeks and ≥1500 gr birth weight were enrolled. Screening protocol included one sample two-tier testing. The first step comprised the measurement of 17α-hydroxyprogesterone (17-OHP) by fluoroimmunoassay in dried blood spots obtained at 3-5th days of life. The cases with positive initial screening were tested by steroid panelling using liquid chromatography-tandem mass spectrometry method to measure 17-OHP, 21-deoxycortisol, cortisol, 11-deoxycortisol, and androstenedione as a second-tier test. The babies with steroid ratio of (21-deoxycortisol+17-OHP)/cortisol ≥ 0.5 were referred to ped endo clinics for further assessment.

Results: From March 3, 2017, through July 15, 2017; 38,935 infants underwent testing. Of newborns screened, 2265 (5.82%) had second-tier testing, 212 (0.54%) of them were referred to paediatric endocrinology clinics for further evaluation, 6 babies were diagnosed with CAH (four males, two females). Four cases were identified as classical salt-wasting 21-OHD (2 males, 2 females), one male baby had simple virilizing 21-OHD, one male baby had 11-OHD CAH. The incidence of classical 21-OHD CAH in the screened population was 1:7.787.

Conclusion: Our data showed that classical 21-OHD CAH incidence in Turkey is higher than those previously reported. Thus, it is recommended that CAH be added to newborn screening panel in Turkey. The use of steroid profiling as a second-tier test for CAH screening is effective in the diagnosis and differential diagnosis of CAH and reduces the burden of follow-up evaluations of false positive cases.

P2-P012

Autoantibodies Against 21-Hydroxylase in Prediction of Adrenal Failure in APECED Patients

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Objectives: To investigate sensitivity, specificity and predictive values (PPV, NPP) of autoantibodies against 21-hydroxylase in APECED patients with and without adrenal insufficiency (AI) and in patients with other forms of AI.

Methods: 42 patients with APECED and 24 patients with other forms of AI were recruited. APECED was confirmed by finding at least two major components of the disease and/or two mutations in AIRE gene and/or high levels of antibodies against interferon-ω. APECED in patients with other forms of AI were excluded by performing genetic test and/or investigating antibodies against interferon-ω. All patients were tested for autoantibodies against 21-hydroxylase by ELISA.

Results: 67% (28/42) patients with APECED had AI. Autoantibodies against 21-hydroxylase were significantly associated with AI ($p<0.0001$). Specificity was 79%, sensitivity – 82%, PPV – 88%, NPV – 69%. Two patients had positive 21-hydroxylase antibodies before the manifestation of AI (AI was diagnosed one year after blood sampling). The level of antibodies has negative correlation with duration of AI by the time of the blood sampling (Spearman -0.396, $p<0.05$). 60% (3/5) patients with AI and negative for 21-hydroxylase antibodies were tested more than 15 yrs after the debut of the AI.

71% of non-APECED patients with AI (17/24) were positive for 21-hydroxylase antibodies, and all of them were diagnosed autoimmune AI. Seven patients were negative for 21-OH autoantibodies, congenital adrenal hypoplasia due to DAX-1 gene mutations was confirmed in two of them, X-linked adrenoleukodystrophy in one patient. In four patients the cause of AI was not clarify.

Conclusions: Detection of autoantibodies against 21-hydroxylase is a reliable method to screen for autoimmune AI and could be recommended also for prediction of AI manifestation in patients with APECED.

P2-P013

A First Combination Case of 21-Hydroxilase Deficiency and CHARGE Syndrome Confirmed by Genetic Analysis

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Introduction: 21-hydroxilase deficiency (21OHD) is the most common form of congenital adrenal hyperplasia. Mutations of *CYP21A2* induces 21OHD, a rare autosomal recessive manner. CHARGE syndrome (CS) is a rare autosomal dominant manner that is typically caused by heterozygous chromodomain helicase DNA binding protein-7 (*CHD7*) mutations. Here, we report the combination cases with genetically diagnosing 21OHD and CS at the first time.

Case: The patient is a boy at the age of 7 years. He had no problems in prenatal period. His parents had no consanguinity. Though he had no symptoms of 21OHD such as pigmentation of scrotum at birth, he was carefully followed up after birth because of his brother suffered from 21OHD. At the age of 9 days, he showed electrolyte abnormality, hypoglycemia and high values of 17-hydroxyprogesterone: 18.3ng/mL (<3.5ng/mL). He was clinically diagnosed with 21OHD and treated by fludrocortisone acetate and cortisol. Genetic analysis was performed, and identified compound heterozygotes mutations as IVS2-13A/C>G/I172N in *CYP21A2*. These mutations were the same of his brother. He showed various complications such as cleft lip and palate, bilateral severe deafness, congenital heart disease (ventricular heart septal defect, patent ductus arteriosus), tracheomalacia, gastroesophageal reflux disease and cryptorchidism. These were not common features with 21OHD, thus he was suspected with CS. At the age of 5 years, we

performed genetic analysis of *CHD7*. A *de novo* variant in a *CHD7* splicing acceptor site (NM_017780.3: c.7165–4A>G) was identified. At last, he was genetically diagnosed with a combination case of 21OHD and CS.

Discussion: The incidence of 21OHD and CS is from 1:10,000 to 20,000, and 1:20,000, respectively. Both 21OHD and CS are rare diseases. The case of combination with 21OHD and CS has not been reported previously. We consider that this case occurs accidentally. When the patients have atypical symptoms, we may should consider that they have another diseases addition to primary disease.

Conclusion: We report a first combination case of 21OHD and CS confirmed by genetic analysis.

P2-P014

Frequency of Enzyme Deficiencies in a Turkish Cohort of Congenital Adrenal Hyperplasia: A Single-Center Experience with 145 Patients

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Background: Congenital adrenal hyperplasia (CAH) is an autosomal recessive disorder caused by a defect in any of the enzymatic steps of adrenal steroidogenesis. It occurs due to mutations in genes that encode enzymes involved in the synthesis of cortisol from cholesterol. The most common cause is 21-hydroxylase deficiency, with 11-beta hydroxylase, 3-beta hydroxysteroid dehydrogenase, 17-alpha hydroxylase and POR deficiency being among rarer causes.

Objective and hypotheses: The aim of this study was to characterize the clinical features and reveal frequency of enzyme deficiencies of Turkish patients with CAH.

Method: One hundred and forty-five patients with CAH were included from one pediatric endocrinology center in Istanbul, Turkey. Clinical profile, age of diagnoses and occurrence of precocious puberty, hypertension, testicular adrenal rest tumors were recorded.

Results: The study included 63 male, 82 female patients. All patients were raised in accordance with their genetic sex. While 88.2% of the patients were diagnosed with 21-hydroxylase deficiency (61.1% salt-wasting type, 17.4% simple virilizing type and 9.7% non-classical type), 9.0% had 11-beta hydroxylase deficiency, 2.1% had 3-beta hydroxysteroid dehydrogenase deficiency and 0.7% had POR deficiency. Consanguinity was present in 73.8% of cases. 67.9% of the female patients were diagnosed with ambiguous genitalia and 68.3% of the male patients were diagnosed with salt loss. 15 patients were treated with GnRH analogues due to central precocious puberty. Testicular adrenal rest tumor was present in 9 patients. The only patient with POR deficiency was diagnosed with Antley-Bixler Syndrome due to her syndromic features.

Conclusion: The frequency of enzyme deficiencies in our center was consistent with the literature. The occurrence of hypertension during follow-up was an important clue for 11-beta hydroxylase deficiency. Patients with clinical and hormonal features incompatible with 21-hydroxylase deficiency should be reevaluated for the rare forms of CAH.

P2-P015

Study of Cardiovascular Risk Factors and Carotid Intima-Media Thickness in Children with Congenital Adrenal Hyperplasia

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Introduction: Congenital Adrenal Hyperplasia (CAH) is the commonest cause of Disorder of Sex development (DSD). It is a group of autosomal recessive disorders caused by deficiency of enzymes involved in synthesis of cortisol, aldosterone or both. The combination of hypocortisolism, hyperandrogenism and adrenal medullary hypofunction due to the disease and side effects of steroids treatment may make these individuals more prone to develop cardiovascular disorders including impaired exercise performance and increased systolic blood pressure. Ultrasonographic assessment of Carotid Intima-media Thickness (CIMT) is a well-established examination for screening individuals at cardiovascular risk.

Aim of the work: The aim of this study is to evaluate the cardiovascular risk factors including assessment of biochemical parameters and carotid intima-media thickness in children with congenital adrenal hyperplasia.

Subjects and Methods: This study included thirty children diagnosed with congenital adrenal hyperplasia for 2 years or more attending the endocrinology clinic in Alexandria University Children's Hospital, Egypt and they were compared with thirty apparently healthy children of matched age and sex. Thorough history taking and clinical examination were done with emphasis on dose and type of steroid used, and anthropometric measurements. Laboratory investigations were done including lipid profile and Insulin resistance index was assessed using homeostatic model assessment (HOMA-IR). High-resolution B-mode ultrasonography was performed to measure the carotid intima-media layer thickness (CIMT) and evaluate the colour Doppler flow characteristics of the carotid arteries.

Results: In the present study, we had 19 females and 11 males with CAH. Their mean age was 6.6 years. No significant difference was found in the age, sex or blood pressure between the cases and controls. About 13% of cases of CAH had high cholesterol levels. It was found that 11 cases had HOMA-IR between 75-95th percentiles and 3 cases above 95th percentiles. The mean CIMT in cases was significantly higher than that of control (p

P2-P016

The Spectrum of Genetic Defects in Congenital Adrenal Hyperplasia in the Population of Cyprus: A Retrospective Analysis

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Background: Congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency (21-OHD) is worldwide the most common autosomal recessive disorder caused by defects in the *CYP21A2* gene.

Objective: The main objective of the study was to evaluate CAH in Cyprus over a 10 year period.

Methods: All known patients were included in a population retrospective subset analysis of Cypriot patients with confirmed CAH and their clinical severity, genotype and sex were evaluated.

Results: Our data, is an extensive description of the diverse clinical forms of CAH over time. From 2007 to 2017, one hundred and twenty one patients with various degrees of CAH were categorized and genotyped at the Molecular Genetics, Function and Therapy department of the Cyprus Institute of Neurology and Genetics. We identified 121 patients with various degrees of the disorder and were categorized in 4 mutation groups (null, A, B and C) based on their clinical and biochemical findings. The majority of patients (85.12%) belonged to the non-classic (NC)-CAH form and the disorder was more often diagnosed in females (61.1%) who exhibited various degrees of hyperandrogenemia. The most severe classic salt-wasting (SW) form was identified in 11 neonates (9.1%). Seven (5.8%) children were also identified with the simple virilising (SV) form and a median presentation age of 5 yrs (interquartile range (IQR) 3.2–6.5). In the 242 nonrelated alleles, the most frequent mutation was found to be p.Val281Leu (59.5%) followed by IVS2-13A/C>G (9.1%), DelEx1-3 (6.2%), p.Val304Met (4.6%) and p.Gln318stop (4.1%). A series of other less frequent mutations including rare deletions were also identified. With an estimated population of 701,000 Greek Cypriots (Cyprus statistical service 2016) the prevalence of CAH is estimated to be around 1.7 cases per 10000 people. Based on the recent study by our group where the true carrier frequency of *CYP21A2* gene was reported to be 1:10, the identified CAH patients in the Greek Cypriot population are about the 6.9% of the ones estimated to exist in the Greek Cypriot population.

Conclusion: Overall, the compiled data of the present work from a coherent population could help physicians in both the treatment and genetic counselling of families affected with 21-hydroxylase deficiency.

P2-P017

Childhood Growth Advancement in Girls with Premature Adrenarche Heralds Anabolic Effects by Adulthood

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Background and aim: Children with premature adrenarche (PA) have often tall stature, advanced bone maturation, and a tendency to be overweight. It has been speculated that PA may lead to unfavourable outcome, including obesity-related metabolic disturbances, but the data on long-term outcome of PA are insufficient. The aim of this work was to describe adult body composition in young females with a history of PA.

Subjects and design: This prospective case-control study included 30 PA and 42 control females who were mostly full-term and appropriate for gestational age -born. They were evaluated first at the median age of 7.6 years[1] and now at 18.1 years. Main outcome measures were body mass index (BMI), fat percentage, lean mass, and bone mineral density (BMD; areal at prepuberty and total body excluding the head at adulthood). Additionally, determinants for parameters of adult body composition were analysed using linear regression models.

Results: When compared to the controls at prepubertal age, the PA females had higher BMI standard deviation score (SDS), fat percentage, and lean mass, but areal BMDs (adjusted for body size) did not differ between the study groups[1]. At adulthood, BMI, waist circumference (including waist-to-height and waist-to-hip ratio), and fat percentage were comparable between the study groups, but lean mass ($p = 0.001$) and BMI-adjusted BMD SDS ($p = 0.008$) were higher in the PA than control females. In all females of the present study, higher prepubertal height SDS and serum insulin concentration were determinants for higher adult lean mass and BMD.

Conclusion: PA seems to induce anabolic effects as adiposity-oriented childhood body composition alters during puberty towards higher adult lean mass and BMD. This modulation is mostly determined by advanced childhood growth and higher serum insulin concentrations, rather than adrenal androgen levels.

Note to reviewers: Adult BMI and waist circumference data (on other aspects than in the present study) are also included in a manuscript which is currently submitted to journal.

Reference

1 Utriainen P, Jääskeläinen J, Saarinen A, Vanninen E, Mäkitie O, Voutilainen R. Body composition and bone mineral density in children with premature adrenarche and the association of *LRP5* gene polymorphisms with bone mineral density. J Clin Endocrinol Metab. 2009; 94:4144-51.

P2-P018

A Novel Mutation in the MC2R Gene in a Two-Year-Old Boy with Adrenal Insufficiency

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Background: Melanocortin-2 receptor (MC2R) is a member of the G protein-coupled receptor family. MC2R is selectively activated by adrenocorticotropic hormone (ACTH); the binding of MC2R and ACTH activates the heterotrimeric G protein complex, and in turn stimulates steroidogenesis. Pathogenic variants in the MC2R gene result in glucocorticoid deficiency-1 (GCCD1), an autosomal recessive disorder in which unresponsiveness to ACTH leads to deficient secretion of cortisol and adrenal C19 androgen precursors. Biochemically serum cortisol levels are low with elevated ACTH. Patients with GCCD1 usually present with failure to thrive, hypoglycemia, recurrent infections, hyperpigmentation, and neurological sequel.

Objective(s): To describe a case of two-year old boy with symptoms of adrenal insufficiency and confirmed novel pathological mutation in the MC2R gene.

Case report: The patient is a two-years old boy, full term, product of uneventful pregnancy and normal vaginal delivery. He had repeated episodes of neonatal sepsis starting at the age of 2 days. He had recurrent symptoms of failure to thrive, hypoactivity, hypoglycemia, and recurrent infections.

Methods: Whole Exome Sequence (WES) Analysis was performed using genomic DNA from the patient and his parents, the exonic regions and flanking splice junctions of the genome were captured and sequenced by NextGen sequencing on an illumine system. Reads were aligned to human genome build GRCh37/UCS hg19, and analyzed for sequence variants using Xome Analyzer. Sequence and copy number variants were described according to the Human Genome Society(HGVS) and International System for Human Cytogenetic Nomenclature (ISCN) guidelines, respectively.

Results: His biochemical investigations showed elevated levels of ACTH >1500 (reference 5-60 pg/ml), low levels of cortisol <22 (69-632 nmol/L), low aldosterone 151 pmol/L (reference 194-2579), and hypoglycemia (1.1 mmol/L). WES has identified a p.Leu109Gln (CTG>CAG): c.326 T>A in exon 2 in the MC2R gene.

Conclusion: We report a novel mutation in the MC2R gene leading to severe cortisol deficiency. The L109Q variant is a non-conservative amino acid substitution, which is likely to impact secondary protein structure as these residues differ in polarity, charge, size, and/or other properties. Further functional analysis will aid in unravelling the molecular mechanism of how the novel mutation leads to adrenal insufficiency.

P2-P019

Two Cases of Apparent Mineralocorticoid Excess Due to Novel Mutations in HSD11B2 Gene

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Background: Human HSD11B2 metabolizes active cortisol into cortisone and protects the mineralocorticoid receptor from glucocorticoid occupancy. Loss of function mutations in HSD11B2 gene cause a rare autosomal recessive disorder, apparent mineralocorticoid excess, resulting in low-renin hypertension and hypokalemia.

Objective: We present 2 children with apparent mineralocorticoid excess. Case 1, a boy presenting at 11 years with growth retardation (SD, -2.8), polyuria, polydipsia, hypertension (160/110-170/140 mm Hg). Biochemical analysis showed hypokalemia (2.2-2.7 mmol/l) with normal sodium (140-142 mmol/l). Plasma renin activity and serum aldosterone were undetectable (PRA 0.14 ng/ml•h, SA <30.0 pmol/l).

Case 2, a girl presenting at the age of 6 years with polyuria, high blood pressure (120/85-130/90 mm Hg) and hypokalemia (2.4 mmol/l). Hormonal study also showed low levels of PRA (<0.1 ng/ml•h) and SA (32.3 pmol/l).

Therapy with spironolactone (50 mg per day) was started. At present the children show normal electrolytes and PRA, and blood pressure 100/70-110/80 mm Hg.

Methods: HSD11B2 gene was analysed by Sanger sequencing.

Results: Compound heterozygous p.G341S/p.H304R and a homozygous p.M243V mutations were found in Case 1 and Case 2, respectively. All mutations were novel.

Conclusion: In the present study we described clinical and molecular genetic characterization of two patients with novel mutations in HSD11B2 gene.

P2-P020

Long-Term Follow-Up of Safety and Disease Control for Hydrocortisone Granules Designed to Give Age-Appropriate Dosing with Taste Masking to Children with Adrenal Insufficiency

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Context: Alkindi® (Hydrocortisone Granules, Diurnal Ltd, UK), was recently licensed for oral administration to children with adrenal insufficiency (AI) from birth to 18 years. Previously, children received compounded hydrocortisone to achieve age appropriate dosing, however almost 25% of batches were out of specification for mass and content uniformity and clinically evident under- and over-dosing was reported.

Objectives: Primary: long-term safety of Alkindi®; Secondary: disease control in children on Alkindi®.

Patients & study design: Of the 24 children who completed the Alkindi® Phase 3 trial 18 children were enrolled in this extension study: 6 withdrew early; 1 subject spat out the first dose and was withdrawn from the study without further dosing, and the remaining 5 subjects withdrew due to local issues as their last dose was to be taken during the night. Median ages at entry were ~3.5 years in Cohort 1; ~2 years Cohort 2; and 46 days in Cohort 3. Follow-up included monthly visits for the first 2 months followed by 3 monthly thereafter. The results reflect the first planned data cut at one year of follow up.

Results: Children were compliant with treatment.

Safety: No cases of adrenal crisis were reported. Between 4 and 9 subjects at each visit had implemented sick day rules in the preceding study period with the primary reason being fever. 80 treatment-emergent adverse events (TEAEs) were reported by 12 out of 18 subjects including viral upper respiratory tract infections, vomiting, and otitis media; typical illnesses seen in young children. There were no deaths, severe TEAEs, TEAEs leading to withdrawal from the study, and no TEAEs with a suspected causal relationship to Alkindi®. One SAE of moderate erysipelas (jellyfish sting) was reported.

Efficacy: Cortisol levels remained above the baseline levels at most visits. All Tanner Development Stage assessments (breast, genitalia, and pubic hair) were Grade 1 (pre-pubertal) at baseline, with no progression seen. Z-scores for height and weight showed no trends for accelerated or reduced growth, during this first year of data collection.

Conclusions: Alkindi® was well tolerated with neither adrenal crisis nor AEs reported related to Alkindi® treatment. The most frequently reported AEs were infections, which were managed appropriately using sick day rules. There was no indication of either under-treatment or over-treatment, which is important for achievement of disease control in the growing child.

P2-P021

Borderline Peak Plasma Cortisol Following Synacthen Stimulation – Single-Centre Analysis of Three Years' Data

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Introduction: The Short Synacthen Test (SST) is the most popular diagnostic investigation of adrenal insufficiency (AI) worldwide. Symptoms of AI are frequently non-specific, often delaying diagnosis, however fortunately cases of adrenal crisis remain relatively rare. Diagnostic cut-offs for plasma cortisol on SST are controversial, made more complicated by modern assays and paediatric normative values extrapolated from adult data. Some advocate a division between biochemical and clinical AI, with different cut-offs and management strategies. For asymptomatic children, with a low-index of suspicion for AI and borderline SST results our department has evolved a tendency to advise hydrocortisone replacement in times of stress/sickness only. We analysed three years of SST data, examining the cases with borderline peak cortisol results for aetiological links and subsequent management strategies.

Methods: Retrospective analysis of all SST performed at Sheffield Children's Hospital, UK, between September 2014 and 2017 was undertaken. Plasma cortisol samples were analysed on the Abbott Architect i1000 immunoassay (CVs <5%). Our diagnostic threshold for a "pass" for both high (HDT) and low-dose SST (LDT) is 450nmol/L. "Borderline" peak cortisol was considered to be 300-449 nmol/L and this group was further subdivided into 300-349, 350-399 and 400-449 nmol/L for analysis in terms of demographics, test indication, dose of synacthen and resultant management plan.

Results: 433 SSTs were performed over the three years, 74 (41M) of which had a borderline peak plasma cortisol (16.7%). The proportion of borderline tests remained similar each year, despite an increasing trend towards HDT over LDT. Management of patients with borderline peak cortisol varied, however there was a tendency to reduce or stop replacement glucocorticoids with higher results, particularly after a HDT. Steroids were more likely to be started or continued with lower borderline values. Patients with known AI were more likely to have their steroids continued or SST repeated at lower peak cortisols and weaned at higher peak cortisols. Those without established AI were less likely to have glucocorticoid replacement commenced if higher borderline value, particularly following a LDT.

Conclusions: There was significant variation in the management of borderline SST results within this single-centre study, with the same cortisol result warranting commencement of regular replacement for one physician and stopping replacement for another. There is a paucity of research in this area and studies to examine both the natural course of children with borderline SSTs and whether stress cover represents pragmatic but safe management are warranted.

P2-P022

Unilateral Adrenalectomy for Primary Pigmented Nodular Adrenocortical Disease Causing Cushing Syndrome

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Background: Bilateral primary pigmented nodular adrenocortical disease (PPNAD) is one of the rare causes of Cushing syndrome, which has traditionally been treated by bilateral adrenalectomy. However, bilateral adrenalectomy mandates life-long adrenal hormone replacement and the patients remain at risk of adrenal failure for the rest of their lives. In adult patients with PPNAD, there have been a few reports of successful unilateral adrenalectomy. However, to our knowledge, there has been no report of unilateral adrenalectomy for pediatric patients with PPNAD in whom slight hypersecretion of cortisol could be detrimental for growth. Here we report successful unilateral adrenalectomy for a 10-year-old boy with PPNAD.

Case Report: The patient was a 10-year-old Japanese boy who presented with growth arrest and excessive weight gain over the past 6 months. He showed a moon face and truncal obesity suggestive of hyperadrenocorticism. Blood cortisol (15.98-17.74 μg/dL) was elevated without diurnal rhythm, which was associated with suppressed ACTH. Blood cortisol was not suppressed by 1 mg- and 8 mg- dexamethasone, and abdominal CE-MRI revealed the presence of multinodular adrenals on both sides, larger on the right side. 131I-adosterol scintigraphy also showed bilateral uptakes which were stronger on the right adrenal. The diagnosis of Cushing syndrome due to multinodular adrenal hyperplasia was made. An endoscopic right adrenalectomy was first performed to preserve adrenal function. Histopathological examination confirmed combined adenoma with PPNAD in the right adrenal gland. On follow up, the patient showed a rapid catch-up growth and diminished Cushingoid features. Blood cortisol levels gradually declined to 3.62 - 4.35 μg/dL after surgery without signs of adrenal insufficiency. Although blood ACTH levels were suppressed and undetectable for an extended period following surgery, it began to rise after 9 month and detectable at 21.0 ng/L. Other than PPNAD, the patient has no findings of Carney complex. Genetic analyses for PPNAD and adenoma are in progress.

Conclusion: Unilateral adrenalectomy could be considered for pediatric patients with Cushing syndrome caused by PPNAD, especially when the uptake of 131I-adosterol and the size of nodules show dominance on one side.

P2-P023

Adrenal Crisis in Children with Adrenal Insufficiency: Prevalence and Risk Factors

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Objectives: To assess the prevalence and risk factors of Adrenal crisis (AC) events in children with Adrenal insufficiency (AI) and to evaluate the effectiveness of the treatment for preventing AC.

Methods: Children diagnosed with AI between 1990 and 2017 and treated with glucocorticoids at four pediatric endocrinology units in Israel were studied. Data were retrieved retrospectively from the patients' files and they included demographic factors (age, sex and ethnic origin), clinical information (age at diagnosis, specific diagnosis and clinical presentation during AC) and therapy regimen details (type, dosage and parental guidance). The collected data underwent statistical analyses.

Results: The study population consisted of 120 children (73 boys, 47 girls). Median age at study was 11.5 years (0.3-25) and median age at diagnosis was 0.3 years (0-17.5). Thirty-one AC events in 26 children took place during the study period, which is equivalent to 3.4 crises per 100 patient years (py). The prevalence of AC in children with primary AI was 4 events to 100 py compared to 1.5 events to 100 py in children with secondary AI (p=0.001). One-hundred thirteen children (94%) were treated with hydrocortisone at a mean dosage of 12.3 ± 5.2 mg/m^2/day. Sixty children also needed treatment with fludrocortisone at a mean dosage of 0.1 mg/day ± 0.04. The risk factors for developing AC in children with AI were: younger age at diagnosis (p=0.003), primary AI compared with secondary AI (p=0.016), specific diagnosis of autoimmune adrenal insufficiency (Addison disease), congenital adrenal hypoplasia, adrenoleukodystrophy, salt wasting congenital adrenal hyperplasia (p<0.001), mineralocorticoid treatment (p<0.001) and hospital admissions (p>0.001). Unexpectedly, the use of an AI identification (ID) tag/card or parental use of the Solucortef kit were not negatively correlated with the development of AC. Among those who developed AC, 96% carried some ID (p=0.18) and 50% also received Solucoref treatment (p=0.82), compared to 82% and 45%, respectively, for those that did not develop AC. There was no AC-associated mortality during the study period, but there were 5 reports of a family history of pediatric AC-associated mortality.

Conclusions: A number of parameters were found to be risk factors for the development of AC in children with AI. Among them, age at diagnosis, etiology of AI, number of hospitalizations and mineralocorticoid treatment. The preventive measures of carrying ID and Solucoref treatment did not arrest the development of AC, calling for further investigation for effective preventive measures.

P2-P024

The Effectiveness of a Stress-Management Intervention Program in Behavioral Parameters and Hair Cortisol Concentrations in Children with Attention Deficit Hyperactivity Disorder

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Background: Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental condition in school-aged children, with a prevalence of 5–8%. In individuals with ADHD, there is an attenuated biologic stress response to challenging situations.

Objective: This study aimed at evaluating the effectiveness of an 8-week stress management program, comprising self-applied

cognitive exercises, on stress perception and anxiety symptoms, sleep quality and hair cortisol concentrations in children with ADHD.

Method: Sixty children (65% males) with ADHD, aged between 7 and 12 years old, and their parents took part in the study. All children were under usual behavioral therapy care, but no pharmacotherapy. The intervention was an 8-week, two-armed, non-blinded, randomized, controlled trial with a 1:1 allocation ratio, intervention *vs.* wait-list, control groups. The Achenbach system (CBCL questionnaires), the ADHD scales (DuPaul et al.), the Personal Control Questionnaire, and the Pittsburg Sleep Questionnaire were completed by parents at baseline and after the intervention in both groups. Hair cortisol concentrations were measured in both groups at the two time-points (i.e. before and after the intervention).

Results: Statistically significant decreases before and after the intervention were found in the subscales of the DuPaul questionnaire scores (inattention, hyperactivity-impulsivity and total, $p<0.001$ for all three scales) only within the stress-management intervention group. Similarly, the intervention group showed decreases before and after the intervention in most scales of the CBCL questionnaire (academic performance and learning, $p<0.001$; internalizing problems $p=0.001$; thought problems $p=0.006$; externalizing problems $p=0.001$; affective problems p-0.001; anxiety problems $p=0.02$; ADHD problems $p<0.001$; oppositional-defiant problems $p=0.001$; conduct problems $p=0.001$; sluggish-cognitive tempo $p<0.001$; obsessive-compulsive problems $p=0.001$; PTSD problems $p<0.001$). Improvement was shown in the Pittsburg Sleep Quality questionnaire scores, after the intervention ($p=0.003$). Although an increase trend was noted after the intervention, no statistically significant differences in hair cortisol concentrations were found between or within groups ($p= 0.309$ & $p=0.061$, respectively).

Conclusion: The intervention group exhibited ameliorated ADHD symptomatology, decreased anxiety, and better sleep quality, as well as reduced internalizing and externalizing problems after the implementation of the stress management program. The lack of a statistically significant difference in the hair cortisol concentrations after the 8-week intervention period, may be attributed to the short time interval between the two assessments. We conclude that a stress management program as a supportive intervention to behavioral therapy, may be beneficial in children with ADHD.

P2-P025

Very High Dehydroepiandrosterone Sulfate (DHEAS) in Serum of an Overweight Female Adolescent Without a Tumor

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Here, we report on a female adolescent with overweight and a very high DHEAS serum level. The hypothesis that the origin of DHEAS excess was the presence of either an ovarian or a suprarenal DHEAS-producing tumor was not confirmed. Sonographic and MRT investigations did not support its presence. In addition, effective dexamethasone suppression of DHEA and DHEAS excluded this diagnosis.

Steroid sulfatase (STS) hydrolyses alkyl and aryl steroid sulfates to their unconjugated forms. STS deficiency was suspected although ichthyosis was absent. Sequence analysis revealed a heterozygote single-base substitution (g.117217G>T) that results in a nonsense mutation at codon 173 (p.G173X). This mutation predicts a truncation of the carboxyl region of the STS enzyme that is implicated in substrate binding. No partial gene deletion of the presumably intact allele outside exon 5 was detected by multiplex ligation-dependent probe amplification. The detected nonsense mutation in the STS gene, however, was in the heterozygote state, therefore it was not supposed to be responsible for STS deficiency. In line with the genetic data, the bioassay revealed normal enzyme activity in patient's leukocyte.

A potential defect of one or more transporter proteins was suggested. Prominent candidate efflux transporter for the present study were MRP2 and BCRP, both highly expressed at the canalicular membrane of hepatocytes and involved in the hepatobiliary elimination of many drugs but also some endogenous substrates such as sulfated steroids. On the uptake site several OATP and OAT carriers were on the list. Using exon-spanning PCR, all exons of the above mentioned membrane transporters were sequenced. Sequence analysis revealed a heterozygous Q141K variant for BCRP. Interestingly, this variant has in its homozygous state previously been associated with reduced efflux transport activity.

In conclusion, a novel heterozygous nonsense mutation in the steroid sulfatase gene and a known heterozygous missense variant of the steroid sulfate efflux transporter were found in this patient. The combination of the two heterozygous mutations could possibly together explain the observed high levels of DHEAS and some other sulfated steroids.

P2-P026

Early Recognition of Adrenal Insufficiency After Hematopoietic Stem Cell Transplantation During Childhood

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Purpose: We try to analyze the prediction capacity of variable factors to diagnose adrenal insufficiency.

Methods: We analyzed clinical and laboratory data of 22 children (Male = 13) who have been checked regular dose ACTH stimulation test for suspected symptoms after HSCT (Lymphoid leukemia=5, Myeloid leukemia=9, Non-malignant=8) at the Catholic HSCT center from Feb 2013 to Feb 2017 at Seoul St. Mary's Hospital. A normal response of ACTH stimulation test was defined as a stimulated serum cortisol >18.1 mcg/dl and an increment from base line of at least 7.2 mcg/dl was considered a partial response.

Result: The suspected symptoms of AI that patients had before ACTH test were as follows: Poor feeding=8, Lethargy or sleeping tendency=7, Nausea or vomiting=6, Fever=6, Elevated ACTH or Low cortisol=2, Facial flusing=2, Hyperkalemia=1, Diaphoresis=1, Fatique=1, Hyponatremia=1, Hypoglycemia=1, Edema=1, Epigastric pain=1, Dizziness=1. Sixteen (72.7%) out of 22 patients underwent ACTH test was diagnosed as AI, 3 patients were partial AI and 3 patients were normal.

In AI group, serum cortisol levels after 60 minutes (3.82 ± 0.68 vs. 16.14 ± 3.00, P<0.008) was lower and serum K level (4.34 ± 0.75 vs. 3.68 ± 0.20, P<0.018) before ACTH stimulation test was higher than normal or partial response group. There were no significant differences age at HSCT, Age at ACTH test, serum FBS, Na level before ACTH test between AI and normal or partial response group.

In a univariate logistic regression analysis, serum K level before ACTH test (OR=317.5; 95% CI, 1.1-191705.1, P < 0.042) and proportion of steroid users at ACTH stimulation (OR=15.0; 95% CI, 1.325-169.87, P < 0.029) were higher was associated with AI.

Conclusion: Serum potassium level and current steroid use could be potential factors for early detection of adrenal insufficiency. These results emphasize the need to pay attention to the small signal including serum normal upper limit K level of children after HSCT for early detecting AI.

P2-P027

Reference Values for Serum 17-Alfa Hydroxyprogesterone and Adrenal Size in Healthy Newborns

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Background and aims: The interpretation of serum 17α-hydroxyprogesterone (17OHP) results is difficult as age-related pediatric reference intervals are scant. The aim of this study is to determine the reference intervals for serum 17OHP according to sex and age groups in newborns. We also aimed to establish reference intervals for right and left adrenal gland sizes, and to evaluate the relation with adrenal size and serum 17OHP concentrations in newborns.

Methods: Healthy newborns (n= 142) were enrolled and divided into two groups. Group 1 included newborns between 4 and 7 days of age and Group 2 included newborns between 26 and 30 days of age. Serum 17OHP concentration was measured in the morning. The right and left adrenal glands' width, length, and depth were measured by ultrasonography and the volumes were calculated. The statistical analyses were performed using SPSS.

Results: The clinical characteristics, serum 17OHP concentrations, and the sizes of left adrenal gland measured by ultrasonography of the male and female newborns were similar. Volume of right adrenal gland was smaller in girls than that of boys in Group 1 (p <0.05). Percentiles for serum 17OHP concentration and the sizes of bilateral adrenal gland by ultrasonography according to age groups were obtained. There was a significant decrease in adrenal sizes at the fourth week of life in both girls and boys. There was no statistically significant correlation between serum 17OHP concentration and adrenal sizes in both sex- and age groups (p >0.05).

Conclusion: It is important to distinguish between diffuse hyperplasia or hypoplasia and normal gland to diagnose congenital adrenal disorders. On the other hand, little is known regarding age and sex-appropriate reference intervals for serum 17OHP during newborn period. To our knowledge, this is the first study which was reported sex-related 17OHP reference intervals combined with bilateral adrenal sizes by US in newborns. Our reference intervals for serum 17OHP and adrenal sizes may improve clinical practice for newborns.

P2-P028

A Rare Case of ACTH- Independent Cushing's Syndrome Due to Bilateral Micronodular Adrenal Hyperplasia and Myoclonic Dystonia

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Background: ACTH- independent adrenal Cushing's syndrome accounts for less than 15% of endogenous Cushing's syndrome in children. We present a rare case of ACTH-independent adrenal Cushing's syndrome, which was associated with myoclonic dystonia.

Case presentation: A 12-year old girl was referred on account of rapid weight gain, fatigue, growth deceleration and facial hypertrichosis. She had a history of gait instability and ataxia till the age of 5 years. Clinical examination revealed buffalo hump, moon facies, central obesity, dysmetria and ataxia. Her height was 128.4 cm (<3rd centile), her weight was 32.3 kg (3rd – 10th centile) and her BMI was 19.6 kg/m^2 (25th- 50th centile). Her Tanner pubertal stages were B1, P3 and AH1.

Laboratory findings: Endocrinologic evaluation revealed elevated 24-hour urine free cortisol excretion [(1699.9 and 1079.7 (normal values: 2.6–37 μg/day)] and supressed plasma ACTH concentrations (< 1 ng/mL) on several measurements. ACTH concentrations remained suppressed throughout a formal CRH Test. A Liddle test showed no suppression of serum cortisol concentrations following stimulation with low dose (22.47 mcg/dL) and high dose (27.95 mcg/dL) dexamethasone. The rest of the endocrinologic investigations were normal. A computed tomography scan of the adrenals showed increased adrenal volume bilaterally. The diagnosis of ACTH – independent Cushing's syndrome was made and the patient underwent bilateral adrenalectomy. The histopathologic examination confirmed isolated micronodular adrenocortical disease. The patient has been on replacement therapy with hydrocortisone and fludrocortisone since. Neurological evaluation confirmed the diagnosis of myoclonic dystonia due to deletion of the *SGCE* gene.

Conclusions: Exogenous Cushing's syndrome is the commonest aetiology of Cushing's syndrome in the pediatric population. Isolated micronodular adrenocortical disease is an extremely rare aetiology of ACTH-independent Cushing's syndrome and bilateral adrenalectomy remains the best therapeutic option. Our case represents the first case of isolated micronodular adrenocortical disease associated with myoclonic dystonia.

P2-P029

Two Siblins and Three Cousins with Allgrove (4A) Syndrome in a Turkısh Family: A Novel Mutation in the 'Aladin' Gene

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Allgrove's or ,4A syndrome , is a rare autosomal recessive multisystem disorder characterised by adrenocorticotropin hormone resistant adrenal insufficiency, alacrima, achalasia and neurological abnormalities. The disease -causing gene(AAAS) encodes a protein of 546 amino acids called ,aladin' (for alacrima-achalasia-adrenal insufficiency-neurologic disorder). We report two siblings and three cousins suffering from Allgrove syndrome in a Turkish family. In this family, a novel homozygous mutation (p.L356Vfs*8, c.1066_1067delCT) in exon 11 in the AAAS gene was identified in all affected family members.

Family report: A 13 -year-old female was admitted to our department with the complaint of fatigue and hyperpigmentation. According to the family history, she had been followed with adrenal insufficiency from 8 months old, then after 3 years of the first diagnosis she had presented with achalasia, alacrima and psychomotor developmental delay. Laboratory examinations were as follows: Serum ACTH>1200 pg/ml, basal kortisol< 1 μg/dl, and she had been followed with the diagnosis of triple A syndrome since three years of age. The family history revealed that her brother(7years 4 months old age) has been followed with adrenal insufficiency, alacrima, achalasia and developmental delay for 3 years. Their cousins are 7 and 12 years age of female, they have also been followed with the same physical and laboratory findigns since 5 years of age. Genetic analysis showed a novel homozygous mutation (p.L356Vfs*8 (c.1066_1067delCT) in exon 11 in the AAAS gene in both siblings and their cousins. This mutation was not reported before. Parents were heterozygous for this mutation.

P2-P030

Ganglioneuroma Presenting as an Adrenal Incidentaloma in a 10-Year-Old Boy-A Rare Entity

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Background: Ganglioneuromas (GN) are rare benign tumours arising from the neural crest cells and it is equally rare to find them arising from the adrenal gland. We report a case of a 10-year old boy with an incidentally identified adrenal GN.

Case report: A 10-year old boy had presented with the complaints of excessive weight gain noticed by the parents since the age of 2 years. There were no other complaints except for sleep apnea. A strong genetic history of obesity in both the parents and their families was present. As part of the workup for obesity, an ultrasound of abdomen was done and incidentally an adrenal tumor was found on the right side, measuring 6cm x 3cm. The find-

ings were confirmed on Computerized Tomography of the adrenal gland.

Hormonal tests were done to ascertain the type and origin of the tumour. Overnight Dexamethasone suppression test showed an 8:00am Cortisol level <1.0μg/dl. Serum aldosterone and DHEAS were within normal range. Serum electrolytes were also normal. Thus, adrenal cortical tumours were excluded. 24 hrs Urinary VMA was 0.89 mg/day (Normal-Upto 15 mg/day). Urine metanephrine was slightly raised 154.05μg/day (Normal – 5-113 μg/day), however plasma metanephrine was normal 38.60 pg/ml (Normal- below 180 pg/ml).

A MIBG Scan was done and delayed imaging at 72 hrs revealed moderate intense tracer concentration in the right suprarenal region corresponding to the lesion seen on CT scan, suggesting an MIBG avid neuroendocrine tissue.

Keeping a close differential of phaeochromocytoma in mind, we decided to surgically remove the lesion after preoperative preparation with alpha and beta-blockers. A highly vascular tumour, measuring 6x 4x 5cm of the right adrenal gland with adhesions to the IVC was found intraoperatively, and right adrenalectomy was performed. The patient had no intraoperative or postoperative complications.

Histological examination revealed mature neural and ganglion cells, suggesting a mature subtype of GN.

The patient on a 1year follow up remains stable and there is no recurrence

Conclusion: GN may mimic other adrenal malignancies such as phaeochromocytoma. Careful evaluation with endocrine tests and imaging procedures are necessary for an accurate diagnosis. Definitive diagnosis is by histological examination. The prognosis is excellent following surgical removal.

P2-P031

The Relationship Between Vitamin D Status and Metabolic Abnormalities in Females with Classical Congenital Adrenal Hyperplasia: A Pilot Study

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Congenital adrenal hyperplasia (CAH) patients have a higher frequency of obesity, visceral adiposity, hyperinsulinism, insulin resistance and hyperandrogenism. There is increasing evidence that low vitamin D status is associated with impaired β-cell function, insulin resistance and impaired glucose tolerance.

Objectives: This pilot aimed to determine the status of serum 25 (OH) D levels in CAH female patients who are followed up in Diabetes Endocrine Metabolism Pediatric Unit clinic over 8 months between 2016 and 2017. We also examined the effect of vitamin D replacement therapy on glucose metabolism, insulin, and androgen levels in female CAH patients.

Methods: Sixteen girls with CAH their ages ranged from 8 to 17 years were included in the study. Six months after the administration of cholecalciferol orally in dose of 4000-6000 IU.

Results: Serum 25 (OH) D level significantly increased from 16.35±5.24 ng/ml to 30.8± 10.6 (P-value=0.0001). Although Homeostatic Model Assessment Insulin Resistance (HOMA-IR) was significantly correlated to serum insulin levels and other insulin resistance and sensitivity indices before and after vitamin D therapy, no significant correlation was witnessed between HOMA-IR and Serum 25 (OH) D level, 17 hydroxy-progesterone and steroid dosage before or after therapy.

Conclusion: Girls with CAH have mostly deficient vitamin D levels. Future research using a randomized control trial with a sufficient sample size and longer duration is required to examine the effect of detected insulin resistance which may affect adrenal androgen production, decrease the therapeutic efficacy of glucocorticoids, and contribute to subsequent development of metabolic syndrome and its complications in these patients.

P2-P032

Adrenal Hypoplasia Seemingly First as a Primary Hypoaldosteronism

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Background: X-linked Congenital Adrenal Hypoplasia (AHC) is a rare cause of primary adrenal insufficiency due to mutations in *NR0B1* gene, causing a loss of function of the nuclear receptor protein DAX-1. Adrenal insufficiency usually presents in the first two months of life, but sometimes can appear later in childhood. Hypogonadotropic Hypogonadism is often associated later in life and all patients develop azoospermia. We describe an unusual onset of AHC started with isolated hypoaldosteronism as first and only sign of disease.

Case presentation: A 18-days-old newborn presented with failure to thrive and feeding difficulties. Blood tests showed severe hyponatremia, hyperkalemia and hypochloremia. Renin was found over the measurable range and aldosterone was low whereas cortisol level was normal with a slightly increased ACTH. In the suspicion of Primary Hypoaldosteronism, correction of plasmatic electrolytes and replacement therapy with Fludrocortisone were promptly started. The subsequent evidence of low plasmatic and urinary cortisol and increased ACTH required the start of Hydrocortisone replacement therapy and it defined a clinical picture of adrenal insufficiency. Genetic analysis demonstrated a novel mutation in *DAX-1* gene leading to the diagnosis of AHC.

Conclusions: NR0B1/DAX-1 mutations should be considered in male infants presenting with isolated hypoaldosteronism as first sign of adrenal insufficiency.

P2-P033

Quantitative Ultrasound Evaluation in a Cohort of 43 Young Adults with Classical CAH Due to 21-Hydroxylase Deficiency (21OHD): Is Bone Mineral Quality Impaired?

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Background: in young adults patients (pts) with CAH due to 21OHD few and conflicting data have been reported on bone mineral quality (BMQ) evaluated by quantitative ultrasound (QUS).

Objective and hypotheses: to evaluate the bone mineral status by QUS variables assessed at proximal phalanges of the hand in a cohort of young adults with classical CAH due to 21OHD and the possible associations with their clinical and metabolic features.

Method: we retrospectively evaluated QUS variables (Amplitude Dependent Speed of Sound - AD-SoS and Bone Transmission Time – BTT, expressed as z scores) measured at a mean age of 21.0 ± 5.0 years, height SD, BMI SD, mean glucocorticoid + mineralocorticoid (GC+MC) equivalent dose of last 3 years, metabolic control [the patients were classified as in good (G), scarce (S) and excessive (E) control by means of 17 OH progesterone (G: <60 nmol/l;) and Androstenedione levels (S: > 9 nmol/l; E:<0.5 nmol/l) at last evaluation], of 43 young adult 21 OHD-CAH pts (21 F and 22 M; 30 salt wasting and 10 simple virilizing forms), diagnosed and treated at our Pediatric Endocrinology Unit in the last 40 years.

Results: No patient showed QUS variables <-2.0 SD. 10/43 pts (23%) (group A) showed slightly reduced AD SoS (-1.47 ± 0.3) and BTT (-1.44 ± 0.9) ; in the other 33 pts (group B) mean AD SoS (0.0±0.9) and BTT (-0.9 ±1.0) were within normal range. In group A and group B, age at evaluation of QUS (19.1± 2.3 vs 21.8±5.7), height SD (-1.2±2.6 vs -1.1± 1.0), BMI SD (0.66±0.9 vs 0.45±1.1), GC equivalent dose (16.2±2.6 vs 17.8 ±5.0) were not significantly different. In Group A 2/10 (20%) and in group B 12/33 (36%) pts. showed scarce metabolic control ($p<0.01$). Linear regression analysis showed negative correlation of AD-SoS with BMI SDS ($P<0.01$).

Conclusion: BMQ evaluated by QUS did not result severely impaired in our group of patients. Prospective studies are needed to confirm the possible correlation between QUS variables, long term metabolic control and BMI SD in young adults with classical CAH due to 21 OHD.

P2-P034

Etiology of Primary Adrenal Insufficiency in Children: A 29-Year Single Center Experience

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Objective: To investigate the etiology and clinical features of Chinese children with PAI.

Method: 427 children(age 0-18 years) with PAI followed at our institution between September 1989 and March 2016 were studied.

Results: 1. 228 males and 199 female (1.14:1) were included. Median age at diagnosis was 1.66(10th-90th, 0.06~8.73 yrs.

2. An identified diagnosis(clinical or genetic) was obtained in 93.4% children(399 of 427). In the other unidentified 28 cases (6.6%), CAH had been excluded.

1) Of which 399 identified cases,

(1)351 cases (82.2%) were CAH, which 21OHD were the most common etiology (341, 97.2%). The other CAH form were 17OHD (5, 1.4%), 11OHD (3, 0.9%), CLAH(2, 0.6%).

(2)48 cases (11.2%) were non-CAH. The etiology were Adrenoleuokodystrophy (ALD) (22, 45.8%), DAX1 mutation (19, 39.6%), Autoimmune Polyglandular Syndrome (APS) (3, 6.8%), Triple A Syndrome (AS) (2, 4.2%), SF1 mutation (1, 2.1%), Adrenalectomy (1, 2.1%).

2) Comparison based on sexual phenotype of 58 cases non-21OHD

(1) Male were predominantly in this study (49/58, 84.5%) with ALD being the most common(49%, 22/49). The other were DAX1 mutation(38.8%,19/49), APS(6.1%, 3/49). 11OHD, CLAH, AS and adrenalectomy only accounted for 2.0% (1/49).

(2) Female patients were fewer than male's (9/58, 15.5%) with 17OHD being the most common, accounting for 44.4%(4/9). The other etiology like 11OHD, LCAH, SF1, AS were rarer, which accounted for 22.2% (2/9), 11.1% (1/9), 11.1% (1/9), 11.1% (1/9) of cases respectively.

3) Clinical features: genital ambiguity was common, accounted for 42.4% (181/427)of cases. The other features include digestive symptoms 35.4%, growth failure 26.7%, gonadal associated symptom 21.1%, hyperpigmentation 9.8%, demyelination of central nervous system 3.3%, prolonged jaundice 2.3%, fatigue 2.3%, convulsion 2.3%. 62.3% patients presented 2 or more onset of symptoms, 4.2% patients with adrenal crisis onset. Physically examination showed that only 57.6% patients were exhibiting hyperpigmentation.

In non-21OHD group, hyperpigmentation were common(82.6%)(significantly higher than CAH 21OHD, $P<0.05$). Genital ambiguity only accounted for 8.1%. The other features are digestive symptoms 12.8%, fatigue 12.8%, growth failure 9.3%, gonadal associated symptom 8.1,prolonged jaundice 4.7%, convulsion 3.5% in turn. 14% patients were having adrenal crisis onset (significantly higher than CAH 21OHD, $P<0.05$).

Conclusion: PAI in pediatric population is commonly in congenital forms, with CAH being the most frequent. Children with PAI have wide range symptoms, lack specificity. Identification its underlying cause is recommended.

P2-P035

Pseudopubertas Praecox in a 4 Year Old Boy with Bilateral Atypical Adrenocortical Adenomas

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Introduction: Adrenocortical tumors are very rare in children, with a prevalence of just 0.3 cases/million/year. Autonomic hormone production by adrenal cortical tumors may cause peripheral precocious puberty.

Case report: A 4-year-old boy was presented by his parents because of pubertal behavior with aggressive features and a significant increase in the size of the penis. The parents also noticed a strong growth spurt and sweat odor. The boy had a good general condition and a very muscular habit. Height and weight were in the 97th percentile range. Tanner Stage was G3-4 P1-2 with a testicular volume of 4 ml and a stretched penis length of 9 cm. He had an adult testosterone concentration and prepubertal gonadotropins. DHEAS and 17-OH progesterone were significantly elevated. ACTH was normal. Congenital adrenal hyperplasia could be excluded by ACTH test and molecular genetic diagnostics. The LHRH test was able to exclude a central precocious puberty. The MRI showed a bilateral, well-defined mass in the area of both adrenal glands. A laparoscopic tumor excision with partial adrenal resection was performed. Histological examination assessed both tumors as benign, but both tumors showed strong nuclear p53 overexpression. In addition, a germline mutation of the p53 tumor suppressor gene could be detected. Li-Fraumeni syndrome (LFS) is a classic cancer predisposition disorder that is commonly associated with p53 germline mutations. After resection of the tumors, serum steroids normalized and clinical signs regressed. The boy receives a tumor follow-up according to the Toronto Protocol: Ultrasound of abdomen and pelvis and determination of tumor markers every 3 months.

Conclusion: Adrenocortical neoplasms are a rare but significant cause for precocious puberty. The bilateral occurrence of adrenal cortical tumors suggests the presence of a genetic tumor predisposition.

Adrenals and HPA Axis P3

P3-P001

Congenital Adrenal Hyperplasia: A Patient's Perspective, A Mother's Story

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Statement of the Problem: Studies suggest that psychosocial factors – in addition to physical barriers – work to impair fertility and successful childbirth in women with Congenital Adrenal Hyperplasia. This includes a reluctance to consult medical professionals as to the scope of the problem and possible solutions. This was the case with Allison Landa, who was not even successfully diagnosed with CAH until the age of 30 due to parental negligence and the terror of discussing her symptoms with a doctor. When successful intervention finally took place, Landa was not only able to stabilize her condition but become pregnant at the age of 40 following a short-term disruption of birth control. Her son Baz was born on Sept. 6, 2015. Landa offers a personal perspective as both a patient and an advocate for fellow CAH sufferers.

Conclusion and Significance: Increased outreach to CAH sufferers on the part of the medical community is indicated in order to reach those who might otherwise not be served.

P3-P002

An Extremely Rare Cause of Cushing Syndrome in Chidhood

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Cushing Syndrome is rare in childhood. Between 2-5 new cases per million people are diagnosed each year, of which only 10% are reported to occur within the paediatric population. There is a female predominance but a male predominance has been reported in infants. Classical clinical indicators of Cushing syndrome in childhood include central weight gain and growth failure. Other clinical manifestations include facial flushing, hypertension, hirsutism, pubertal delay, acne, striae and bruising. Compulsive overachieving behaviour is seen in about 40% of children and adolescents.

Causes of Cushing syndrome include the exogenous administration of glucocorticoids and ACTH, pituitary adenomas (Cushing disease), adrenal tumours and very rarely ectopic ACTH production.

It has been reported that ectopic ACTH production accounts for less than 1% of causes of Cushing Syndrome in adolescents. Tumours that secrete ACTH include small cell carcinoma of the lung, carcinoid tumours of the bronchus, thymus or pancreas, pheochromocytomas and neuroendocrine tumours, particularly that of the pancreas and gut.

We report a rare case of a 3 year old child who presented with Cushings Syndrome secondary to ectopic ACTH production from a pancreatoblastoma.

Pancreatoblastoma, a pancreatic neuroendocrine tumour known to produce ACTH is a very rare malignant tumour. It arises from multipotential stem cells and may bear resemblance to other embryonic neoplasms such as nephroblastoma and hepatoblastoma. These tumours usually occur in the first decade of life and there is a slight male predominance. An incidental mass is the most common form of presentation. The head and tail of the pancreas is the most common site of tumour occurrence while the liver is the most frequent site of metastatic disease. Complete surgical resection of the tumour is the treatment of choice. Chemotherapy maybe beneficial prior to surgery to reduce tumour size. Even though these tumours are curable, long-term surveillance for recurrence is mandatory.

The clinical presentation, management and outcome of this rare tumour in a 3 year old child will be presented in this paper.

P3-P003

Nelson's Syndrome After Bilateral Adrenalectomy for Cushing's Disease in Pediatric Age – Report of a Case

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Introduction: Nelson's syndrome is a potentially severe complication of bilateral adrenalectomy, a radical procedure performed in the treatment of hypercortisolism in Cushing's disease (CD). We report a case of CD in pediatric age submitted to bilateral adrenalectomy with subsequent Nelson's syndrome.

Case Report: Male, 5-year-old, referred to a Pediatric outpatient clinic because of growth failure, rapid weight gain and high blood pressure. He was diagnosed with ACTH-dependent hypercortisolism, with no focal lesion on pituitary MRI. He was unfit for transsphenoidal surgery and therefore started on adrenolytic therapy. Ketoconazole was not tolerated due to liver dysfunction. He tried metyrapone, but it wasn't tolerated. Because he maintained elevated serum cortisol levels he underwent bilateral adrenalectomy at age 6. Post-surgical 9am cortisol levels were compatible with a cure of his CD. Hydrocortisone and fludrocortisone treatment was started following surgery. He maintained regular clinical and MRI surveillance. Four years after surgery, the patient showed significant skin hyperpigmentation and elevated plasma ACTH (>1250pg/mL), compatible with Nelson's syndrome. Pituitary MRI performed at this time showed a pituitary microadenoma located at the stalk, more evident than in previous studies. After discussion with Neurosurgery and review of therapeutic options, a conservative approach was decided, with close radiological and clinical follow up, since hypophysectomy or radiotherapy would likely compromise pituitary function. The patient is now 19 years-old and maintains remission of Cushing's signs and symptoms. He shows neither symptoms of visual field loss nor compressive symptoms suggestive of a growing pituitary neoplasm. Pituitary microadenoma remains stable and he's now scheduled for a pituitary surgery.

Conclusion: The authors present a case of Nelson's Syndrome after bilateral adrenalectomy performed for CD. Transsphenoidal hypophysectomy is the treatment of choice in patients with CD but it frequently causes hypopituitarism and may not be effective in microadenomas. Because of this, treatment of children with CD may be challenging, once the aim is to cure hypercortisolism and to preserve pituitary function, in order not to compromise their normal development.

P3-P004

Basal Levels of 17-Hydroxyprogesterone Can Distinguish Isolated Precocious Pubarche from Non-Classical Congenital Adrenal Hyperplasia in Children: A Prospective Observational Study

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Background: Basal levels of androgens, in particular 17-OHprogesterone (17OHP), are widely debated as predictors of non-classical congenital adrenal hyperplasia (NCCAH) among patients with precocious pubarche (PP). So many authors suggested the execution of ACTH stimulation test in all children with PP. The aim of our study was to identify clinical and biochemical predictors of NCCAH in children with PP.

Methods: We conducted a prospective study of 92 patients with PP undergoing an ACTH stimulation test. We tested the association of basal clinical and biochemical factors with NCCAH diagnosis. Patients were suspected to have NCCAH if their stimulated 17-OHP plasma levels were >10ng/ml and then genotyped to confirm the diagnosis.

Results: Seven (7.6%) patients resulted having NCCAH. The best basal biochemical predictor for NCCAH was 17OHP level >2ng/ml. In fact a basal 17OHP level >2ng/ml had 100% (95%CI, 59.04–100) sensitivity, and 93% (95%CI, 85.3–97.37) specificity. The area under the ROC curve for 17OHP was 0.99 (95% CI, 0.98–1.007).

Conclusions: basal 17-OHP cut-off of 2 ng/mL was very effective in predicting NCCAH among our patients with PP. Assay specific cut-off would probably be the best strategy to avoid unnecessary ACTH test.

P3-P005

Age at Diagnosis and Outcome in Maghreb Patients with 21-Hydroxylase Deficient Congenital Adrenal Hyperplasia; Urgent Need for Newborn Screening

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Objectives: To examine age at presentation and outcome in children diagnosed with 21-hydroxylase deficient congenital adrenal hyperplasia (21-OHD CAH) in Algeria in the absence of a national neonatal screening program.

Design: Retrospective analysis of patients followed in a single centre from 2007 to 2017. The diagnosis of CAH was established on clinical and biochemical grounds ± genetic analysis.

Results: Of 168 patients (114F, sex ratio 2:1) from 145 families (61% consanguineous), the classical salt-wasting (SW) form of 21-OHD CAH was most common (81%) comprising 136 (66% F) patients, while 30 (77% F) had simple virilising (SV-21OHD) and 2 (F) non-classical (NC-21OHD).

Initial referral [n;%] was with disorder of sex development (DSD) [45;27%] (100% F); dehydration [47;28%] (96% M); DSD and dehydration [59;35%] (100% F); sexual precocity [12;7%] (58% M) and family history of CAH [5].

At presentation DSD was found in all but four 46,XX patients (2 NC-21OHD and 2 treated prenatally). Dehydration occurred in 86 (51.5%) neonates, more frequently in males than females - 53.4 vs 33.6 %.

Mean (SD) ages at presentation and start of hydrocortisone were significantly later in males than females: 191±524 vs 82±332 ; and 152±511 vs 262±639 days (p<0.001), attributable to DSD being the presenting feature in the latter. Mean age at diagnosis was significantly earlier in SW than SV 21-OHD - 51±135 vs 637±946 days (p=<0.001).

Mean plasma sodium at diagnosis was lower in males than females (118±11 vs 123 ±10 mmol/L, p< 0.03) and between the SW and SV 21-OHD - 120±10 vs 130±3 mmol/L (p<0.001).

Sixty-two (%) of 114 46,XX patients were initially assigned as males, mean ± SD (range) age at sex re-assignment 3.8±8 (0-36) months in 58, with 4 raised as males according to parental wishes. Since diagnosis, 8 (4.7%) patients have died in adrenal crisis while 18 of 89 patients aged ≥ 4 years have moderate to severe mental delay.

Conclusions: Currently, males with 21-OHD are diagnosed half as often as females, reflecting death from SW during the first few weeks. Delayed age at diagnosis causes severe hyponatremia in SW patients which increasing the risk of mortality and developmental delay. National screening for CAH in Algeria, where consanguinity rate and hence CAH prevalence is high, is urgently required.

P3-P006

An Adrenal Tumor Presenting as a Premature Pubarche in a 7 Year-Old Girl

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Introduction: Premature pubarche is the most frequent diagnosis when children present moderate pubic hair development, but other diagnosis must be ruled out. We report the case of a child with premature pubarche with hormonal results in the physiological range, corresponding to an adrenal tumor.

Observation: A girl aged 6.8 years consulted for precocious pubertal development (pubic hair stage 3, breast stage 2), with moderate acne. There was no virilization. Her height had changed from 0.8 to 1.8 SD score within 1 year. Bone age was 7.5 years. The 17-hydroxyprogesterone level was 3.2 ng/mL, and 17hydroxyprogesterone and 11-deoxycortisol responses to an ACTH test were normal. The LH and FSH peak to GnRH test were 0.9 U/l and 5.8 U/l, respectively. Uterine length was 23 mm on pelvic ultrasound, ovaries were normal in size. Circulating S-DHEA was 1.9 mg/L, and testosterone 0.3 ng/mL. Breast development resumed spontaneously within 3 months. Because the clinical presentation was more marked than usually, associating an accelerated growth rate and a detectable testosterone level, an adrenal tomodensitometry was performed, showing a left adrenal 3.5 cm mass. The child underwent laparoscopic adrenalectomy. The tumor histopathological analysis diagnosed an encapsulated adrenal adenoma. The level of all circulating androgens returned to normal after the removal of the adrenal mass.

Conclusion: Adrenal tomodensitometry is not to be performed in all cases of precocious pubic hair development in subjects aged more than 6 years. However, it is advised when the clinical presentation is unusually active (here accelerated growth rate), even if S-DHEA and testosterone levels are in the normal range for a physiological premature pubarche.

P3-P007

Refractory Cyclical Cushing's Disease -A Case of Multiple Pituitary Micro-Adenomas in a Three Year Old Girl After 8 Years Follow Up

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Case presentation: A 3 years 10 months old British white girl presented with rapid weight gain of 11 Kg over 4 months, hirsutism, central obesity, moon face, buffalo hump and hypertension.

Investigations: Plasma cortisol, IGF-1 and ACTH levels were elevated. The 9am plasma cortisol was 1035 nmol/L (140-500) with simultaneous plasma ACTH 13 pmol/L (1-11). Plasma cortisol and ACTH levels responded to both dexamethasone suppression and CRH stimulation. Inferior petrosal sinus venous blood samples showed no significant ACTH left to right gradient before and after CRH stimulation. Magnetic resonance images of the adrenals and pituitary were normal. The findings suggested a pituitary cause, but no unilateral pituitary adenoma was identified.

Surgery: The whole anterior pituitary gland was removed by endoscopic trans-sphenoidal excision.

Histology and immunohistochemistry: Multiple pituitary micro-adenoma fragments were found within normal anterior pituitary tissue on histological examination. The fragments showed positive reactivity for both growth hormone and ACTH by immunohistochemistry. This confirmed a diagnosis of Cushing's disease with growth hormone excess.

Follow up: She made a good recovery over 3 years after surgery on hydrocortisone, growth hormone and thyroxine replacement therapy. No MEN1 gene mutation was found on genetic analysis. A relapse of Cushing's disease occurred 6 years after surgery and she was treated with repeat trans-sphenoidal pituitary surgery fol-

lowed by pituitary radiotherapy. This further treatment was unsuccessful and she hence underwent a bilateral adrenalectomy eight years after initial presentation. A diagnosis of resistant cyclical Cushing's disease was made.

Consent: Written informed consent was obtained from her parents for presentation of the clinical details & patient photographs.

Discussion: A review of the literature on endogenous Cushing's Syndrome in children identified that:

(a) 2-5 new paediatric cases occur per 10 million people per year, (b) pituitary adenoma causing Cushing's disease is the commonest cause above age 7 years and adrenal tumour is the commonest cause below age 7 years, (c) multiple pituitary adenomas are very rare, occurring in up to 2.6% in surgical series, (d) the youngest previous case of paediatric Cushing's disease reported was in a five year old child.

Conclusion: This may be the one of the youngest children ever reported with multiple pituitary micro-adenomas causing refractory cyclical Cushing's disease. No genetic cause was identified. This report demonstrates that pituitary driven Cushing's disease may present difficult diagnostic and long term therapeutic challenges.

P3-P008

Topical Corticosteroid-Induced Adrenal Insufficiency

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Introduction: Topical corticosteroids are often used for the treatment of dermatological diseases. However, systemic adrenal insufficiency may result from their overuse. Patients at risk for development of adrenal insufficiency include especially young children and patients with damaged skin barriers.

Case presentation: We report the case of a 11-year-old boy who was seen in our clinic for suspicion of Cushing syndrome. He was adressed by a dermatologist who treated his dishydrotic eczema of the hands with 0.05% betametason cream during three years. He used the cream only during exacerbations (twice a day on the hands during one week).

The physical examination revealed an obesity, a weight of 79kg height of 157 cm, (body mass index [BMI] 32.3kg/m^2), His sitting blood pressure was 121/60mm Hg.

Laboratory data revealed fasting blood glucose 98mg/dL, plasma sodium 140mEq/L, plasma potassium 4.3mEq/L, hemoglobin 14.4g/dL, free T4 1.11ng/dL [0.8–1.7], TSH 1.2mU/L [0.7–4.65]. Basal serum cortisol levels (at 8 :00 AM) were <1 µg/dL [3.7–19.4] and basal ACTH was 1.3ng/L [7.2–63.3]. Twenty four hours urinary cortisol was <16 µg/24hours [16–176].

Topical corticosteroid was stopped and hydrocortison at physiological doses (10 mg/m^2/day) was started as well as recommendations in case of fever or disease.

Four months later, a 250 µg cosyntropin stimulation test (Synacthen®) was performed. Cortisol levels were 241 ng/mL [62–180], ACTH was 77.3 pg/mL [7.2-63.3],DHEAS 139 µg/dL[35-430], 17 OH-progesterone 4.5 nmol/L [2.7-10]. The hypothalamic-pituitary-adrenal (HPA) axis was no longer suppressed. Hydrocortison was stopped. Five months later, twenty four hours urinary cortisol was performed: 45 µg/24hours [16–176]. Physical examination showed a weight of 86 kg, a height of 160 cm, (body mass index [BMI] 33.7kg/m^2), His sitting blood pressure was 119/63mmHg. The obesity was probably not due to a topical corticosteroid.

Conclusion and Teaching Points: Among the adverse effects associated with topical corticosteroid use, the most dangerous is HPA axis suppression, which in some cases, can be life threatening. Therefore, it should be used with an increased awareness of the potential risk of adrenal axis suppressive effects.

P3-P009

Early Diagnosis of Duchenne Muscular Dystrophy in 6-Months-Old Male with Primary Adrenal Insufficiency

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Background: Adrenal hypoplasia congenital associated with DAX-1 (NROB1) gene mutations is a rare cause of primary adrenal insufficiency in male. It can be presented as a part of Xp21 contiguous gene deletion syndrome which characterized by complex glycerol kinase deficiency (GK), adrenal hypoplasia congenital (NROB1), intellectual disability (IL1RAPL1) and/or Duchenne muscular dystrophy (DMD).

Case report: We report a 6-month-old male infant, which presented a congenital primary adrenal insufficiency, unilateral cryptorchidism and high levels of transaminases. An adrenal insufficiency was diagnosed at 6 weeks after birth due to low weight gain, hyperpigmentation,hypotonia, hyponatremia (125 mmol/l), hyperkalemia (8 mmol/l), high levels of ACTH and renin (293 pg/ml and 500 U/l, respectively). Evaluation at 6 months of age revealed elevated liver enzymes (ALT 281 U/L, AST 275 U/L), increased levels triglyceride (5.18 mmol/L) and extremely increased creatine phosphokinase (15000 U/L). It was suggestive for myodystrophy.We supposed that the combination of adrenal insufficiency with cryptorchidism, and laboratory signs of myodystrophy could result from the Xp21 contiguous gene deletion syndrome. Further investigations showed massive glyceroluria, and the glycerol kinase deficiency was suspected. Microarray analysis showed the Xp microdeletion in Xp21.2-p21.3(28332614_34432348) loci, which involved IL1RAPL1, NR0B1, GK, DMD genes. During last examination at the age of 6 month the mental retardation and/or symptoms of muscular dystrophy were not seen.

Conclusion: Congenital adrenal hypoplasia is a rare disease that could be associated with of Xp21 contiguous gene deletion syndrome. Patients should be screened for other components such as complex glycerol kinase deficiency, Duchenne's muscular

dystrophy and mental retardation. Early diagnosis of Duchenne's muscular dystrophy can be helpful for appropriate treatment strategy and prenatal diagnosis in the family.

P3-P010

Lipoid Adrenal Hyperplasia Diagnosed with Severe Cholestasis in Newborn

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Introduction: Congenital lipoid adrenal hyperplasia is the most severe form of congenital adrenal hyperplasia and is rarely seen. Steroid synthesis cannot be done in the adrenal gonads. Adrenal glands have hyperplasia and lipid accumulation. Male babies are born to girls. Most of the cases are lost with severe adrenal insufficiency. Patients diagnosed and treated at supraphysiological doses during neonatal period

Here we present a case of lipoid adrenal hyperplasia diagnosed with severe cholestasis, hyponatremia and hyperpotassaemia. In this case phenotype was female and the testis was palpated in the inguinal canal.

Case: A 26-day-old baby was transferred to our clinic with the doubt of adrenal insufficiency. Her parents were first-degree cousins. She was born in term there was nutritional intolerance. Phenotype was girl's appearance and two-handed testicles in the inguinal region. There was extensive hyperpigmentation throughout the body. A complete blood count was normal. Direct bilirubin: 18 mg / dl, total cholesterol: 371 mg / dl, LDL cholesterol: 12 mg / dl, Na: 126 meq / Dl, Triglyceride: 230 mg / dl, ACTH: 1250, Cortisol: 1,63 ug / dl, LH: 1,49 mU / ml, Progesterone 1,15 ng /, Testosterone 24 ng / dl, Aldosterone 49 pg / ml. Pelvic ultrasonography revealed no uterus or over. Karyotype analysis was 46 XY. Congenital lipoid adrenal hyperplasia was suspected. Hydrocortisone and fludrocortisone treatment were administered at high doses. The cholestasis of the patient was also recovered when the adrenal crisis resolved. The homozygous mutation in the star gene was detected in the genetic screening. The patient was diagnosed with congenital lipoid adrenal hyperplasia.

Conclusion: 46 XY congenital lipoid adrenal hyperplasia is a disease that should be considered in the newborn with signs of sexual dysfunction and adrenal insufficiency. In these cases cholestasis may be problem. These patients can survive at supraphysiological doses with hydrocortisone and fludrocortisone treatment.

P3-P011

Severe Hyponatraemia with Absence of Hyperkalaemia in a Patient with Addison's Disease

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Objective: Autoimmunity of the adrenal gland, also known as Addison's disease, is characterised by cell mediated immune destruction of the adrenal cortex. We present a child with Addison's disease who has severe hyponatraemia and normokalemia, which led to an inappropriately low index of suspicion initially at presentation.

Case: A 12-year-old boy diagnosed with adrenal deficiency was admitted to hospital with 2 weeks of vomiting, fatigue and weight loss. He has been taking hydrocortisone but not fludrocortisone therapy. Serum electrolytes obtained 6 months prior to presentation were normal, except for mild hyponatraemia at 129 mmol/L, which dropped to 117 mmol/L on the last admission. He had normal serum potassium, low-serum osmolality, elevated urine sodium and osmolality, low serum aldosterone, and high plasma renin levels. 21-hydroxylase antibody in serum was positive. Addison's disease was diagnosed on the basis of gingival hyperpigmentation and undetectable cortisol on adrenocorticotropic hormone stimulation test. He rapidly responded to stress dose hydrocortisone, followed by hydrocortisone, fludrocortisone, and salt therapy.

Conclusion: The absence of hyperkalaemia in the presence of severe hyponatraemia cannot rule out Addison's disease in children. In this situation urine sodium, serum aldosterone, and plasma renin levels were examined.

P3-P012

Deep Bronze Skin Without Sun Exposition in a 16-Year Old Girl

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Introduction: Adrenal insufficiency (AI) leads to a diminished production of steroid hormones. AI is subdivided into a primary and a secondary form. In primary AI, the underlying defect affects the adrenal gland itself resulting in a low steroid production and an overproduction of adrenocorticotropic hormone (ACTH). On the contrary, the cause of secondary AI lies in the pituitary, leading to a reduced production of ACTH and consecutively to a reduced excretion of corticosteroids.

In primary AI, which is also called Addison´s Disease or hypocortisolism, low serum cortisol levels lead – due to negative feedback mechanisms - to an increase in ACTH-levels. ACTH is generated by cleavage of proopiomelanocortin (POMC) into ACTH, melanocyte-stimulation hormone (MSH) and beta-lipoprotein. ACTH undergoes further cleavage to produce alpha-MSH. This is

the most important MSH for skin pigmentation leading to hyperpigmentation of the skin.

Case report: A 16-year old girl came to our outpatient clinic because of hyperpigmentation of the skin. She reported to have a very dark skin without sun exposition for one year. Especially palmar creases, nipples and armpits were affected. Moreover, she reported tiredness and craving for salt. Longterm history was without pathological findings, family history showed an increase in autoimmune diseases (coeliac disease, pernicious anaemia).

Clinical diagnostics: Laboratory values showed low cortisol (16,6 ng/ml) whereas ACTH and Renin were elevated (1250 pg/ml and 506,5 µU/ml, respectively). Parathyroid hormone and electrolytes were in normal range. ACTH stimulation test showed an insufficient increase in cortisol, which – in combination with elevated 21-hydoxylase-antibodies – confirmed the diagnosis of Addisons´s Disease due to autoimmune adrenalitis. Genetic testing of the AIRE gene turned out negative.

Course of disease: An oral therapy with hydrocortisone and fludrocortisone was started. The well-being of the patient improved, as well as fatigue and blood pressure. The colour of the skin became considerably lighter.

Conclusions: Whereas tuberculosis used to be the most common cause for Addison´s Disease in former days, autoimmune adrenalitis is the major cause nowadays. It can appear isolated or in coincidence with the APECED Syndrome (Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy). It is associated with mutations in the AIRE gene which plays an important role in immune tolerance.

P3-P013

Case of Primary Pigmented Nodular Adrenocortical

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Introduction: Primary pigmented nodular adrenocortical disease (PPNAD) is a rare cause of ACTH-independent Cushing's syndrome and has characteristic gross and microscopic pathologic findings.

Case presentation: We report a case of PPNAD in a 11-year-old girl. She was admitted to our hospital with a chief complaint of rapid weight gain in 1.5 years. She also had hypertension and the signs of Cushing syndrome. Examination associated with laboratory tests detected hypertension and ACTH- independent cushing syndrome. Images of bilateral nodular adrenal hyperplasia were revealed by abdominal CT Scan. Total bilateral adrenalectomy following by renal hormones therapy was the choice of treatment. After 3 months of surgery, improvement of hypertension, weight gain and cushing syndrmome were noted. In addition, there was normalization of adrenal hormones levels.

Conclusions: Primary pigmented nodular adrenocortical disease (PPNAD) is a rare cause of ACTH-independent Cushing's syndrome. Total bilateral adrenalectomy followed by hormone therapy is the optimal treatment. Assessment of cushing syndrome's improvement associated with periodic evaluation of CNC should be performed.

P3-P014

Two Case Report of Adrenocortical Adenoma

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Adrenal cortical tumor is rare in children and aldolescents. It is more common in girls and almost hormone overproduction with Cushing syndrome and virilization. Resection is the main management in order to control defenitively. Differentiating from begnin to malignancy lesion still remains a big obstacle for the clinicians and histopathologist.

We report two cases of adrenal cortical tumor in children with different signs and symptoms and review their clinical presentations, pathology and follow-up data. All of them are girls. The first one is 18 months, presented at our clinic with the symptom of Cushing syndrome and abdomen mass. She also had hypertension leading to hypertrophy of her left ventricle. Her plasma and urine cortisol were elevated and the plasma ACTH were decreased. Imagine studies revealed neoplasm which size is 4.5cm×3cm×2 cm in her right adrenal gland. The second one is 4 year olds, complained the symptom of virilization: enlarged clitoris, man-like pubarche, facial hair and deep voice. The plasma testosterone concentration, plasma and urine cortisol concentration elevated. Ultrasound and CTscan revealed neoplasm which size is 5.5cm×5cm×3.5 cm on her left adrenal gland. Two of them were experienced to unilateral adrenalectomy and had characteristis of adrenal corticol adenoma on microscopic examination.

On follow-up section, the first girl still had hypertension, the plasma and urine cortisol remained increasing. She was re-evaluated for recurrent tumor and was discovered sign of metastatis to the lung on chest CTscan. Unfortunaltely, her family refused to treament. Follow-up of the last patient showed that signs of virilization were suppressed. Serum testosterone levels dropped to normal after surgery, and remained normal. Two to six months after adrenalectomy, she was noticed to have significant symptoms of adrenal insufficiency and gradual enlargement of breast (Tanner B2). Laboratory tests showed: AM cortisol levels and ACTH levels were low on several occasions. The tests of diagnosis for precocious puberty (PP) were performed. After confirming the diagnosis adrenal insufficiency and PP the patient was given 5mg of hydrocortisone a day and 3.75mg of Diphereline a month.

Adrenalcortiacal tumor is needed to diagnosis and surgery as early as possible to prevent the effect of hormone over production. Althought our two cases were almost effectively treatmented by surgery but long term follow up is very importance to detect postoperative complications.

P3-P015

A Homozygous Mutation c.518T>A (p.ILe173Asn) of the CYP21A2 Gene Presenting as Non-Classical Congenital Adrenal Hyperplasia (NCAH)

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Congenital adrenal hyperplasia due to P450c21 (21-hydroxylase) deficiency is an autosomal recessive disorder presenting as three phenotypes dependent on the residual enzyme activity: two classical ones (salt wasting and simple virilizing, SV) and the milder NCAH. All forms have increased adrenal androgens. Around 0.1% of Caucasians and up to several percent of certain ethnic groups are affected by NCAH. Most NCAH patients remain undiagnosed. Symptoms of NCAH may develop at any age, but are more typical during late childhood/adolescence. We present a 20-year-old patient followed since she was 14 due to hirsutism and overweight. Menarche started at 12 years, initially with regular periods. After 15 years of age periods started to occur 6-8 times a year with increase in body hairs. Metabolic syndrome was also diagnosed and Metformin therapy was administered at 850 mg/day. Weight was reduced with 10%, but hirsutism and irregular menstruation persisted. Baseline 17-OH-Progesterone (17OHPG) was 8 nmol/l and Dehydrocortisone was added to therapy. Over the years, the level of 17OHPG has decreased without full normalization (Tabl. 1). In the last year the patient had regular periods and no further progression of hirsutism. Family history was non-contributory. The patient was selected as a candidate for CYP21A2 genotyping because of the elevated basal 17OHPG, hirsutism and metabolic syndrome, as well as menstrual irregularities. By Sanger sequencing a homozygous missense mutation c.518T>A (p.Ile173Asn) was found, also known as p.I172N. The mutation leads to markedly reduced enzyme activity and has been associated with SV.

Conclusion: The precise etiological diagnosis was established at 20 yrs of age with subsequent changes of the therapeutic strategy. Sequencing of the CYP21A2 gene was established after the introduction of the 17OHPG screening and is of great importance not only for the classical forms of CAH. This patient contributes to the variability in the genotype-phenotype relations in CAH due to CYP21A2 mutations.

P3-P016

Adrenals and HPA Axisa; Atypical Presentation of Adrenal Insufficiency

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Case report:Atypical presentation of adrenal insufficiency : 13 year old presented with vomiting(one day), lethargy two weeks. mild dehydration, vitals stable,generally healthy, examination unremarkable, medication nill, history of insect bite two weeks ago, no allergies,started on I. V maintenance fluids, investigations(blood) normal, the only abnormal was low soduim, normal glucose and potassium, soduim was 122 mol/ l,repeated soduim was 119 after the maintain ace 0.9% normal saline.3% soduim was added to the maintanance to correct the soduim.fluid was restricted to 60% because of SIADH.repeated was not improving.short synecthen showed no response to cortisol.the child was started on hydrocortisone with full maintenance iv fluids.the repeated soduim was coming back to normal.auto adrenal antibodies were negative,ACTH was normal, renin was normal.MRI brain showed small pineal cyst as incidental finding.serum osmolality normal, no pigmentation noted,child Blood pressure was normal.

Conclusion: initial impression was gastro.Despite replacement of fluids the soduim was not responding.in 30% of case potassium can be normal. his 17OHP was normal.genitic studies were normal.our impression was adrenal insufficieny secondary to? Allergic reaction to insect bite.the child is followed up on maintanance dose of hydrocortisone and advice for stress dose.

Table 1. Clinical and hormonal studies (for Abstract no P3-P015)

Age	14.5 years	15.0 years	15.5 years	19 years
We (kg)/He (cm)/ BMI(kg/m^2)	65/158/26.1	60.5/159/24.0	58/159/23.0	58/159/23.0
17OHPG ng/ml (r.r. 0.2–1.3)	–	8.0	2.5	1.8
LH mIU/ml (r.r. 1.1–11.6)	5.5	6.8	8.5	-
FSH mIU/ml (r.r.2.8–11.3)	5.5	4.9	5.5	-
Testosterone nmol/l (r.r. 0–1.38)	1.9	1.8	0.9	-
Treatment	Metformin 850 mg/d	Metformin850 g/d Dehydrocortisone 2.5 mg/d	Metformin850 g/d Dehydrocortisone 2.5 mg/d	Dehydrocortisone 5 mg/d

P3-P017

Non-Classic Congenital Adrenal Hyperplasia Causing Alleles Among Adolescent Girls with PCOS – Genetical Study

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Introduction: Polycystic ovary syndrome (PCOS) is one of the most common endocrinopathies in adult women. Syndrome is characterised by hiperandrogenism, oligo/amenorrhoea and polycystic ovary morphology in ultrasound. Clinical signs of the syndrome usually start already during adolescent years. Non-classic congenital adrenal hyperplasia (NCAH), caused by several mutations in CYP21A2 (6p21.3) gene, is the most common differential diagnosis for girls presented with symptoms of PCOS. Level of 17 – OH progesterone and AKTH stimulation test is the main diagnostic tool. Nevertheless, genetic testing provides more accurate diagnosis.

Aim: To asess prevalence of NCAH causing alleles among adolescent patients with PCOS according to Rotterdam criteria.

Methods: 40 adolescent patients at least two years after menarche attending paediatric gyneacologist with PCOS according to Rotterdam criteria were included in the study. Hyperandrogenism was defined as Ferriman – Gallway score more than seven or elevated testosterone, androstendione or DHEASO4 levels. DNA was extracted from venous blood using fenole – chloroform methode. Genetic variations in the CYP21A2 gene were tested by using standart Multiplex Ligation-dependent Probe Amplification test (SALSA MLPA probemix P050-C1 CAH, MRC Holland), according to methodology established by producers. Research was approved by Central Medical Ethics Committee of Latvia.

Results: Median age of the study group was 16 (SD 1.4) years. Average score in Ferriman-Gallway scale was 10.8 (SD 6.3). We detected pathogenic variants in CYP21A2 for four patients, that constitutes 10% of the tested alleles. All discovered variants were in heterozygous state, that does not establish definitive diagnosis of NCAH. Two patients had c.-113 A>G, I172N (rs6475) and other two I2G (rs6467). Interestingly, all of the patients had normal 17 – OH level - below 2 ng/ml.

Conlusions: NCAH is one of the reasons for hiperandrogenism that is masked by clinical appereance of PCOS. Genetical testing is an important tool to distinguish between these two conditions. Prevalence of NCAH among PCOS patients in our study was lower than in literature (usually around 10%). Further studies in this area are required in order to test less prevalent mutations.

P3-P018

Adequate Interpretation of Cortisol Levels in Children

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Adrenocortical tumours are a rare disease in the paediatric population, with a higher prevalence in children under 5 years. The aetiology is partially known; in some cases it is related to mutations in the tumour suppressor gene p53 (TP 53). The classical symptoms of the Cushing syndrome are not usually present in children, so we should suspect this disease in children and teenagers with obesity or with slow growth velocity.

Methods: We report a case of adrenal tumour in which cortisol levels at diagnosis were in the normal reference range for age.

Results: An 18 month old girl was referred to the endocrinology unit because of obesity. She showed no other symptoms or personal background of interest.

The endocrine analysis showed cortisol levels within normal range, 14,8 ug/dl (VN 5-18), with suppressed ACTH levels 2 pg/ml (VN 10-46). Cortisol levels at 8:00pm showed a loss of normal circadian cycles (14,1 ug/dl). Cortisol levels were not suppressed after the short dexamethasone test (13,8 ug/dl). With the suspicion of a cortisol producing adrenal tumour the study was completed with image tests (ultrasound, MRI and CT). The images were compatible with left adrenal neuroblastoma (diameter 41,5 cm), so an extension study was performed with catecholamines in urine, enolase and MIBG scintigraphy; they were all negative.

She was diagnosed of cortisol producing adrenal tumour, and surgery was performed with no incidences. The histological study confirmed that it was a benign adrenocortical tumour (Score Wieneke). Extension studies where negative (thoracic TC, bone scintigraphy). Genetic study was also negative (TP53, APC, CDKN1C, MEN1, NF1, RET, SDHB, SDHC, SDHD, VHL genes).

At present, she has had a satisfactory evolution, with normal cortisol levels under substitutive treatment with hydrocortisone.

Conclusions: An appropriate interpretation of the cortisol levels, based on age, with the clinical manifestations is required.

Alteration of the cortisol circadian cycles with suppressed ACTH levels and the loss of suppression of cortisol with the dexamethasone test, guide to the diagnosis of cortisol producing adrenal tumour.

An early diagnosis is crucial to prevent the morbidity of the Cushing syndrome.

P3-P019

Erythrocytosis as First Manifestation of Adrenal Mass

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Background: Erythrocytosis is characterized by increased number of red blood cells. Primary form is also known as polycythemia vera, while secondary forms can be due to several causes, among which hyperandrogenism. Although the association of severe hyperandrogenism and polyglobulia is known, literature data concerning this comorbidity are overall scanty, and completely lacking in pediatric age.

Case report: We report the history of a 14 years-old girl admitted to our Pediatric Unit due to both polyglobulia (Hb 18.1 gr%) and virilization, as a consequence of a testosterone-secreting adrenal cancer.

In this girl increased Hb levels were incidentally demonstrated for the first time when she was 13 years-old, but no specific investigations were performed until a clinical picture of hyperandrogenism became evident (severe hirsutism, clitoromegaly and deepening of the voice). Biochemical evaluation showed a very severe increase of total testosterone, dehydroepiandrosterone-solfate and delta-4 androstenedione with normal cortisol levels. Ultrasonography and computerized tomography showed a wide solid lesion (14 x 11 cm) in the right adrenal gland. On the basis of the severe virilization and the imaging features, a unilateral adrenalectomy was performed. The adrenal mass measured 14 cm and was 500 g of weight. Histology was compatible with an adrenal cortical carcinoma. Both hematological abnormalities and hyperandrogenism rapidly regressed after tumor removal. CT total body did not show remnant lesions, and for this reason no adjuvant therapy was performed.

Conclusion: Hyperandrogenism due to adrenal tumors is a very rare cause of secondary erythrocytosis, especially in children. For this reason, the diagnosis can be challenging and delayed. The physicians should consider this etiology in the diagnostic work-up of erythrocytosis, in order to obtain a correct diagnosis and a rapid normalization of clinical picture.

P3-P020

A Neonatal Case with Familial Glucocorticoid Deficiency Type 1 Having Adrenal Crisis in Early Period

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Objective: Familial glucocorticoid deficiency (ACTH resistance); is a rare chronic adrenal insufficiency problem. Genetic tranmission is autosomal recessive. Glucocorticoid deficiency is characterized by increased ACTH levels and normal or partial incomplete aldosterone production. The familial glucocorticoid deficiency, which is a defect in the melanocortin receptor. Hypoglycemia, convulsions, increased pigmentation in the skin can be seen from the earliest stages of life.

Case: Forty day old baby with postnatal hypoglycemia, hyponatremia, hyperkalemia, intensive hiperpigmentation, convulsions due to adrenal insufficiency was forwarded to starting treatment. Parents were relative and their first baby with similar findings was lost at the first day. On physical examination, there was severe hyperpigmentation. Hydrocortisone and fludrocortisone was continued in appropriate doses. Fludrocortisone was cut off on follow-up. The color began to opening. The genetic analysis showed that familial glucocorticoid deficiency type 1 with MC2R gene homozygous deletion of the entire gene.

Conclusion: In this study; we showed that treatment with familial glucocorticoid deficiency type 1 must be quickly and effectively because of adrenal insufficiency and hyperpigmentation develop very early and rapidly in neonatal period.

P3-P021

Presenting Features, Clinical Characteristics and Follow Up of Familial Isolated Glucocorticoid Deficiency (FGD) Due to Mutations in *MC2R* and *MRAP* Genes

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Objectives: Familial glucocorticoid deficiency(FGD) is a rare autosomal recessive disorder characterized with isolated glucocorticoid deficiency. Melanocortin receptor 2(MC2R) mediates the

Table 1. (for Abstract no P3-P021)

	At presentation							At latest follow-up visit				
	Age (month)/ sex	Complaints	Mutation	Cortisol (mcg/dL)	ACTH (pg/mL)	Weight (SDS)	Height (SDS)	Age (month)	ACTH (pg/mL)	Weight (SDS)	Height (SDS)	Additional findings
Case 1	4/F	Hyperpigmentation Hypoglycemia Convulsion	MC2R (560delT)	0.04	>1500	4.9 (–0.51)	6 (–2)	61	132	17.8 (–0.31)	103 (–1.33)	–
Case 2	12/F	Hyperpigmentation Hypoglycemia Convulsion IUGR	MC2R (560delT)	0.6	2000	12.7 (2.58)	92.2 (5.98)	46	2000	16 (0.11)	108 (1.53)	NDD Spasticity
Case 3	9/M	Hyperpigmentation Hypoglycemia Convulsion	MC2R (A233P)	0.3	2000	10.7 (1.45)	76.5 (1.78)	66	6.48	20.8 (0.41)	109.3 (–0.88)	–
Case 4	18/F	Hyperpigmentation Hypoglycemia Hypothyroidism	MC2R (G226R)	1.0	>1250	18.3 (4.67)	96.6 (4.63)	106	19.3	67 (4.07)	138.2 (1.19)	Primary hypothyroidism Obesity NDD
Case 5	5days/F	Hyperpigmentation Hypoglycemia Convulsion Respiratory distress	MC2R (560delT)	0.26	826	2.3 (–2.61)	48 (–0.93)	26	4.49	9.5 (–2.09)	78.5 (–2.75)	–
Case 6	34/F	Hyperpigmentation Hypoglycemia Convulsion Hyperbilirubinemi	MRAP (IVS3ds+1delG)	<1.0	>1250	19.7 (2.99)	102.2 (2.03)	115	38.4	61.3 (3.18)	136.5 (0.15)	NDD Obesity Epilepsy

functions of adrenocorticotropic hormone (ACTH) in the adrenal cortex. MC2R accessory *protein* (*MRAP*), a transmembrane protein, involves in the trafficking of MC2R to the cell surface. Mutations in *MC2R* and *MRAP* genes cause FGD type 1 and 2. Herein, we evaluate the clinical characteristics and follow-up of 6 cases with FGD due to mutations in *MC2R* and *MRAP*.

Patients and method: Data of 6 cases with FGD(5 with *MC2R* and one with *MRAP* mutations) followed at our pediatric endocrine center was collected from hospital files. Diagnosis of FGD was considered in case of elevated ACTH, inappropriately low cortisol and exclusion of other etiologies. Hydrocortisone was commenced as standard therapy. The results of molecular genetic analysis of the cases were already reported elsewhere [1].

Results: Case characteristics, mutations and follow-up features are summarized in Table 1. During 26 to 115 months follow-up, case 2,4 and 6 had neurodevelopmental delay(NDD), while the other 3 patients had completely normal neurodevelopment.

Conclusion: In this series evaluating a small number of FGD cases due to *MC2R* and *MRAP* mutations, early diagnosis and adherence to the hydrocortisone therapy found related to normal neurodevelopment, while, delay in diagnosis and poor compliance was associated with severe hypoglycemic convulsions and subsequent NDD.

Reference

1 Guran T, et al, JCEM 2015.

P3-P022

Identification of X-Linked Adrenoleukodystrophy in Boys Presenting with Adrenal Insufficiency in the Absence of Adrenal Antibodies

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Adrenoleukodystrophy (ALD) is an X-linked, metabolic disorder caused by genetic deficiency of peroxisomal ALD protein resulting in accumulation of very-long chain fatty acids (VLCFA) primarily in the adrenal cortex and central nervous system. Approximately 35-40% of boys with ALD develop cerebral ALD (CALD), which causes rapidly progressive cerebral demyelination, loss of neurologic function, and death. Disease progress can be halted by allogeneic hematopoietic cell transplantation (HCT), but only if HCT is performed prior to the occurrence of extensive neurologic damage. Radiologic diagnosis of CALD in presymptomatic boys is critical in ensuring early treatment and optimal long-term outcomes. Approximately 85% of boys with ALD present with adrenal insufficiency prior to the onset of neurologic symptoms. Therefore, ALD should be included in the differential diagnosis of boys presenting with adrenal insufficiency without adrenal antibodies.

We present the case of a boy who had recurrent episodes of hypoglycaemia starting at age 2. A diagnostic fast showed nor-

mal endocrine and metabolic responses to fasting. At 5.5 years, he presented with adrenal insufficiency without adrenal antibodies and commenced hydrocortisone replacement therapy. Subsequent VLCFA analysis demonstrated elevated C26 fatty acids consistent with peroxisomal dysfunction and suggestive of ALD, which was confirmed via molecular genetic analysis of the *ABCD1* gene. Apart from a history of temper tantrums, there were no other behavioural or psychological problems. MRI evidence of cerebral involvement emerged at age 7, CALD was suspected, and the child underwent successful unrelated bone marrow transplantation. At last assessment (11.5 years of age), he was performing as expected for age. He is being followed-up for potential endocrine complications of transplantation.

Recognition of adrenal insufficiency without adrenal antibodies in this boy prompted VLCFA analysis which identified the underlying diagnosis of ALD. MRI surveillance detected early, pre-symptomatic cerebral disease and permitted a timely bone marrow transplant which successfully arrested cerebral disease progression. Results from a pilot educational program intended to encourage reflex VLCFA testing in cases of negative adrenal antibody lab results suggest that increased awareness of VLCFA test availability doubles the number of patients receiving adrenal antibody and VLCFA tests concurrently. However, reflex testing was not done for most boys, highlighting the continued need for education that adrenal insufficiency in the absence of adrenal antibodies should be a red flag for a potential ALD diagnosis. In patients diagnosed with ALD, ongoing MRI monitoring should be implemented to detect brain changes suggestive of CALD to ensure early treatment.

P3-P023

Secondary Hyperaldosteronism in the Course of Cystic Fibrosis

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The electrolyte disorders are commonly considered as symptoms of the endocrine diseases concerning the secretion of aldosterone or antidiuretic hormone (ADH).

This study is the case report of the 6-month-old girl admitted to the hospital because of the exacerbation of the chronic cough. Failure to thrive and malnutrition was also significant despite the patient's good appetite reported by parents. She was referred to the department of the paediatric endocrinology due to metabolic alkalosis with hypokalemia, hypochloremia and low concentration of plasma sodium with extremely high level of plasma aldosterone. The initial intravenous fluid therapy was ineffective and only the oral intake of potassium chloride within 7 days compensated the electrolyte abnormalities.

These findings suggested the Bartter Syndrome (BS) – a rare disease caused by the renal salt wasting due to a mutation of the ion channel in the loop of Henle. Nevertheless the associated clinical features presented by the patient (chronic cough and malnutrition) indicated Pseudo Bartter Syndrome (PBS). PBS develops due to salt wasting in varied mechanisms. The dysfunctional cystic fibrosis transmembrane regulator (CFTR) in the sweat ducts of Cystic Fibrosis (CF) patients are responsible for excessive chloride and sodium loses, especially in infants exclusively breast-fed (human milk with a low-salt level) during the warm seasons, as it was in the case of our patient. The high secretion of aldosterone in the response to excessive skin salt loss caused increased renal loss of kalium and alkalosis. Our patient had negative neonatal screening test for CF based on blood concentration of immunoreactive trypsinogen. It has 99,5% sensitivity. However in the patient twice-repeated sweat tests revealed elevated sweat chloride concentration. CF diagnosis was confirmed by the genotyping. It has exposed two rare CTFR mutations on different alleles of chromosome 7 (3849+10kbC->T; p.His199Arg). These mutations are usually connected with residual activity of the CFTR, later onset and longer life expectancy.

Finally the diagnosis of Pseudo Bartter Syndrome in the course of CF was made. The proper CF therapy was started and for now the girl is developing properly without electrolyte disorders and normal level of aldosterone.

Secondary hyperaldosteronism as PBS is very rare in the course of CF but it should be always considered in CF patients with electrolyte imbalance during the warm seasons.

P3-P024

The P30L Mutation in the *CYP21A2* Gene in a Girl with Congenital Adrenal Hyperplasia with Hidden Salt Loosing and Central Precocious Puberty

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In CAH due to 21-OH deficiency, phenotype-genotype correlation is known. However, the same genetic events may cause different clinical forms of the disease.

A case of CAH associated with the P30L in the *CYP21A2* gene in presented.

The Caucasian girl was born normally and growing healthy till the age of 3.y., when her mother noticed pubic hair growth; at the age of 4 she had acne and an increasing sweating. At 6 y. of age, she was brought to paediatric endocrinologist for the first time due to adrenarche progression and accelerated growth. At examination, her height was +2,5 SDS with no weight excess, when MPH was Median. Her BA was 5 y. accelerated and counted 11y., with poor final adult height prognosis, i.e. 140 cm (- 4SDS). Blood biochemistry found moderately elevated 17-OP and normal cortisol. The child was diagnosed with CAH, most probably non-classical, and treatment with 12 mg/m2/day of hydrocortisone divided in 3 doses was prescribed. The karyotype was 46,XX. At 6,5 y., breast development started with continuing growth acceleration and some BA progression. Pelvic US found pubertal uterine size. The test with GnRH-agonist confirmed central precocious puberty in the child. A low serum sodium with elevated potassium levels were found at the next biochemical exam. Simultaneously, treatment with GnRH-agonist 3,75 mg once in 28 days, and fludrocortisone 50-

100 μg daily was prescribed. The patient was under this combined therapy for 3,5 y. Neither salt loosing no further puberty progression was seen. At the age of 10 y., GnRH-agonist was withdrawn. When molecular diagnosis became available, the homozygous mutation P30L in the *CYP21A2* gene was discovered. The patient is currently 11 y.o., under GC and MC replacement, her BA is 12 y., with final height prognosis of 160 cm.

As it is known, the P30L mutation is mostly associated with NC CAH. The clinical course in our patient is more in favor for SV CAH and confirmes again that genotype-phenotype correlation in CAH is not always absolute. Combination of the replacement GC therapy with MC and "experimental" GnRH-analogues may improve auxological outcome of the patient and provide better quality-of-life in the future.

P3-P025

Congenital Adrenal Hyperplasia Due to a Rare Homozygous Mutation R483P in the *CYP21A2* Gene and Coexisting Growth Hormone Deficiency

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In CAH due to 21-OH deficiency, GH treatment combined to GC and MC replacement is still considered to be experimental. We present a patient who has benefited from such treatment.

A baby girl was born in term with clitoromegaly and manifested with salt loose at neonatal period. Low serum morning cortisol and sodium with high potassium and 17-OH levels were found resulted in the clinical diagnosis of CAH. The karyotype was 46,XX. Prednisolone and DOXA, the only available hormone replacement therapy in the country, was initiated with patient condition's improvement. Later, the therapy was switched to hydrocortisone 12 mg/m2/day divided in 3 times, combined to small daily fludrocortisones dose, as 0,025-0,050 mg. However, the girl height was -4SDS and MPH was -1SDS. The bone age was 4 y. delayed, while the girl was euthyroid. Two GH stimulation tests performed demonstrated GH deficiency. Pituitary MRI was normal. After Institution Review Board approval, GH therapy was started at the age of 13,5 y. and completed when she was 18 y.e. after bone plate fusion. In 4,5 y. of GH treatment she has got 32 cm (3 SDS) in height. Her final adult height is 157 cm. Puberty was delayed, clitorovaginoplasty was performed at the teen age, menarche started at 18y. Due to menstrual irregularities, hydrocortisone was switched to dexamethasone 0,375mg daily, with regular cycle and no adverse metabolic effects. Finally, genetic diagnosis of CAH was done due to homozygous point mutation R483P in the *CYP21A2*gene.

The story of our patient presents an example of the association of CAH with GH deficiency which mimics the typical clinical course of main disease. This particular case emphasizes that treatment with prednisolone at early age may worse final patient's height; however, the patient may benefit from combined GC, mineralocorticoid and GH treatment. Finally, according to our knowledge, this is the first case of the R483P homozygous mutation in the *CYP21A2*gene described in patient with salt-wasting CAH.

P3-P026

Rare Case of Androgen Producing Tumor in 14 Month Old Girl

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Background: Adrenocortical tumors (ACT) are rare in children. Mostly occurs in younger age, before 4 years and predominantly in girls. ACT represents 1.3% of all carcinomas in paediatric age group and 0.2% of all pediatric neoplasms.

Case report: 14 month old girl presented with signs of progressive hirsutism started first few months of life. She was referred to our clinic due to suspect diagnosis of virilizing CAH.

Physical exams showed virilization in combination with signs of overproduction of other adrenal hormones: pronounced hirsutism (Ferriman Gallway score 25), clitoromegaly, hoarse voice, widespread acne on face. She has varus deformation of legs and a signs of pronounced rickets.She had accelerated growth. Her weight was over 98th percentile and height corresponded to 75th percentile for age and sex.

Lab tests: 17-OHP – 3.51 ng/ml (0.16-1.02), Testosterone – 7.06 ng/ml (0.03-0.32), BG- 75 mg/dl, insulin 16.51 MicU/ml, Cortisole 232 ng/ml (30-210). DHEAs -2.58 μg/ml (0.05-0.55).

Advanced Bone age, more than 2 years compared to chronological was noted.Abdominal ultrasound revealed enlarged liver and spleen. MRT showed tumor size 5.5/4/4.7 cm in left upper quadrant in retroperitonium.

Complete resection of encapsulated tumor without connection to adrenal was performed. No signs of local invasion or metastasis was found. Tumor was assessed locally, as well as by Institute of Pathology in Kiel, Germany as adrenal cortical tumor, immunohistochemicaly expressing Inhibin, Melanin A and Synaptophysin. Pathologist could not differentiate between adenoma and carcinoma.Postoperatively a brief episode of hypertension and polyuria occurred, therefore 24-hour blood pressure monitoring was conducted twice. The ambulatory BP monitoring recommended further. Testosterone was normalized in a week after surgery.

Follow up visit 1.5 years later showed no signs of metastasis, change in appearance with decrease of virilisation and hirsutism to Ferriman Gallway score 9. Hormonal profile is normal, re-measured on multiple occasions. She follows up to monitor for possible metastasis every three month.

P3-P027

Adrenocortical Tumours in Children – A Case Series

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Background: Paediatric adrenocortical tumours (ACT) are rare and typically present with virilising symptoms and signs which can be similar to other virilising conditions such as congenital adrenal hyperplasia.

Case description: We describe three cases of ACT diagnosed and managed at our institution over the past 10 years. The three girls presented with symptoms of virilisation. The mean interval between first symptoms and diagnosis was 19.6 months (ranging from 12 to 31 months). Age of presentation ranged from birth to 12 years. One patient was misdiagnosed and treated for congenital adrenal hyperplasia for 7 months.Diagnosis of ACT was confirmed by laboratory ,diagnostic imaging and histopathology (Table 1&2). All three patients underwent complete resection of tumour and affected adrenal gland. Hormone levels returned to normal after surgical resection. Two patients had recurrence – one had right lung metastasis while the other had local tumour recurrence. Both patients achieved complete remission since completion of chemotherapy.

Conclusion: This descriptive analysis of our cases concurs with many findings in the literature. Based on our experience, we propose that it may be prudent to perform ultrasound abdomen (with emphasis on the adrenal glands) for all girls who present with virilising features.

P3-P028

Discrete Virilization in Girls with the Classic Form of Congenital Adrenal Hyperplasia: The Importance of a Detailed Genital Examination at Birth

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Introduction: Differentiation of the external genitalia depends on serum androgen concentrations in the foetal life. The classic form of Congenital Adrenal Hyperplasia due to 21-hydroxylase

Table 1. Laboratory findings (for Abstract no P3-P027)

	Patient 1	Patient 2	Patient 3	Normal values
Adrenocortical hormones				
17alpha-OH progesterone (nmol/L)	>36.6	34.2	4.45	0.6–5.5 <3.3 (<1 year old)
Aldosterone (pmol/L)	284.8	120.8	ND	97.3–834.0
8am Cortisol (nmol/L)	228	207	ND	101–536
DHEA-S (micromol/L)	40.4	71.6	2.9	1.1–11.8
Androstenedione (nmol/L)	60.7	67.6	ND	0.1–2.8
Total Testosterone (nmol/L)	9.9	33.2	22.5	0.4–2.0
Estradiol (pmol/L)	79	96	83	77–2382
Short Synacthen test	Failed	Passed	Not done	

Table 2. Surgical and histopathological findings with reference to proposed criteria by Wieneke (for Abstract no P3-P027)

	Patient 1	Patient 2	Patient 3	
Tumour weight (g)	67	371	Well below 500	
Tumour size (cm)	7.5 x 4.5 x 3.5	10.5 x 9.5 x 6.5	3.0 x 2.5 x 2.3	
Periadrenal extension	No	Yes	No	
Invasion into vena cava	No	No	No	
Venous invasion	No	No	No	
Capsular invasion	Focal invasion seen	No	No	
Lymph node biopsy	Negative for malignancy	Not done	Not done	
Presence of tumour necrosis	Yes	Yes	No	
Mitoses	Up to 23 per 50 HPF*, atypical mitoses seen	Up to 8 per 50 HPF, atypical mitoses seen	6 per 50 HPF	
Immunohisto-chemistry	p53 positive cells	Strongly positive	Patchy positivity	positive
Ki67 index (%)	4–50	10–25	5–20	
Tumour staging	II	II	I	

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deficiency (21OHD) is the most frequent cause of female genital ambiguity. It is an autosomal recessive disorder due to CYP21A2 mutations that are classified in groups based on their *in vitro* residual enzymatic activity. The phenotype usually is predicted by the less severe mutation and the virilisation usually correlates to the degree of enzyme deficiency. Clinically 21OHD is classified in Classic, comprising the salt-wasting (SW) and the simple virilising (SV) forms, and nonclassic (NC) form.

Description of the cases: We present data obtained at the 21OHD diagnosis of six female children.

The degree of virilisation of the external genitalia was described using Prader criteria and varied among stage 1 (isolated clitoromegaly), stage 2 (clitoromegaly and partial labioscrotal fusion) and stage 3 (clitoromegaly and total labioscrotal fusion with a perineal opening).

The molecular study showed that all children carried a salt-wasting and a simple virilising mutation in either allele (Allele-SW and Allele-SV), being, therefore, the predicted phenotype SV.

The age at diagnosis in months (Age), the bone age in years (BA), the genital virilisation according to Prader criteria (Prader), the serum levels of 17OHP in ng/mL (17OHP), mutations (Allele-SW and Allele-SV) are presented below:

ACSC 44m; BA 5.2y; Prader 2; 17OHP 79.5; Allele-SW c.-315C>T; c.290-13A/C>G; Allele-SV c.-103A>G; p.Ile172Asn.

EVSC 31m; BA 5.6y; Prader 1; 17OHP 158.8; Allele-SW c.-315C>T; c.290-13A/C>G; Allele-SV c.-103A>G; p.Ile172Asn.

ARSC 7m; Prader 3; 17OHP 82.0; Allele-SW large gene conversion; Allele-SV p.Ile172Asn.

AJRM 19m; BA 3.8y; Prader 3; 17OHP 224.4; Allele-SW p.Arg356Trp; Allele-SV p.Ile172Asn.

ACAS 23m; BA 5.1y; Prader 1; 17OHP 206.8; Allele-SW p.[Leu308Phefs*6;Gln318*; Arg356Trp]; Allele-SV p.Ile172Asn.

LFTR 27m; BA 5.3y; Prader 1; 17OHP > 50.0; Allele-SW p.[Gln318*; Arg356Trp]; Allele-SV p.Ile172Asn.

Comments: We report six cases of CAH due to 21OHD, all with the classic, simple virilising form confirmed by molecular study, whose discrete genital virilisation was not identified at birth by the paediatrician.

According to the relatives, all of them had clitoromegaly and in 3 cases there was also labial fusion at birth.

Through this presentation, we would like to draw attention to the importance of a careful examination of the external genitalia at birth, in order to identify small alterations and obtain early 21OHD diagnosis.

P3-P029

A New Methodology for Early Identification of Steroid Resistant Acute Graft-Versus-Host Disease Patients

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Background: For many patients with high-risk cancers, allogeneic stem cell transplant (SCT) is the only curative option. A major risk of SCT is acute graft versus host disease (aGVHD). About 50% of SCT patients develop aGVHD as a part of their course. Glucocorticoids are the mainstay of therapy in aGVHD patients. Of the patients that develop aGVHD, about 50% develop a steroid refractory/resistant form. These patients tend to require higher doses of steroids and many will require additional medications to manage them appropriately. Identifying these patients early is important in order to optimize treatment and avoid transplant related morbidity and mortality. Although there have been biomarkers to help identify these patients, they have not been optimal. Therefore, there have been no validated prognostic tests to identify these patients. Also, there have not been studies to examine whether host factors play a role in influencing the steroid sensitivity of SCT patients. Therefore, there is a need for a prognostic test to identify these patients and study these factors. We have used a Fluorescein labeled dexamethasone (F-Dex) monocyte binding assay to study glucocorticoid sensitivity in other patients populations. We propose to use this assay to identify and study this aGVHD subset.

Objectives: To study the steroid sensitivity of recipients and their related donors prior to SCT using a Fluorescein labeled dexamethasone (F-Dex) monocyte binding assay to help identify potential aGVHD patients with steroid resistance.

To use the F-Dex assay to analyze SCT patients at the time of the development of aGVHD in order to determine whether host cell factors can influence the glucocorticoid sensitivity of SCT patients and cause steroid resistant aGVHD.

Methods: Collection blood samples from 90 recipient/donor pairs 30 days prior to the SCT and at the time of the development of aGVHD. The samples will be analyzed using a Fluorescein labeled dexamethasone (F-DEX) monocyte binding assay.

Results: Currently preliminary results are being ascertained.

Conclusion: Our hope is that the use of the F-Dex binding assay will help in the early identification of steroid refractory/resistant aGVHD patients, as well as to study whether host cell factors influence steroid sensitivity. This study can allow identified steroid refractory/resistant aGVHD patients to be treated appropriately, avoiding transplant related morbidity and mortality and help to elucidate factors that may cause their steroid resistance.

P3-P030

Delayed Diagnosis of a Patient with Antley-Bixler Syndrome

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Objective: Antley-Bixler syndrome Type 1 (ABS1) is a rare form of craniosynostosis characterized by multiple dysmorphic features, radio-humeral synostosis and urogenital abnormalities due to P450 oxidoreductase (*POR*) gene mutations. ABS is also associated with adrenal and gonadal failure which are sometimes underrecognized due to predominance of skeletal findings in various clinics. We report a female patient with very characteristic skeletal and facial features of ABS due to a homozygous *POR* mutation. Her diagnosis has been established while evaluating the etiology of primary amenorrhea at 16 years of age.

Case: A sixteen years old girl was referred to our clinic for primary amenorrhea. She was born to parents from close villages at 39 weeks gestation with a birth weight of 3400 g. The pregnancy was normal, and no virilization of the mother was detected. She was diagnosed with nephrolcalcinosis in 2008 and recurrent urinary tract infections were noted. At the presentation, facial dysmorphism including retro-micrognathia, high arched palate, and low-set deformed ears and multiple skeletal abnormalities such as bilateral radio-humeral synostosis, hallux longus, arachnondatyly, shortening of the fourth metatarsal bones, pes planus, kyphoscoliosis, bilateral elbow dysplasia, were observed. Laboratory investigations showed high FSH (21.5 mIU/ml), LH (12.6 mIU/ml) and progesterone (38.9 ng/ml) levels, and, normal thyroid function test with normal sodium (137 mmol/L) and potassium (4.6 mmol/L)levels. Ultrasonography revealed normaluterus and ovaries but 6 mm neprocalcinosis in right kidney. High dose synacthen test revealed an exaggerated 17-hydroxyprogesterone, progesterone and a blunted cortisol response. Urinary steroid profiling by gas chromatography-mass spectrometry (GC-MS) and plasma steroid panel revealed a unique steroid metabolome suggestive of POR deficiency. Hydrocortisone and combined estrogen and progesterone treatments were initiated. *POR* gene sequencing revealed a homozygous *c.859G>C (p.A287P)* mutation.

Conclusion: ABS should be kept in mind in the differential diagnosis of skeletal dysplasia. Impaired adrenal and gonadal steroidogenesis are important considerations for the clinicians dealing with ABS for early treatment.

P3-P404

Clinical and Biochemical Phenotype of Aldosterone Synthase Deficiency

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Background: Biallelic mutations of the CYP11B2 aldosterone synthase gene cause deficiency of aldosterone synthesis. Patients exhibit isolated deficiency of aldosterone biosynthesis, increased plasma renin activity, increased steroid precursors desoxycorticosterone, corticosterone, as well as 18-hydroxy-desoxycorticosterone, and show salt wasting and poor growth. The aldosterone synthase enzyme has 18-hydroxylase (corticosterone methyloxidase type I, CMO I) and 18-oxidase (CMO II) activity. Depending on which of these catalytic activities is predominantly affected, this leads to aldosterone synthase deficiency type 1 or type 2. CMO I deficiency is characterized by missing significant aldosterone secretion, low or normal secretion of 18-hydroxy-corticosterone (18-OHB), and patients are always found to have mutations that completely inactivate the encoded CYP11B2 enzyme. The second form (CMO II or type 2 deficiency) has low to normal levels of aldosterone, but increased levels of its immediate precursor 18-OHB.

Objective: We report seven patients from five families diagnosed with aldosterone synthase deficiency, and characterize their biochemical and clinical phenotype.

Results: All seven patients presented with failure to thrive. In three patients this was the main reason for hospital admission. Clinical deterioration with suspected sepsis and electrolyte shift was the reason in three other cases. In one case, diagnostic workup was started due to an affected sibling. Neonatal screening for inborn errors of metabolism in all of them was unremarkable.

In all patients laboratory examinations showed persistent hyponatremia and hyperkalemia, decreased aldosterone, increased plasma renin, increased steroid precursors desoxycorticosterone, corticosterone as well as 18-hydroxy-desoxycorticosterone. Levels of 17-hydroxyprogesterone and adrenocorticotropic hormone found within normal ranges.

Treatment was initiated with 20-25 µg/kg of fludrocortisone daily. Electrolytes and renin levels normalized within a few weeks and all patients showed rapid catch-up growth and weight gain.

Conclusion: A defect in mineralocorticoid synthesis should be part of the differential diagnoses in patients with failure to thrive and persistent abnormal serum electrolyte levels.

P3-P414

Is the Third Time Really a Charm? The Story About Three Brothers Suffering from Adrenoleukodystrophy and About HSCT Being a Chance to Stop the Unstoppable Disease

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Introduction: Adrenoleukodystrophy (ALD) is a genetic diseases classified in the group of peroxisomal disorders caused by mutations in ABCD1, a gene located on the X chromosome. It is the most common monogenetically inherited neurodegenerative diseases. X-ALD is an inborn error of metabolism characterized by impaired peroxisomal beta-oxidation of very long-chain fatty acids (VLCFA) with a heterogeneous clinical spectrum. VLCFA accumulate principally in the CNS and adrenal glands. It results in a beakdown of the myelin sheath and axons, and slowly progressive axonopathy affecting sensory ascending and motor descending spinal cord tracts. Symptoms such as auditory impairment, diminished visual acuity, signs of adrenal failure, memory loss, and speech difficulties occur early. No causal treatment for ALD is known, although hematopoietic stem cell transplantation (HSCT) is allowed for early diagnosis. Lorenzo's oil is used in the treatment of symptomatic patients.

Case report: The study presents a case of 3 boys (siblings) suffering from X-ALD, aged: 6 months, 8 and 11 years old, with confirmed mutation in ABCD1 gene. In boys' mother blood mutation has also been confirmed. The oldest one is currently in poor condition. Due to late diagnosis, he was not qualified for HSCT. His brother, 8yo is 1.5 year after HSCT. He develops properly with only symptoms of adrenal insufficiency. The 6 month-old boy has now started to develop adrenal insufficiency without any symptoms from CNS. HSCT is planned for him in 2-3 years. All boys take hydrocortisone and Lorenzo's oil.

Conclusions: ALD is associated with severe morbidity and mortality, and the symptoms are unspecific. It occurs mostly among young boys and progresses rapidly. In early stages HSCT gives the best chances of slowing down the progression of disease and allows to alleviate the subsequent consequences of the disease. Therefore, parents' awareness and early genetic testing (including prenatal testing) are very significant for the progress of ALD.

Bone, Growth Plate & Mineral Metabolism P1

P1-P025

Intrauterine Growth Restriction, Antenatal Steroids, Gestational Age and Breast Feeding Influence Bone Health in Prepubertal Children Born Preterm

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Objectives: To assess the long-term impact of prematurity on bone and body composition by using Dual-energy X-ray absorptiometry (DXA).

Methods: DXA scans were performed in 100 preterm (PT) (n=42F, n=58M, mean weeks'gestation 31.5±2.6; range 26-36) and 51 born at term (BT) healthy infants (n=28F, n=23M).

DXA measures of total body and lumbar spine mineral density (TB/L1-L4 BMD, g/cm^2 and Z-score), bone mineral content (TB-BMC, g), fat mass (FM%, kg) and free-fat mass (FFM, kg) were obtained. Height (SDS), BMI (SDS) and 25-Hydroxyvitamin D, PTH, CTx, BAP were measured. Twenty-seven subjects (n=21PT, n=6BT) were born IUGR, 55 PT underwent antenatal steroids and 43 (n=20PT, n=23BT) were breastfed.

Results: Median age at study was 6.7±1.3yrs (range5-9). There were no significant differences in anthropometrics, DXA and biochemical markers between PT and BT children. However, positive correlations were found between gestational age or birth weight and BMC, BMD, BMD Z-score both at TB and L1-L4. Steroids and breastfeeding were negatively (-0,16<r's<-0,39; all P's<0.04) and positively (0,18<r's<0,29; all P's<0.02), respectively, associated with all bone parameters. IUGR (17.9%) were shorter with significantly lower DXA BM (all P's<0,05). In multiple regression analyses gestational age was predictive of BM (4.8%) in PT but not in BT children.

Conclusions: DXA and biochemical measurements represent a promising diagnostic tool for bone assessment in preterm children after the age of 5 years. Breastfeeding is associated with better bone health while gestational age, IUGR and antenatal steroids might represent long-lasting risk factors.

P1-P026

Duration of Breastfeeding and Bone Mineral Density in Childhood – A Prospective Study Among Preschool Children

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Background: Bone growth and mineralization during childhood are now recognized as important for bone health in adulthood, leading to renewed interest in identifying modifiable factors that impact bone mineral density (BMD) in childhood. Emerging data suggest that duration of breastfeeding may affect BMD in later childhood and adult life. However, such data are sparse and inconsistent.

Objectives: This study examined the relationship between the duration of breastfeeding and BMD in young Asian children.

Methods: 149 healthy children (73 girls, 76 boys; 81 Chinese, 45 Malay and 23 Indian) from the Growing up in Singapore Towards healthy Outcomes (GUSTO) mother-offspring cohort participated in this study. Children born from IVF pregnancies and twins were excluded. Duration of any breastfeeding (BF) regardless of exclusivity was categorized into 3 groups; never/short duration (never breastfed or breastfed till 3 months), intermediate duration (breastfed >3-6 months) and longer duration (breastfed >6 months). Dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine were performed (Hologic QDR discovery scanner) at age 6 years. Lumbar spine bone mineral apparent density (BMAD), i.e. volumetric BMD, was estimated from bone mineral content and bone area from L2-L4 ($BMC/A_p^{3/2}$). BMAD, areal BMD (aBMD), standard deviation scores for BMAD ($Z_{L\text{-}BMAD}$)

and aBMD (Z_{aBMD}) were used as outcomes. Co-variates related to child's BMD were adjusted for in linear regression analyses: ethnicity, maternal pre-pregnancy BMI, smoking, physical activity, plasma 25(OH) vitamin D status, gestational diabetes, and gestational age, child's sex and weight on the day of DXA scan.

Results: Compared to children who had never/short BF duration (N=67), those who were breastfed longer (N=53) had significantly lower $Z_{L\text{-}BMAD}$ and BMAD, b (95%CI) -0.356 (-0.694,-0.018), P=0.039 and -0.005 (-0.0089,-0.0002) g/cm^3, P=0.039, respectively. The association between duration of BF and $Z_{L\text{-}BMAD}$ was significant only for boys -0.565 (1.079, -0.052) g/cm^3 in a stratified analysis. The observed associations were independent of level of child's adiposity. However, these associations were non-significant when using lumbar spine aBMD and Z_{aBMD}, highlighting the importance of considering bone size when assessing BMD in children. The $Z_{L\text{-}BMAD}$ of children were similar between children who had short and intermediate BF (N=29) duration.

Conclusion: Duration of breastfeeding may have a long term impact on bone mass in young children. As society advocates for longer duration of breastfeeding, it may be important to determine interventions to enhance bone development in infants through a longer duration of breastfeeding.

P1-P027

Bone Health in Adolescents Born Small for Gestational Age (SGA)

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Background: Subjects born small for gestational age (SGA) are at higher risk for metabolic, hormonal and reproductive problems later in life and about 2 to 10% of children born SGA do not catch-up in height. All these changes may influence bone mineral density (BMD).

Aim: To evaluate hormonal profile and BMD in adolescents born SGA in comparison to their peers born appropriate for gestational age (AGA).

Methods: 103 children were examined from prospective cohort followed from birth (47 SGA and 56 AGA). At the time of current examination, the mean age of children was 12.5±0.1 years, median Tanner pubertal stage 3 [2-3]. Serum calcium, phosphate, parathormone (PTH), vitamin D, insulin-like growth factor 1 (IGF-1) and leptin concentrations were evaluated in all adolescents. BMD was determined by dual-energy X-ray absorptiometry (DXA) (Hologic Discovery). Fat mass percent was measured using bioelectric impedance (Jawon Medical BODYPASS X SCAN BIA).

Analyses were adjusted for sex, age, pubertal stage and current BMI. Vitamin D and PTH analyses were additionally adjusted for the month of the year when blood samples were taken. Pearson correlation coefficients and hierarchical multiple regression model were used to analyze associations between BMD Z-score and perinatal and postnatal factors.

Results: There were no differences in calcium, phosphate, PTH, vitamin D, IGF-1, leptin levels and fat mass percent between SGA and AGA groups, even when SGA children with or without catch-up growth (CU+/CU-) were analyzed separately. BMD Z-score was comparable in SGA and AGA groups. However, SGA CU- children had lower BMD Z-score compared to AGA (-0.75±0.36 vs. 0.18±0.11, p=0.018). There was no significant difference in BMD Z-score in SGA CU+ compared to SGA CU- and AGA children (-0.06±0.12, p=0.071 and p=0.146, respectively).

BMD Z-score correlated directly with birth length, birth weight, birth BMI (p=0.001, p=0.001 and p=0.005, respectively), height, weight and BMI standard deviation scores (SDS) up to 6 years (all p<0.05), weight gain from birth to 2 years, waist circumference, waist to height ratio, leptin concentration and fat mass percent in adolescence (p<0.001, p=0.001, p=0.024, p=0.001 and p=0.027, respectively).

In the multiple regression model, birth length, birth weight, BMI at birth, BMI at 2 years of age, waist to height ratio and fat mass percent in adolescence were the most significant factors related to adolescents' BMD Z-score (p=0.012, p=0.004, p<0.001, p=0.008, p=0.004, p<0.001, p<0.001 and p<0.001, respectively).

Conclusion: In adolescence, parameters related to BMD did not differ between SGA CU+ and AGA children. However, SGA CU- children had lower BMD Z-score compared to AGA. BMD Z-score in adolescence was directly related to size at birth, BMI at 2 years of age, waist to height ratio and fat mass percent in adolescence.

P1-P028

Longitudinal Study of Bone Mass in Swedish Children Treated with Modified Ketogenic Diet

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Purpose: Modified ketogenic diet (MKD) is one treatment option for intractable epilepsy and metabolic conditions such as glucose transporter type 1 deficiency syndrome (GLUT1-DS) and pyruvate dehydrogenase complex (PDC) deficiency. MKD is a less restrictive diet than the classical ketogenic diet (KD) and thus more tolerable. Childhood is an important period for bone acquisition. Some studies indicate a negative effect on bone mass during KD treatment, probably as a consequence of the chronic acidic environment. Long-term data is missing regarding the effects of MKD on bone mass in children.

Aim: To prospectively assess the effect of MKD on bone mass in children treated with MKD for 24 months.

Methods: The included 23 patients (median age 4.8 years; 12 girls, 11 boys) were evaluated with whole body dual-energy X-ray

absorptiometry (DXA) and/or calcaneal DXA and laser (DXL) at baseline and after 12 and 24 months on MKD. Underlying etiologies were genetic epilepsy (n=3), GLUT1-DS (n=6), PDC deficiency (n=5), cortical malformation (n=1), mitochondriopathy (n=1), tuberous sclerosis complex (n=2), encephalitis (n=1), Aicardi syndrome (n=1) and of unknown etiology (n=3). Growth parameters were assessed at baseline, 6, 12 and 24 months. DXA and DXL scans were performed at baseline, 12 and 24 months.

Results: In patients with seizures, 76% responded to the diet with >50% seizure reduction. DXA scans are missing in 11 patients due to low age (<5 years) and movement artefacts. Median (min-max) total body bone mineral density head excluded (TB BMD HE) Z-score was -0.6 (-2.5 to 1.4) at baseline and -0.5 (-2.9 to 1.0) after 24 months, *P*=0.25. Lumbar spine (LS) BMD Z-score was median -0.7 (-2.2 to 2.0) and -1.05 (-2.5 to 0.6), *P*=0.41. TB BMD HE Z-score was <-1 in 2 patients at baseline and <-1 in 3 patients after 24 months. LS BMD Z-score was <-1 in 3 patients at baseline and in 4 patients after 24 months. MKD treatment for 24 months did not have an effect on LS and TB bone mineral content (BMC). No differences in fat mass or lean mass were observed during the study period. Calcaneal BMD and BMC increased slightly during the study period, *P*=0.047 and 0.014, respectively.

Conclusions: This study demonstrates that MKD is effective for seizure reduction. Bone mass remained stable during MKD treatment for 24 months. MKD could be considered an effective and safe treatment option in childhood and adolescence.

P1-P029

Fracture Epidemiology for Children in Western Australia Between 2005-2015: Do We Need to Be Concerned About Bone Health?

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Aim: Western Australia is a state with unique geography and population distribution having only a single tertiary paediatric hospital (Princess Margaret Hospital, PMH in Perth) managing the majority of children and adolescents with fractures in the Emergency Department (ED). Fracture incidence in 0-16 year olds is known to be high and varies between countries with boys having a 1.5 fold higher fracture incidence than girls. There are no specific data for Australia. The aims of this study were to characterize presentations with upper and lower limb fractures to PMH-ED and compare trends in the incidence rate to population data.

Methods: This is a database audit of fracture presentations between 2005-2015 for fracture rates with a sub-analysis for gender, fracture site and age relative to Perth Metropolitan and Western Australian population data.

Results: The audit reported a total of 31,340 fracture presentations from 27,516 individual children (87.8%) with 3,036 children reporting two or more fractures (9.7%). Fracture incidence, adjusted for the annual population size, increased from 0.63% in 2005 to 0.85% in 2015 ($p < 0.001$). The winter months had a higher incidence of fractures than the summer months.

Males had a higher fracture incidence than females: 18,763 versus 12,577, ratio 1.5:1 ($p < 0.001$), with upper limb fractures three times more common than lower limb fractures ($p < 0.001$). Fracture incidence increased with age until the early teenage years when a decline occurred.

Conclusions: Increased fracture incidence in Western Australia between 2005 and 2015 identifies a concerning trend for bone health in children and adolescents. Further research is needed to identify potential lifestyle factors that impact fracture incidence in order to reverse increasing fracture incidencein childhood.

P1-P030

Bone Biochemistry in Children with Fractures Presenting with Suspected Non-Accidental Injury

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Introduction: Fractures have been recorded in up to one third of children who have suffered from physical abuse. The British Paediatric and Adolescent Bone Group (BPABG) position statement on vitamin D states that the level of 25 hydroxyvitamin D is not relevant to causation of fractures unless there is radiological or biochemical evidence of rickets. Clinicians are often asked in the court setting about the relevance of abnormal serum investigations in children who have fractures where there is a concern about non-accidental injury (NAI).

Aim: The primary aim of this study was to measure adherence to RCPCH recommendations: Children under two years, who have unexplained fractures raising suspicion of NAI, have the following investigations:- Vitamin D (VitD), Parathyroid hormone (PTH), Calcium (Ca), Phosphate (Ph) and Alkaline Phosphatase (Alkphos). In addition to analyse the pattern of these biochemical investigations in this population.

Method: A retrospective review of case notes, electronic results and radiology records over five years (2012-2016) at The Royal Hospital for Children, Glasgow. Children were included who were under two years and had undergone a skeletal survey as part of a child protection investigation and were found to have one or more fractures. Bone biochemical markers (Ca,Ph, Alk Phos, PTH and Vit D) were compared to age specific local reference ranges and classified as normal or abnormal.

Results: In 64 (59.8%) children the decision was made to request bone investigations, complete bone biochemistry was sent and reported in 57 (89%) of these. One child was found to be Vit D deficient, a further 19(33%) were found to be insufficient. 29/57 (50.8%) had one or more biochemical marker (Vit D, PTH, Ph, Ca, Alk Phos) outside reference range. In cases where NAI was confirmed either at case conference or by criminal conviction 12/27 (44.4%) had one or more biochemical marker outside reference range.

Conclusion: We have demonstrated that in children under going investigation of a fracture in suspected NAI vitamin D is often in the deficient or insufficient range in the absence of radiological or biochemical evidence of rickets. This review has also demonstrated that other bone biochemical markers are frequently outside the normal reference ranges in this population.

P1-P031

Systematic Screening Using DXA Lateral Vertebral Morphometry is Associated With a High Prevalence of Vertebral Fractures in Duchenne Muscular Dystrophy: Results from ScOT-DMD Study

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Background: The prevalence of vertebral fractures(VF) in Duchenne Muscular Dystrophy(DMD) is currently unknown as systematic spine imaging is rarely performed.

Objective: To determine the prevalence of VF in DMD and factors associated with VF.

Method: A prospective study utilising systematic screening with DXA vertebral fracture assessment(VFA) was performed in all 47 eligible boys. 6/47 were excluded due to spinal instrumentations and movement artefacts. Presence and grade of VF were determined by the Genant method by two independent observers and any disagreement resolved by consensus agreement with a third observer. Results expressed as median(range).

Results: Of 41 boys aged 9.9 years(5.0,18.3), 37(90%) had been on glucocorticoid(GC) for 3.8yrs(0.2,13.4) and three were GC naïve. Eighteen (43.9%)boys were non-ambulant for 2.1 yrs(0.3,6.5). Four boys were on testosterone, and nine on bisphosphonate. Height and BMI SDS were -1.5(-7.0,+2.3) and +2.0(-1.4,+4,0), respectively. Total body less head bone mineral content (BMC) SDS was -1.4(-4.3,+1.2) and lumbar spine (LS) bone mineral apparent density(BMAD) SDS was -0.8(-3.0,+0.9). Bone turnover was low with bone alkaline phosphatase and c-terminal telopeptide SDS of -1.5(-2.8, -0.3) and -2.0(-3.3,+0.1), respectively. 10/41 boys(24.3%) had non-VF only. A total of 8/41(19.5%) had evidence of VF from DXA-VFA, including one boy with VF and non-VF. Of 8 with VF, four(50%) had newly diagnosed VF identified from DXA-VFA. Of 43 VFs identified in the eight boys, 11(26%), 21(48%) and 11(26%) were grade 1, 2 and 3, respectively. The distribution of VFs was bimodal with most occurring at T7 and T12. Back pain was only reported in 2/8(25%) with VFs. There were no differences in mobility[p=0.70], 25-hydroxy-vitamin D[p=0.87] and LS-BMAD SDS[p=0.73] in those with or without VF. Odds of VF increased by 1.5 times[95%CI:1.03 to2.20, p=0.04] for every 1-year-increase in GC exposure after adjusting for GCdose, mobility, back pain and LS-BMAD SDS.

Conclusion: In this cohort of DMD boys with relatively short duration of GC exposure, VF was present in approximately 20%. Of those, half were identified only from screening DXA-VFA. DXA bone density was not discriminatory for VF. Our result provides the evidence-base for the recommendation of routine spine imaging for vertebral fractures in DMD in the new international DMD standards of care(2018).

P1-P032

Bone Mineral Density and Glycemic Control in Children and Adolescents with Type 1 Diabetes Mellitus

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Background/Aim: Osteoporosis is a known complication in adults with type 1 diabetes mellitus (T1DM), but whether the bones are affected in children and adolescents with T1DM remains controversial. The study aim was to evaluate bone mineral density (BMD) in children and adolescents with T1DM and identify risk factors associated to lower BMD.

Method: In a single-center cohort of children and adolescents with T1DM, BMD was examined by dual-energy X-ray absorptiometry. Puberty Tanner stage, HbA1c, disease duration and age at diabetes onset were investigated for associations to BMD and its Z-scores using multiple regression.

Results: We included 85 patients, 46 males, with a median (range) age of 13.2 (6-17) years; disease duration 4.2 (0.4-15.9) years; last year HbA1c 61.8 (41-106) mmol/mol. Boys had a significantly increased mean Z-score, 0.38 (95%CI 0.13;0.62), adjusted for height and body mass index. The Z-score of boys increased with increasing Tanner stage. For the whole cohort, a negative

correlation between mean latest year HbA1c and BMD Z-score was found, adjusted ß -0.019 (95%CI -0.034;-0.004, p=001). Poor glycaemic control (HbA1c >58mmol/mol) within the latest year was likewise negatively correlated with BMD Z-score, adjusted ß -0.35 (95%CI -0.69;-0.014, p=0.04). Similar negative correlations were found between HbA1c and BMD.

Conclusion: BMD Z-score showed sex differences in children and adolescents with T1DM. Poor glycaemic control within the last year was correlated to decreased BMD and BMD Z-score regardless of sex. Our study suggests that elevated blood glucose levels affects bone health already before adulthood in T1DM patients.

P1-P033

Comparison of Manual and Automated Bone Age Assessment in 1285 Children and Adolescents Aged 5 to 16 Years

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Background: Skeletal maturation is the most reliable indicator of biological age in children and adolescents. The evaluation of hand and wrist X-Ray according to Tanner-Whitehouse (TW3) or Greulich-Pyle (GP) are the most commonly used methods for biological age assessment. Automated bone age assessment has recently become increasingly popular, however a large independent study comparing automated and manual evaluation of bone age is still missing. The aim of this study was to assess the differences between automated and manual evaluation of bone age using TW3 and GP method.

Methods: In this cross-sectional study we evaluated bone age scans using TW3 and GP methods in 1285 children and adolescents (659 boys, range 5.0 - 15.9 years, median 10.3, IQR 4.9 years) with various endocrine conditions in parallel manually and using BoneXpert software (Visiana, Holte, Denmark). Root mean square errors (RMSE) were calculated for the whole group and for sex-specific one-year age categories (girls between 5 and 15 years, boys between 5 and 16 years, over 50 children in each category).

Results: In total RMSE were 0.61 years and 0.58 years in boys and 0.79 years and 0.60 years in girls, respectively for TW3 and GP. Sex- and age-specific analysis showed the greatest differences between manual and automated TW3 evaluation in girls between 6-7, 12-13 and 13-14 years with RMSE 0.90, 0.90 and 1.05 years, respectively. Manual and automated evaluation differed by more than 1 year in 9.7% and 7.0% boys and 18.2% and 8.6% girls, respectively for TW3 and GP.

Conclusion: Automated bone age assessment provides sufficient agreement with manual evaluation in most scans of children with common endocrine disorders. Bone age assessment provided by BoneXpert tends to be underestimated, especially in girls during puberty using TW3 method. Further analysis is required to indentify the source of these differences.

P1-P034

Is Plasma C-Type Natriuretic Peptide Level Available for Typing and Diagnosis of Skeletal Dysplasia Cases?

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Introduction: Skeletal dysplasia is a heterogeneous group of disease, leading to abnormal enchondral ossification and typing of the disease is quite complex. C-type natriuretic peptide (CNP), one of the members of the natriuretic peptide family, has been implicated to play a role in bone development. CNP levels were high in some types of the skeletal dysplasia.

Objective: The aim of this study is to evaluate the possibility of using CNP, as a marker for skeletal dysplasia types and to investigate its role in typing.

Methods: Thirty-seven patients [ages 6 months to 18 years (26 girls, 11 boys)], who accepted to participate in the study from 75 skeletal dysplasia patients were included. All subjects were physically examined and anthropometric measurements were obtained, bone surveys were evaluated. 49 healthy children [ages 6 months to 18 years (24 girls, 25 boys)], were included as a control group. ELISA method was used to assess CNP (pg/ml) plasma levels. The patient group consisted of 17 patients (45.9%) with achondroplasia, 6 patients (16.2%) with spondyloepiphysial dysplasia, 5 patients (13.5%) with metaphysical dysplasia, 2 patients (5.4%) with epiphysial dysplasia, 2 patients (5.4%) with hypochondroplasia, one patient with acromesomelic dysplasia (2.7%) and 4 patients (10.8%) with unclassified skeletal dysplasia. Genetic mutation analyses were performed on 16 of the patients previously and 16 heterozygous mutations were found [9 (53.6%) of these were p.G379R, 3 (17.6%) were p.G308R, 1 (2.7%) was p.N540K and 1 (2.7%) was p.N542K].

Results: The height SD scores (SDS) of the patient group were -4.58 ± 2.87 (n=37) and the height SD scores (SDS) of the control group were 0.05 ± 0.79 (n=49) (p<0.001). No significant difference was found between median CNP concentration of the patient group and the control group (p=0,207). On the other hand, median CNP of the achondroplasia patients (n=17) were higher than the control group (n=49)(p=0.032). CNP concentration of the patient group was 1,31 ± 1,40 ng/ml (n=37) and CNP concentration of the control group was 1,04± 1,40 ng/ml (n=49) (p=0.207), whereas CNP concentration of achondroplasia patients [1,79 ± 1,64 ng/ml (n=17)] was higher than the control group] (p 0,032). CNP values were similar in both males and females. (male=51; female=35)

Conclusion: Achondroplasia patients have elevated plasma levels of CNP. In order to use CNP as a marker for the diagnosis and typing of skeletal dysplasia, more clinical studies with molecular genetic analyzes are needed.

P1-P035

Long-Term Outcomes of Osteogenesis Imperfecta in the Bisphosphonate Era

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Background: Bisphosphonates have been used for treatment of bone fragility disorders for over 25 years to increase bone mineral density (BMD). Anecdotally, bisphosphonate-treated Osteogenesis Imperfecta (OI) has a different trajectory to the natural history of untreated OI, with minimal published evidence to support this clinical observation.

Aims: To describe functional outcomes of a cohort of adults with OI, stratified according to severity and treated with bisphosphonates as children, including fracture incidence before and after puberty, mobility and BMD outcomes of this cohort, compared to adults with OI who were never treated as children.

Methods: All participants completed four questionnaires: a study specific questionnaire addressing fracture and treatment history, WHOQOL-BREF (quality of life), SF-36 (musculoskeletal function) and IPAQ (physical activity), and medical records were reviewed.

Results: Fifty-two adults with OI (80% response rate) completed the questionnaires; 33 of whom were treated with bisphosphonates in childhood. The childhood treated cohort had higher lumbar spine BMD than the adult treated cohort (z-score -0.5 at mean age 21.3 years versus -2.1 at mean age 40.9 years; p=0.005). There were less post-pubertal fractures in severe forms of OI in the childhood treated cohort compared to the adult treated cohort. In less severe OI, childhood treated individuals had higher levels of physical activity and physical functioning than adult treated individuals. Incidence of scoliosis was not different between cohorts. There were no differences in quality of life scores between the two cohorts.

Conclusions: Improvements in BMD correlate with reduction of post-pubertal fracture rates in severe OI but do not appear to influence the prevalence of scoliosis. Results suggest that treatment with bisphosphonates at an earlier age improves physical activity, particularly in less severe forms of OI but may not alter quality of life.

P1-P036

Novel *LRP5* Loss-Of-Function Mutation Causes Osteoporosis-Pseudoglioma Syndrome

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Background: Osteoporosis is a complex disorder, influenced by both environmental and genetic factors. Primary osteoporosis is a rare early onset disorder with high morbidity and mortality. Wnt signaling pathway has been shown to be involved in the regulation of bone remodeling.

Case: Native Argentinean boy born from a consanguineous family with history of retinal detachment in the maternal line. Delivered at term, birth weight 2900 g (-0.95 SDS), birth length 50.5 cm (0.06 SDS), microcephaly (head circumference -1.93 SDS). Bilateral congenital retinal folds caused him progressive irreversible vision loss and acquired microophthalmy.

Since the age of 5 y he developed four low trauma long bone fractures and two vertebral fractures. Referred at 8.6 y, weight 27.4 kg (P50), height 129 cm (P50), normal growth velocity, Tanner stage I, microcephaly and bulky vision. White sclera, normal teeth, absence of hyperlaxity, slight kyphosis and adequate neurodevelopment were observed.

Dual-energy X-ray absorptiometry (DXA) demonstrated low bone mineral density (BMD): Lunar L2-L4: 0.370 g/m^2 (Z score -3.9 SDS) and measurement of bone metabolism markers were within normal range (calcium 10.3 mg/dL; phosphate 4.9 mg/dL; magnesium 1.9 mg/dL; ALP 195 IU/L; bone ALP 61.5 ng/L; PTH 54 pg/ml; 25OH vitamin D 24 ng/ml; CTX 1231 pg/ml; urine Calcium/Creatinine ratio 0.2; PTR 91%). Known secondary causes of osteoporosis were ruled out. There is no history of familial fractures and his parents have normal BMD. After two years of Zoledronic acid: 0.0125 mg/kg/dose every six months and specific exercises, his BMD has improved to 0.522 g/m^2 (Zscore -2.2 SDS), affected vertebras slightly reshaped without fractures recurrence.

SNP array (850k, Illumina) showed loss of heterozygosity in chromosomal region 11p15.1-11q13.3, containing the low-density lipoprotein receptor-related protein-5 gene (*LRP5)*, a gene expressed in fetal ocular macrophages and in osteoblasts, thus, our first candidate gene. A novel homozygous nonsense variant (NM_002335.3:c.441G>A, p.Trp147Ter) was identified using a skeletal dysplasia NGS panel, SkeletalSeq.V7. Both parents are heterozygous for this variant.

Conclusions: LRP5 is a single-span transmembrane protein required for Wnt/βcatenin signaling pathway, relevant for fetal and

postnatal osteogenesis. We identified a novel homozygous *LRP5* loss-of-function mutation, which causes autosomal recessive Osteoporosis-pseudoglioma syndrome (OPPG, MIM 259770). Scarce information exists regarding OPPG treatment in children. Thus, understanding the molecular mechanisms underlying primary osteoporosis is important for improving screening for co-morbidities, genetic counselling and development of novel therapies.

P1-P037

Hypercalcaemia After Treatment with Denosumab in Children: Bisphosphonates as an Option for Therapy And/or Prevention?

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Background: Pharmacologic options for treatment of osteolytic diseases especially in children are limited. Although not licensed for use, denosumab, a fully humanized antibody to RANKL, is used in children and shows good effects. Among others, one indication are giant cell tumors of the bone. Yet, there are reports of severe hypercalcemia after stop of denosumab, an adverse effect which is rarely seen in adults.

Case reports: Four patients, aged 6, 13 and 17 years and otherwise healthy, developed severe hypercalcemia some weeks after the end of successful treatment with high-dose denosumab for unresectable giant cell tumor of the bone. In one patient, calcium levels normalized and remained low under long-term high dose steroid therapy, but with the consequence of typical Cushing's syndrome. In another patient, denosumab was restarted, but he had relapses every time the medication was stopped. Finally in the two other patients, hypercalcemia ceded definitely after two respectively three doses of bisphosphonates.

Discussion: Hypercalcemia after denosumab in children has been described in several case reports. It is supposed to be caused by a reactive hyperactivity of osteoclasts, formerly blocked by denosumab. As a consequence of extra bone accumulation apart from the osteolytic spaces, which is above the individual set point. The generally higher turn-over of bone in growing children might be a reason for the more aggravated problems in them compared to adults. Bisphosphonates seem to be an effective and well-tolerated strategy for its treatment and might also be used for prevention.

Conclusion: There is a considerable risk of hypercalcemia as a frequent adverse effect after denosumab treatment in children, especially when using high doses. Therapeutic or, even better, preventive strategies are urgently needed. In our opinion, bisphosphonates could be an option for both.

P1-P038

Disease Burden and Systemic Manifestations of HPP in Children Enrolled in the Global HPP Registry

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Hypophosphatasia (HPP) is a rare, inherited, systemic disease caused by mutation(s) of the *ALPL* gene encoding tissue-nonspecific alkaline phosphatase (ALP), resulting in deficient ALP activity. Asfotase alfa is an enzyme replacement therapy approved for treatment of patients with pediatric-onset HPP. The global HPP Registry is an observational, prospective, multinational study (NCT02306720; EUPAS13514) established to collect real world clinical data from patients of all ages with HPP, regardless of asfotase alfa treatment status. We report characteristics of children aged <18 y enrolled in the HPP Registry by asfotase alfa treatment status at enrollment. Children included in this analysis had signs and symptoms consistent with a diagnosis of HPP confirmed by low serum ALP activity and/or *ALPL* mutation; deceased patients were not included per protocol. Of 269 patients enrolled from 11 countries from January 2015 through September 2017, 121 (45.0%) were children, of whom 45 (37.2%) were being treated with asfotase alfa at enrollment and 76 (62.8%) were untreated. Of the treated patients, 16 were former participants in asfotase alfa clinical studies. Treated children were mostly female (66.7%) and Asian (67.4%); untreated children were mostly female (57.9%) and white (73.5%). Median (min, max) age at earliest HPP manifestation was 0 (−0.2 y, 4.3 y) for treated children and 2.2 years (0, 15.9 y) for untreated children. Median (min, max) age at time of diagnosis was 0 (−0.02 y, 13.2 y) for treated children (diagnostic delay: 1.1 d [0, 11.5 y]) and 3.3 years (0, 16.0 y) for untreated children (diagnostic delay: 0.7 y [0, 10.7 y]). Medical histories showed that patients frequently reported skeletal signs and symptoms (treated: 75.6%; untreated: 25.3% [e.g., bone deformity, rickets, fractures]), failure to thrive (treated: 46.7%; untreated: 14.7%), respiratory support (treated: 46.5%; untreated: 2.7%), neurologic manifestations (treated: 42.2%; untreated: 17.3% [e.g., developmental delay, craniosynostosis, seizures]), renal signs and symptoms (treated: 31.8%; untreated: 18.7% [e.g., hypercalcemia, nephrocalcinosis, hyperphosphatemia]), premature loss of deciduous teeth (treated: 25.0%; untreated: 59.5%), and muscular manifestations (treated:

15.9%; untreated: 21.3% [e.g., abnormal gait, weakness]). These data show that treated children with HPP presented at an earlier age and had minimal diagnostic delay compared with untreated children. Medical histories suggest that systemic manifestations of HPP are common among children with HPP. The Registry does not capture data from neonates and young infants, either treated or untreated, who died before enrollment, thus potentially underestimating or not reflecting the spectrum of disease burden in HPP.

P1-P039

3-Epi-25 Serum 25-Hydroxyvitamin D3 Concentrations in Chilean Children Between 5 and 8 Years

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Background: The C3 epimer of 25-hydroxi-vitamin D3 (Epi25OHD3) is present in the pediatric and adult population and varies according to age. If it measurement is clinically relevant and should be considered to classify Vitamin D status is still unknown.

Objective: To measure 25OHD3, 25-hydroxy-Vitamin D2 (25OHD2) and Epi25OHD3 and to compare them with PTH and calcemia.

Method: Subjects: Children between 5 and 8 years of age born very preterm (VPT: <32 weeks of gestation) and term (≥38 weeks of gestation).

Exclusion criteria: SGA (weight ≤ -2 SD), multiple pregnancy, chronic and acute disease and use of oral corticosteroids.

Measurements: 25OHD2, 25OHD3 and Epi25OHD3 by mass spectrometry (LC-MS/MS)

25OHD3 status (ng/mL): deficient <20, insufficient 20-30, sufficient ≥ 30

Total 25OHD3: 25OHD3 + Epi25OHD3

Statistical test: U-Mann Whitney.

Results: Seventy seven (83%) of a total of 93 subjects (45% female) had detectable Epi25OHD3 concentrations and only 2 subjects 25OHD2.

An association was found between Epi25OHD3 and 25OHD3 ($r = 0.57$, $p < 0.0001$), calcemia ($r = 0.84$, $p = 0.005$) and PTH ($r = 0.18$, $p < 0.0001$).

Gestational age was correlated to Epi25OHD3 ($r = 0.265$, $p = 0.011$) and 25OHD3 ($r = 0.229$, $p = 0.036$).

There were differences in the percentage of total Epi25OHD3 / 25OHD3 between very premature and term subjects ($p = 0.04$). When adding the concentrations of Epi25OHD3 to those of 25OHD3 (25OHD3 total) the percentage of Epi25OHD3 / total 25OHD3 in VPT and term children was different (9,7% and 10,6% respectively). Vitamin D status changed.

When categorizing Vitamin D status using total 25OHD3, the percentage of children with deficiency dropped from 19.4% to 12.9%, with insufficient from 54.8% to 47%, those with a sufficient status raised from 25.8% to 39.8%.

Conclusion: At school age, term as well as very preterm children have detectable levels of Epi25OHD3.

It is necessary to establish the physiological role of Epi25OHD3, since when considered to establish Vitamin D status, it changed in an important proportion of children. Including its measurement in routinely used immunoassays and their harmonization in this regard, could be relevant in the classification of Vitamin D status.

Bone, Growth Plate & Mineral Metabolism P2

P2-P036

Length Estimation Based on Clinical and Anthropometric Measures in Newborns

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Background and Aims: The hospitalized neonates requires specialized and multidisciplinary approach and the nutritional follow-up is an essential part of the care. The anthropometry is required to evaluate the nutritional status of patients over time. The main measurements to determine the nutritional status in infants are weight and length. These measures are used to evaluate indexes as length for age, weight for length and body mass index. According to the above, the measurement of length is essential; however, in some patients due to their clinical conditions it is difficult to obtain this measure. In these cases it is necessary to estimate the length through indirect parameters using body segments measures. However, these methods have not proven to be useful in newborns. For all the above, the aim of this study is to identify clinical and anthropometric variables that explain the variability of length in newborns.

Methods: We conducted a cross-sectional study. We obtained sociodemographic and perinatal information of 30 preterm and term newborns at Mexico City public and private hospitals. We also measure weight, length, head circumference and limb measurements (arm span, ulna, tibia and lower leg) with standardized techniques. These data was included in regression models in order to estimate the crown-heel length obtained with an infantometer (gold standard).

Results: A total of 30 neonates were measured (23 term and 7 pre-term), age less than 28 days and equal gender distribution (15 males). According stepwise regression, the best model to predict the crown-heel length includes lower leg length, head circumference and sex (R^2=0.85). This equation was better than previously reported equations with a mean difference of 0.004 (95CI -0.31;0.31) vs -8.612 (95CI -9.28;-7.94) and -9.69 (95CI -10.20;-9.18) for Stevenson's, and -10.95 (95CI -12.11;-9.79) and -13.13 (95CI -14.36;-11.90) for Gauld's. We observed a little difference

between the estimated crown-heel length with this model and the crown-heel length measure (47.6246 cm ±2.09 vs 47.6250 cm ±2.25, p=0.998). The limits of agreement in the Bland-Altman plot were -1.69 to 1.69.

Conclusions: An equation using sex, lower leg length and head circumference is accurate to predict crown-heel length in newborns. This method could be a good tool to estimate the crown-heel length in hospitalized neonates in whom this measurement is not available.

P2-P037

Vitamin D Deficient (Nutritional) Rickets Presenting in Infancy

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Background: Nutritional rickets is a disorder of defective chondrocyte differentiation and mineralization of the growth plate and osteoid due to vitamin D deficiency with or without low calcium intake in growing children. Maternal Vitamin D deficiency and exclusive breastfeeding without supplementation are the most frequent causes of rickets in the infancy. Vitamin D deficiency is still a problem in Sri Lanka in spite of sun shine throughout the year.

We present a case series of seven infants presenting with nutritional rickets.

Presentation ranged from 1 to 4 months of age. One presented with febrile seizures with a negative septic screen. Six presented with afebrile seizures in which two had been treated for status epilepticus. None of them had clinical features of rickets. Cardiac assessment was normal. Biochemistry revealed normal blood sugar, Na, Mg, renal functions and liver functions. All had hypocalcaemia with a range of corrected calcium between 0.85 mmol/L to 1.68mmol/L. The vitamin D level ranged from 8.5 nmol/L to 38 nmol/L. All had high alkaline phosphatase, high parathyroid hormone levels indicating secondary hyperparathyroidism with radiological features of early rickets.

They were term babies born to nonconsanguineous healthy parents. No perinatal complications. All were exclusively breast fed and weight gain was satisfactory. Mothers were multiparous with previously healthy children. Three were from Muslim community and others were Sinhalese. Mothers were clinically asymptomatic and had taken only Ca without vitamin D supplementations during pregnancy. They had normal bone profiles with low or insufficient vitamin D level.

All of them were started with oral Ergocalciferol with Ca supplementation for three months and followed up. Mothers were given vitamin D and Ca supplementation.

Conclusion: Rickets in infancy can present only with seizures without any other clinical features. Vitamin D deficient rickets should be one of the differential diagnosis in the evaluation of an infant with seizures as this can be diagnosed and treated easily. All the pregnant mothers and the infants should be supplemented with vitamin D as recommended by the global consensus to prevent this deadly life threatening complication.

P2-P038

The Effect of Vitamin D Receptor Polymorphism on Bone Mineral Density in Egyptian Patients With Beta Thalassemia Major

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Background: Beta thalassemia major (BTM) is considered a major health problem. Despite optimal conventional treatment, bone disease comprising of low bone mineral density (BMD), bone pain, and fractures is still a characteristic feature of thalassemia. The etiology of bone disease in thalassemia is multifactorial. vitamin D receptor (VDR) mediates the action of 1,25(OH)2D, The VDR genetic variations may be responsible for modifying the activity of VDR protein.

Objective: To study the effect of Vitamin D status and Vitamin D receptor genetic variation in bone mineral density in Egyptian patients with BTM

Subjects and Methods: The Study included eighty children with BTM and eighty age & sex- matched controls group. Patients with any renal or hepatic impairment, hyperparathyroidism or using medications affecting bone mineral metabolism (as glucocorticoids or anticonvulsant drugs) were excluded.serum calcium, phosphorus and ALP and 25 vitamin D were measured, VDR genotyping regarding BsmI, TaqI, FokI single nucleotide polymorphisms was carried out. Every patient underwent dual-energy X-ray absorption (DEXA) scan of the lumbar spine.

Results: There was a significantly lower 25 vitamin D with bb, Ff and ff vitamine D receptor genotype. The Z score of BMD of the lumbar spine was significantly lower with Bb, bb, Ff and ff vitamine D receptor genotype. No significant association was observed in 25 vitamin D and the Z score of BMD with TaqI polymorphism.

Conclusion: The VDR genotyping can be used as an additional test in children who are vulnerable to osteoporosis so that early preventive can be taken

P2-P039

Vitamin D in Adolescents: A Comprehensive Review of Guidelines and Recommendations

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Introduction: Vitamin D plays a key role in bone health of adolescents. Meanwhile, its potential extra-skeletal health benefits have resulted in the association of vitamin D deficiency with a wide range of acute and chronic diseases. As a consequence, hypovitaminosis D in adolescence is considered to have serious adverse effects and is highlighted as a global public health concern. Practical guidelines help clinicians make their preventive and therapeutic choices and improve care management.

Objective: Our purpose was to collect and synthesize available recommendations concerning vitamin D in adolescents, mainly vitamin D thresholds and vitamin D status, dietary requirements, prophylactic supplementation and treatment of deficiency.

Methods: We conducted a systematic review of the literature. We searched guidance published by different professional associations and governments from different regions of the world.

Results: We identified thirty-one documents. Most of them targeted the general population and not specifically the age group of adolescents. There is general agreement that adolescents should not have serum 25hydroxyvitamin D concentrations below 25-30 nmol/L in order to avoid poor bone health. However, there is lack of consensus on the optimal concentration to aim for, levels varying between 25 nmol/L and 125 nmol/L. Adequate nutritional requirements of vitamin D are also controversial with values varying between 200 IU/d and 1,000 IU/d. The upper tolerable intake is estimated at 4,000 IU/d by all study groups. Certain associations recommend routine vitamin D supplementation in adolescents. The recommended daily doses vary between 400 IU and 2,000 IU, depending on skin pigmentation, sun exposure, consumption of vitamin D-fortified foods, body mass index and coexistence of certain medical conditions. In case of deficiency, an oral daily regimen of vitamin D, ergocalciferol/D2 or cholecalciferol/D3, is recommended for at least 4 weeks. A maintenance dose after the end of treatment is essential and is usually equivalent to the daily dietary intake recommended by the relevant study group.

Conclusion: At present, there is no consensus among the different societies and countries about vitamin D during adolescence. In clinical settings, this lack of consent makes decisions difficult or problematic under certain clinical conditions. Strong guidance is needed to establish homogenous, evidence-based recommendations.

P2-P040

X-Linked Hypophosphatemia Registry – An International Prospective Patient Registry

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Introduction: X-linked hypophosphatemia (XLH) is a rare, inherited disease that affects approximately 1 in 20,000 individuals. XLH is a disorder of renal phosphate wasting caused by high circulating levels of fibroblast growth factor 23 (FGF23) that impairs normal phosphate reabsorption in the kidney and production of the active form of vitamin D. Children with XLH experience abnormal bone development, rickets, osteomalacia, impaired growth, dental abscesses, craniosynostosis and bone and muscular pain. Affected adults may present with articular consequences of bone deformities, fractures, stiffness, enthesopathy, hearing loss, hyperparathyroidism, and periodontitis.

As XLH is a progressive, often debilitating disease, it is important to improve understanding of both its natural history and outcomes on available therapies. Currently, there is no international registry that collects large-scale data on disease progression in XLH.

Objectives: An international, multicentre, prospective, non-interventional disease registry has recently been launched to collect natural history data and characterise the treatment, disease progression and long-term outcomes in children and adults with XLH (ClinicalTrials.gov Identifier: NCT03193476).

Methods: Design and implementation of the registry was informed by recommendations from a recent European Medicines Agency workshop (EMA/69716/2017) and approved by a steering committee of European experts. The XLH Registry is planned to run for at least 5 years aiming to recruit 1200 patients in total. Data entry is via an online data capture tool (Castor EDC, Netherlands).

Patients with confirmed XLH will be included under informed consent. As a non-interventional study, all data entered will be from routine practice at the participating sites, measured at baseline and prospectively at regular intervals. No data or investigations are mandated by the protocol.

The registry will collect demographic variables, age and symptoms at diagnosis, family history as well as quantitative and qualitative disease markers including: rickets, bone shape, growth, oral health, muscular function, quality of life, phosphate wasting, alkaline phosphatase and complications including nephrocalcinosis, hyperparathyroidism, hearing and neurological features.

Results: At time of submission the XLH Registry has recruited 21 patients from 11 sites across the UK, Denmark and Italy. National regulatory approval in 8 other countries is pending, with 56 sites expected to be live by December 2018.

Conclusions: The XLH Registry will generate epidemiological data that may provide improved understanding of the natural history, the disease-burden, as well as the long-term treatment outcomes of XLH. Ultimately, the XLH registry will support development of future XLH treatment guidelines and inform best practice.

P2-P041

Clinical and Biological Parameters Associated to the Severity of X-Linked Hypophosphatemia in Children

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Introduction: X-linked hypophosphatemia or XLH is a rare genetic disease, often revealed in children by rickets, growth failure, delayed walking, and leg bowing. Clinically the severity is reflected

by leg deformities. The aim of our study was to assess the clinical and biochemical parameters correlated to the severity of XLH at the end of growth.

Materiel and methods: Monocentric retrospective study of patients treated with phosphate supplements and vitamin D analogs followed from diagnosis of XLH to their final height with data available all along follow-up. Patients treated with recombinant human growth hormone or who had orthopedic surgery before the end of growth were excluded. Data concerning final height, family history of XLH, age at diagnosis, adherence to treatment (range from 0 to 5), history of tooth abscesses, alkaline phosphatase (ALK) level at diagnosis, ALK levels outside the therapeutic target during follow-up were collected. Severity was defined by leg deformities (intermalleolar distance > 0 cm and intercondylar distance ≥ 6 cm) at end of growth.

Results: Among the 234 patients screened, 101 were still growing, 17 had surgery before the end of growth, 27 received recombinant human growth hormone treatment and 58 had missing data. Finally, 31 patients were included of which 22 women with a mean age of 27.3 years. 14 patients had straight legs at the end of growth and 17 had leg deformities. On univariate analysis, only age (31.3 vs 22.5 OR=1.06 [1.00-1.15] p=0.078) familial history of XLH (7 vs 10 OR=0.39 [0.11-1.55] p=0.068), treatment adherence (2.5 vs 3.8 OR=0.03 [0.01-0.02] p=0.0041) and ALK level outside the therapeutic target (106 vs 54 OR=1.01 [0.99-1.03] p=0.086) were significantly different between the two groups. On multivariate analysis only treatment adherence appears to be significantly associated to the severity of the disease (OR=0.02 [0.00-0.022] p=0.007).

Conclusion: This retrospective study suggests that non-adherence to treatment is a major factor associated to severe disease at the end of growth, emphasizing the importance of therapeutic education of patients and their caregivers.

P2-P042

High Fibroblast Growth Factor (FGF) 23: An Unusual Cause of Severe Osteoporosis in a Patient with Chronic Liver Disease

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Case description: A 14-year old boy with autoimmune hepatitis who was on long term oral steroids for 10 years, presented with acute onset lower back pain without preceding trauma. Lumbar spine radiograph showed severe osteopenia and compression fractures of vertebrae T12 to L1. Bone mineral density T-score at the lumbar region was -4.9. Biochemically, there was hypocalcaemia and severe hypophosphataemia with adjusted calcium 2.03 (2.20-2.65) mmol/L and phosphate 0.87 (1.18–1.89) mmol. Serum PTH levels were normal. Serum 25-hydroxy-vitamin-D3 was insufficient at 14.9 ug/L despite him being on daily cholecalciferol 1000 units for vitamin D deficiency from cholestasis-induced malabsorption. Urine phosphate levels were grossly elevated at 8.3 (1.29-1.94) mmol/L. Work up for renal tubular acidosis was negative.

The patient was placed on calcium, phosphate and vitamin D replacements and treated with intravenous bisphosphonates. Despite supraphysiological doses of oral phosphate replacement at 3 mmol/kg/day, phosphate levels remained suboptimal at 0.8-0.9 mmol/L. High levels of fibroblast growth factor 23 (FGF23) at 840 (<230) RU/mL provided a clue to the etiology behind this new onset hypophosphataemia and hyperphosphaturia. As the high FGF23 could be from a paraneoplastic tumour secretion, the Ga68-DATONAC PET-CT was performed and was normal. The age of onset of the hypophosphataemia made hereditary hypophosphataemic rickets (HHR) an unlikely cause for this.

The patient underwent a living-related liver transplant for end-stage liver disease (ESLD) 6 months later. Two months post-transplant, phosphate levels normalized and FGF23 levels dropped to 180 RU/mL. He was weaned off phosphate replacements and was able to maintain normal serum phosphate levels thereafter.

Discussion: FGF23 is a key regulator of phosphate homeostasis. It acts at the proximal renal collecting tubules to increase urine phosphate excretion and reduces 1,25-dihydroxyvitamin-D3 production. Elevated serum FGF23 occurs in HHR due to the *PHEX* gene mutation and in tumour-induced osteomalacia in children.

High levels of FGF23 have been described in patients with cholestatic liver disease and ESLD. Elevated FGF23 mRNA re-expression has been demonstrated in hepatocytes of patients with ESLD. FGF23 levels are associated with an increased risk of mortality in an adult cohort with ESLD awaiting transplant.

Conclusions: High FGF23 levels should be considered in children with ESLD who develop severe osteoporosis. This condition requires treatment with high levels of phosphate and vitamin D replacements until eventual liver transplantation, which can provide a cure.

P2-P043

Metabolic Syndrome in Children with X-Linked Hypophosphatemic Rickets (XLHR)

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Introduction: X-linked hypophosphatemic rickets (XLHR) is due to mutations in the PHEX gene inducing increased levels of fibroblast growth factor 23 (FGF23), phosphate wasting, hence rickets. FGF23 is suspected to be as an important metabolic regulator of glucose and lipid metabolism.

Objective: To describe the metabolic profile (body mass index, blood pressure, glucid and lipid profile) in patients with XLHR and evaluate the correlation between FGF23 levels and metabolic biomarkers.

Results: 53 XLH patients (17 boys and 36 girls)(PHEX mutated) were included (mean age : 8.0 ± 4.3 years [range 0.3-18]). Each subject was classified based on International Obesity Taskforce (IOTF) cut off values of BMI for age and sex as overweight

(IOTF >25) or obese (IOTF >30). Mean IOTF of study population was 23.9±3.2. 42% of patients had IOTF > 25 of which 12/53 (22%) were overweight (IOTF mean : 25.9± 1.13) and 11/53 (20%) were obese (IOTF mean: 31.2±3). When stratified by age, children show a dramatic increase of BMI z-score (SDS) over time (at 2 years : 0.5±0.3, 5 years : 0.9±0.3 , 10 years : 1.1±0.4 and 15 years : 1.4±0.5). None of the patients had hypertension. 4 patients out of 53 had hyperglycemia, i.e. fasting blood sugar > 1.1 g/dl ; 7 patients had HDLc < 1.03 mmol/L, 7 had low HDL cholesterol and 11 had high LDL cholesterol level (> 1.24 mmol/L) which correlated with FGF23 level (p=0.0237).

Conclusion: This pilot study shows that children with XLHR gain too much weight during childhood, and that there may be an association between FGF23 and the development of metabolic syndrome. Further investigations are needed in a larger cohort of children and in adults to define the specific roles of FGF23 and PHEX in the development of metabolic syndrome.

P2-P044

High Incidence of Cranial Synostosis and Chiari Malformation in Children with X-Linked Hypophosphatemic Rickets

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Background: X-linked hypophosphatemic rickets (XLH) represents the most common form of hypophosphatemia and leads to vitamin D resistant rickets in children.

Even though cranial vault and craniovertebral anomalies of potential neurosurgical interest, namely early closure of the cranial sutures and Chiari type I malformation- have been observed in XLH patients their actual incidence is not established.

Aim: Describe and analyze the incidence of cranial and cervico-occipital junction (COJ) in children with XLH.

Patients and Methods: Retrospective study of CT scans of the head and skull in 44 XLH children followed at the French Reference Center for Rare Diseases of the Calcium and Phosphate Metabolism. The patency of the sutures was noted. The cranial index was calculated and the position of the cerebellar tonsils was analyzed.

Results: Forty-four XLH children, 15 boys and 29 girls, age 8.7 ± 3.9 years at time of CT scan in whom XLH was diagnosed and treatment initiated at 2.4 ± 2.1 years were analyzed.

25% of XLH children showed protrusion of the cerebellar tonsils (7 children > 5 mm and 3 children < 5 mm). 59% of XLH children had a complete or partial fusion of the saggital suture and craniosynostosis was associated to abnormal descent of cerebellar tonsils. A history of dental abcesses was associated to craniosynostosis.

36% of XLH children presented scaphocéphalie (cranial index <75%). Patients with craniosynostosis had a smaller cranial index compared to patients without craniosynostosis.

Conclusion: This study highlights that sagittal suture fusion and Chiari malformation are two possible complications of XLH. The incidence of sagittal synostosis in patients affected by XLH is actually extremely high and it has been probably underestimated in previous reports. Chiari malformation is also relatively common in this population. Because the diagnosis can be underestimated on a purely clinical basis, radiological studies should be considered in XLH children if a proper diagnosis is warranted.

Further studies are needed to better assess the clinical impact of these complications in this population.

P2-P045

An Unusual Case of Hypophosphatemia in a Child Affected by Di George Syndrome

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A female child born from non consanguineous parents of Pakistani origin presented with congenital heart anomaly at prenatal ultrasound and confirmed at birth, with type B aortic arch interruption, right-sided aortic arch, wide ventricular and atrium septum defects, which required repeated surgical corrections during the first 9 months of life. The ultrasound also reported absence of the thymus. Suspecting Di Deorge Syndrome, a fluorescent in situ hybridization (FISH) was performed, which reported a microdeletion of chromosome 22 therefore confirming the diagnosis.

Routine screening for features associated with Di George syndrome were performed at 18 months of age. The patient's weight, length and head circumference were inferior to the 3rd percentile. She presented with widened wrists and ankles and slight bowing of the legs. She managed to walk independently at 16 months of age. Her diet was reported to be slightly deficient in milk products, and otherwise varied. She had previously suffered a post-traumatic fracture of the left arm. The patient never experienced a severe infection requiring hospitalization. The exams showed normal T-cell count and normal hearing tests. Routine calcium and phosphate metabolism documented hypophosphatemia in multiple occasions, associated with normal total and ionized calcium, normal PTH, increased alkaline phosphatase, slightly low 25OHVitamin D, however not low enough to cause hypophosphatemia. Urinary phosphate reabsorption was reduced. Wrist and knee radiographs showed signs of rickets.

Di George Syndrome is usually characterized by hypoparathyroidism and consequent hyperphosphatemia and hypocalcaemia, therefore the patient's biochemical and radiological findings were very unusual.

A genetic analysis on PHEX gene was performed, which documented a heterozygous deletion on exon 12, responsible for X-linked hypophosphatemia. The genetic analysis was extended to the parents, who resulted non affected.

Treatment with alfacalcidol and phosphate was initiated, and the patient showed progressive normalization of bone metabolites

and improvement of the radiographic signs of rickets. Severe impairment of linear growth persisted, likely due to the coexistence of the two pathologies and the resulting therapeutic challenges.

No cases of hypophosphatemia in Di George Syndrome and coexistence of XLH and Di George Syndrome have previously been reported in literature.

P2-P046

Novel SLC34A1 Mutation in a Girl Infant with Idiopathic Infantile Hypercalcemia

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SLC34A1 encodes renal sodium-phosphate cotransporter 2A. It has been identified as being a part of the etiology of idiopathic infantile hypercalcemia. We report a case of a 1-month old girl, initially hospitalized due to perinatal detection of nephrocalcinosis. Blood tests showed hypercalcemia, hypophosphatemia, hypercalciuria and increased 1,25-(OH)2D3. Renal ultrasound revealed medullary nephrocalcinosis. An abnormality in vitamin-D metabolism was suspected and genetic testing was performed. This revealed the patient to be compound heterozygous for novel (likely) disease-causing mutation (p.Gly446Asp, p.Arg495Cys) in the SLC34A1 gene. No mutations were found in CYP24A1. The hypercalcemia normalized following a calcium depleted diet and discontinuation of vitamin-D supplementation without phosphate supplementation. But hypercalciuria was wax and wane. Increased awareness of the typical symptoms of hypercalcemia, such as anorexia, polydipsia, vomiting and failure to thrive, is of utmost importance in diagnosing IHH early and preventing long-term complications such as nephrocalcinosis. Further identification of as many disease-causing mutations in the SLC34A1 gene as possible can help identification of predisposed individuals in whom vitamin-D supplementation should be reconsidered

P2-P047

A Novel Variant of SLC34A1 Gene in an Infant with Idiopathic Infantile Hypercalcemia

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Bacground & objective: Idiopathic infantile hypercalcemia is one of rare diseases characterizing hypercalcemia in infancy. Renal phosphate absorption in proximal tubules plays a very important role in the phosphate and calcium homeostasis. SLC34A1 is known a key regulator of renal phosphate reabsorption. SLC34A1 gene mutation is one of very uncommon causes of idiopathic infantile hypercalcemia. We have experienced a case of idiopathic infantile hypercalcemia caused by a homozygous novel variant c.1483C>T(p.Arg495Cys) of SLC34A1 gene.

Materials & Methods: A study patient was 5 months-old boy. His medical records were reviewed retrospectively.

Results: A 5-month-old boy was transferred to Kyungpook National University Children's Hospital because of sustained hypercalcemia with hypercalciuria. Laboratory investigations revealed a serum calcium level of 12.6 mg/dL (normal range: 9.0–10.6), phosphate level of 3.7 mg/dL (normal range: 4.8–8.2), serum magnesium level of 2.0 mEq/L (normal range: 1.44–3.12), intact PTH level of 0.6 pg/mL (normal range: 10–65), PTHrP <1.1pmol/L (normal range: <2.0), 25(OH)vitamin D3 level of 65 ng/mL (normal range: 8.0–51.9) and 1,25(OH) vitamin D3 level of 79 pg/mL (normal range: 25-65). Spot urine calcium/urinary creatinine ratio (mg%: mg%) was elevated 1.4 (normal level: <0.8 for infant). Targeted exome sequencing in the patient was performed, resulting in a homozygous novel variant c.1483C>T(p.Arg495Cys) of *SLC34A1* gene confirmed by Sanger sequencing.

Conclusions: We report a case with idiopathic infantile hypercalcemia caused by a novel variant of *SLC34A1* gene mutation

P2-P048

Infantile Arterial Calcification and Subsequent Hypophosphatemia Due to *ENPP1* Mutation – a Case Followed Through to Adulthood

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Introduction: Infantile Arterial Calcification (IAC) is a rare and frequently lethal condition. Children who survive the infantile period may develop fibroblast growth factor 23 (FGF23) mediated hypophosphatemia and rickets when IAC is due to mutations in the *ENPP1* gene.

Case: We present a female patient born to a family whose previous child died at birth with extensive vascular calcifications. Akin to the first sibling, our case presented with extensive calcifications noted antenatally, involving the coronary arteries and cardiac valves. The patient survived infancy, treated compassionately with a first-generation bisphosphonate (Etidronate). However, by 4-months-of-age, hypophosphatemia and rickets developed requiring phosphate and calcitriol treatment while calcifications remained stable. During puberty, new calcifications developed and hypophosphatemia therapy was discontinued. Calcifications remained stable as an adult until the initiation of an oral contraceptive pill (OCP), where acute worsening of calcifications was noted necessitating exploration of further therapies. A compound heterozygous genetic mutations in the *ENPP1* gene was confirmed.

Discussion: Patients with *ENPP1* mutations that survive infancy present a unique balance between bone hypomineralization paradoxically coexisting with extraskeletal calcifications. In our patient, the onset of new calcifications during puberty, followed by further exacerbation upon OCP initiation, has led the authors to query if estrogen may modulate extraskeletal calcifications.

Symptoms and calcifications seemingly occurred exclusively during three distinct periods of predicted increased estrogen concentrations: early infancy, puberty and with OCP initiation. There is no literature to support this hypothesis to our knowledge, yet it is an intriguing avenue of exploration. While a great deal remains to be delineated in FGF23 regulation, clear differences have been observed in infancy, adolescence and between sexes that may offer understanding in mineral homeostasis. Experimental therapies to minimize calcium deposits and reverse systemic calcifications in IAC and other conditions have been proposed. These therapies include first-generation bisphosphonates, oral sodium thiosulfate and oral acetazolamide, although little literature support exists for these therapies outside of isolated case reports and series.

Conclusion: IAC is a rare and often fatal condition in infancy. Here, we present an adult survivor of IAC arising from a proven *ENPP1* mutation, allowing a unique look at possible exacerbating and mitigating factors for calcium-phosphate deposition. The apparent exacerbation of calcification formation during times of increased estrogen exposures prompts consideration for a mechanistic link. Further analysis of the disease course may offer insights into the underlying mechanisms of mineral homeostasis and opportunities for future therapeutic targets.

P2-P049

Pediatric Quality of Life Inventory in Children with Osteogenesis Imperfect in Dr Soetomo Hospital Surabaya

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Osteogenesis imperfecta is a heritable systemic disorder of bone and connective tissue. Acceptance of children and their family is associated with medical, growth, developmental conflicts, physical, social and emotional. The study about impact of OI in children's quality of life is still limited.

Aims is to analyze PedsQL score in OI children in Dr. Soetomo Hospital, Surabaya.

Methode: this study is a cross sectional study held in pediatric endocrine outpatient clinic Dr Soetomo Hospital Surabaya, Indonesia on January 15th, 2018. Questionnaire used was PedsQL 4.0 General Score Questionnaire. The range was 0 until 100. (The higher result showed the better PedsQL).

Results: There were 18 patients diagnosed with OI in Pediatric endocrine outpatient clinic Dr. Soetomo Hospital Surabaya, 12 children were included in this study. The gender was male 6(50%), mean of age was 61 months, family history of OI was 1(8.3%) and the commonest fracture site was 12(100%) in femur. Side effect of biphosponate treatment was fever in 5(41.6%). Pediatric QL dimension showed that physical,emotional,social and school were 55.8; 66.1; 42.4; 67.7 respectively. The correlation between age and Peds QL in emotional dimension was rs= -0.765 (p=0.004). Correlation betwee bisphosphonate administration and Peds QL was -0.627(p=0.029).

Conclusion: PedsQL in OI showed that the social functioning was the lowest score while the school functioning was the highest score. There was correlation between age and PedsQL emotional functioning score and also correlation between bisphosphonate administration and Peds QL physical functioning.

Keywords: osteogenesis imperfecta, children, pediatric quality of life

P2-P050

Osteoporosis-Pseudoglioma Syndrome (OPPG): Improvement of Osteoporosis on Biphosphonate Therapy

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Background: Osteoporosis-pseudoglioma syndrome (OPPG), rare autosomal recessive entity, is characterized by juvenile osteoporosis, bone deformities, neuromotor retardation, and congenital blindness. This syndrome is due to the loss-of-function mutation in LRP5 (Low-density lipoprotein receptor-related protein 5). Here report four cases from three families, with confirmed molecular diagnosis who showed improvement of osteoporosis improved with biphosphonate therapy.

Case Reports: Four patients were followed-up at medical genetics, neurology and ophthalmology clinics due to congenital blindness and neuromotor retardation including a 6,5-year-old girl [case 1], two siblings: a 7-year-old girl [case 2] and a 3-year-old boy [case 3], and a 2,5-year-old boy [case 4]) were referred to our clinic for assessment of osteoporosis. All patients had born at term, appropriate for gestational age to consanguineous parents, and vision disorders were noted at around postnatal 2nd week. At presentation, cases 1 and 2 had fractures after mild trauma, case 3 had no fracture and case 4 had fractures at follow-up. Heights SDS of the all patients were within target height ranges. Mental retardation, microphthalmia, corneal opacity and bone deformities such as dorsal kyphosis, pectus excavatus were present in all of the patients. Stereotypic movements were observed in cases 3 and 4. Case 1 was wheelchair-bound since age-four, and others were able to walk with assistance. In all cases, levels of serum calcium, phosphorus, creatinine, alkaline phosphatase, parathormone, 25 OH vitamin D, urinary calcium/creatinine and urinary USG were normal. Bone mineral density (BMD) measurements on DEXA, expressed as z-scores were found as -6.0, -6.9, -2.6 and -4.3 respectively. In all cases, mutations in LRP5 gene confirmed the diagnosis. All patients were given vitamin D and oral calcium, and pamidronate infusion was started in all cases varying from 3 to 6 months intervals. Follow-up period of case 1 was twelve years, and in other patients three years. On biphosphonate therapy, improvements in BMD were observed in all patients. BMD z-scores showed an improvement to -1.3,-3.7, 1.8, and -3.6 respectively.

Conclusion: Osteoporosis-pseudoglioma syndrome should be taken into consideration in patients where osteoporosis is accompanied by congenital ocular findings. Osteoporosis is an expected finding of the disease which shows an improvement with biphosphonate treatment.

P2-P051

Bone Marrow Adiposity and IGF System in Obese Children and Adolescents

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Background: Body weight has a close correlation with bone mass in humans and high fracture rates has been reported in both obese and underweighted individuals. It is not clear the role of bone marrow adiposity (BMA) and the IGF system in this process.

Aim: The aim of this study was to analyze bone composition and BMA in obese and non-obese children/adolescents and correlate them with the expression of the IGF type-1 receptor (IGF1R) in peripheral lymphocytes and serum concentrations of IGF-I and IGFBP-3.

Methods: thirty subjects aged 8 to 18 years old were enrolled and divided into 2 age-matched groups: obese (n=15) and non-obese (n=15). These groups were submitted to anthropometric evaluation, lumbar spine (L1-L4 and L3) and total body bone densitometry and lumbar spine and total abdominal magnetic resonance. Blood sample was collected at the same moment for IGF-I, IGFBP-3, IGF1R and biochemical evaluation.

Results: BMA was similar in the obese group and non-obese. Bone mineral density (BMD) was higher in the obese group compared to non-obese even after adjustment for bone age or volumetric densitometry analysis. No correlation was found between BMA and BMD. A positive correlation between BMD and both fat mass and lean mass was observed in obese patients. On the other hand, in the non-obese group a positive correlation was found only between BMD and fat mass. IGF-I and IGFBP-3 concentrations were similar in both groups. No difference was observed regarding IGF1R gene expression. No correlation was observed between BMA or BMD and IGF1R gene expression, serum IGF-I or IGFBP-3 concentrations.

Conclusion: It was shown that there is no difference in BMA between obese and non-obese children/adolescents. A possible role for the IGF system in the BMA determination seems to be more important at paracrine/autocrine level. Body composition, especially fat mass, seems to be important in determining bone mass in obese children/adolescents.

P2-P052

Evaluation of Bone Mineral Density in a Cohort of Children with Growth Hormone Deficiency

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Background: Growth Hormone (GH) plays an important role in linear growth and in bone turnover during childhood. GH deficiency (GHD) may cause secondary osteoporosis associated to low bone mineral density (BMD), impairment of bone turnover and increased fracture rate. The effects of treatment with recombinant human Growth Hormone (rhGH) on bone metabolism are controversial. We aimed to assess BMD using dual energy x-ray absorptiometry (DEXA) among a cohort of children with GHD before rhGH therapy. Furthermore, we aimed to evaluate the association between BMD and auxological, biochemical and therapeutic data at baseline and during rhGH therapy.

Methods: We enrolled 193 patients (9.68 ± 3.27 years, 58% males, 75% in a pre-pubertal age) with diagnosed GHD. DEXA was performed before treatment. Anamnestic, anthropometric, biochemical and radiological data were evaluated at baseline and during rhGH treatment (6, 12 and 24 months).

Results: The median value of BMD Z-score before rhGH therapy was -1.15 ± 0.97. Analyzing BMD values at baseline, we found differences between pubertal and pre-pubertal patients (BMD SDS -1.54± 0.95 vs. -0.97±0.93; $p < 0.001$) and between patients with a normal brain magnetic resonance imaging (MRI) and subjects with a pathologic MRI (BMD SDS -1.09±0.99 vs.-1.48±0.82 p 0.03, respectively). The absolute value of BMD (g/cm^2) was positively correlated with height SDS (r 0.20, $p < 0.05$), BMI SDS (r 0.24, $p < 0.05$) and IGF-1 values (r 0.33, $p < 0.05$); BMD SDS value was positively correlated with target height SDS (r 0.28, $p < 0.05$) and BMI SDS (r 0.36, $p < 0.05$) whereas there was a negative correlation between BMD SDS and the age at GHD diagnosis (r^2 0.40, $p < 0.05$). There was no association between BMD values and biochemical and therapeutic data.

Conclusions: Our study shows that pubertal patients have a lower BMD than pre-pubertal ones as a consequence of the mild bone demineralization (BMD Z-score -1.15±0.97) secondary to GHD. Therefore, our data suggest starting rhGH therapy early as to promote an optimal growth. DEXA might represent a valid mean to complete the diagnosis in GHD patients and to optimally orient the therapeutic decisions; it should be repeated at the end of treatment in order to evaluate its effect on bone metabolism.

P2-P053

Follow-Up on Bone Health in Children with Acute Lymphoblastic Leukemia (ALL)

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Background: Acute lymphoblastic leukemia (ALL) is the most common paediatric cancer. Skeletal morbidity has been recognized as a complication of ALL and its treatment, occurring at diagnosis, during chemotherapy and/or years later.

Aim: to describe the adversely effect on bone health, in terms of vertebral fractures (VF) and bone mineral density (BMD), in the follow-up of children with ALL.

Design, patients and methods: descriptive and retrospective study. Children with ALL were selected from the Endocrinology Division of Hospital de Niños Ricardo Gutierrez. Clinical and auxological characteristic were recorded. VF and BMD which were assessed by lateral thoracolumbar spine radiographs (according to the Genant method) and dual-energy x-ray absorptiometry (DXA, using either Hologic or Lunar Prodigy), respectively. Estimates (months) of the presence of VF or abnormal BMD were evaluated since diagnosis.

Results: 29 children with ALL were included (age at diagnosis: 5.38 ± 3.16 years). The follow up time was 46.21 ± 42.10 months. Twenty-two were assessed with lateral spine radiograph and 26 with DXA. Only 7/29 children under chemotherapy had VF, 5 within the first 12 months of treatment and 2 during the second year of treatment. No further VF were detected along follow-up. A low BMD was identified in 5/26 patients, 2 of them during the first year of treatment (DXA Lunar Z score= -4.0, and DXA Hologic Z score= -3.9) and both also had VF in the second year. The other 3 children developed low BMD on follow up (84.33 ± 74.54 months): DXA Hologic Z score = -2.1 (n=1) and DXA Z Score Lunar= -3.05 ± 1.3 (n=2). All patients improve their BMD. However, only 2/5 normalized their values. Back pain was not a constant symptom associated with VF and only appeared in 2/7 children with VF.

Conclusion: VF are common in children with ALL and is more prevalent along the first year of treatment. Usually are asymptomatic, therefore might remain undetected if routine surveillance is not performed. The BMD can be affected too, so an early diagnosis and intervention should be considered in order to prevent compromise of future peak bone mass.

P2-P054

Effect of Pubertal Inductionn Bone Mass Accrual, in Adolescent Boys with Duchenne Muscular Dystrophy

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Background: DMD is an X-linked recessive disorder, due to mutations of the DMD gene on Xp21, encoding dystrophin, characterized by high cytokines and progressive muscle degeneration, with loss of ambulation, increasing immobility and complicated by late cardio-respiratory failure. Use of high dose corticosteroid aims to prolong mobility, delay/reduce complications and to increase lifespan but adverse effects on bone health include bone loss and increased vertebral and long bone fracture risk. Corticosteroids also suppress DHEAS and the hypothalamic pituitary testicular axis, resulting in near universal profound pubertal delay. Bisphosphonates harden bone and are used in DMD to try to reduce fracture frequency. Normal progress through puberty has a major impact upon bone mass accrual, with increased cortical thickness and trabecular mineralization.

Aims: To assess the effect of pubertal induction with testosterone (T) on rate of change of bone mineral density(BMD), as a measure of bone mass accrual, in a cohort of adolescent boys with DMD most of whom were concurrently treated with bisphosphonate as zoledronic acid (ZA). Methods: Boys with DMD aged 14 and above (N=16), who were prepubertal, were commenced on HRT. Zoledronic acid was continued at 6 monthly intervals. Graduated increases of oral T undecanoate were made, with transition to long acting parenteral T as intramuscular T undecanoate, over 24 months, to mimic normal pubertal progress. Rate of change of BMD was calculated for the year prior to and for 12 and 24. months after onset of T.

Results: IM testosterone undecanoate group (N= 11): Median age at start of androgen 14.5yr Median age at start of IM T 16.3 y. Mean % change of BMD before androgen + 2.15% Mean % change of BMD 1 year after androgen + 10.15%, Mean % change of BMD 2 year after androgen +25.4%.10 of 11 were on ZA prior to androgen, 8 of 11 have 2 year data.

Oral testosterone undecanoate group (N= 4): Median age at start of oral T 14.5yr, Mean latest dose of oral T 109mg/ day. Mean % change of BMD before androgens -3.6%, Mean % change of BMD in first year of androgen 19.48%, Mean % change of BMD after 6-18months of oral T 19.48%. 4/4 were on ZA prior to androgen

Conclusion: Pubertal induction and ongoing use of T in adolescent boys with DMD has a major positive effect on bone mass accrual, that is likely to reduce current and future fracture risk.

P2-P055

Oxandrolone Improves the Linear Growth and Osteoporosis in Teenage Bays with Osteogenesis Imperfecta

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Background: Severe osteogenesis imperfecta (OI) is a disorder characterized by osteoporosis, frequent fractures, progressive deformity and short stature. We determine the effect of oxandrolone on predicted adult height (PAH), fracture incidence and bone mineral density in teenage boys with OI.

Methods: In a prospective, double-blind, randomized, placebo-controlled clinical trial, 31 boys (12.1-16.6 years old) who were genetically proved to have OI with an annual fracture rate more than 3 in spite of receiving cyclic pamidronate were treated with oxandrolone (2.5 mg/day), or placebo, at an outpatient pediatric endocrine clinic in Tehran for 2 years.

Results: Oxandrolone differed from placebo in significantly increasing PAH ($p < 0.01$), and the height standard deviation score($p < 0.01$) and bone mineral density ($p < 0.005$) and reducing fracture incidence compared to placebo.

Conclusion: This first randomized controlled clinical trial in male teenagers with severe OI shows that oxandrolone increases PAH, height standard deviation score and bone mineral density and reduces fracture incidence.

P2-P056

First Reported Cases of a Novel Variant of GNAS 1 Gene

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Background: GNAS 1 gene (guanine nucleotide binding protein, alpha stimulating) encodes the alpha subunit of the stimulatory guanine nucleotide-binding protein (G-protein). Variations in the GNAS 1 can cause several disorders including Pseudohypoparathyroisism Type 1A (PHP1A), Type 1B (PHP1B), Type 1C (PPHP1C), Progressive Osseous Heteroplasia(POH), Pseudopseudohypoparathyroidism(PPHP) and McCune-Albright syndrome(MAS).

Objectives: To report 2 patients, a father and his son who were identified to have the same pathogenic heterozygous GNAS1:c.1A>T variant in exon 1 of the GNAS1 gene.

Case Presentation: Our patient presented at the age of 4 months with a complaint of multiple cutaneous atrophies on his body. He was born at term, with IUGR and a weight of 2,145 kg after an IVF assisted conception. Laboratory tests showed an increased PTH, serum Phosphate in the upper limits and normal Calcium. A skin biopsy revealed dermal ossifications. Subsequently a GNAS genetic analysis identified a pathogenic heterozygous GNAS1:c1A>T variant in exon 1 of the GNAS1 gene. He is now 5 years old, with a short height of 96 cm (-3.0 SDS) and Weight of 14 Kg (-1.69). PTH, Calcium, and Phosphate measurements are within normal limits. IGF1 levels are low and GH provocations tests revealed normal GH secretion. Subsequentely he developed hypothyroidism, and is now on thyroxine. Despite being hypotonic as an infant he has neurologically improved but still has dermal ossifications. Following the diagnosis, genetical analysis performed in both parents, revealed that the father carries the same variant. He is now 43 years old, has a height of 165 cm (-1,73 SDS), short fourth fingers and has been operated for scoliosis. At diagnosis he had an increased PTH, low 25 OH vitamin D, normal Calcium and Phosphate.

Conclusion: GNAS1: c.1A>T is a novel variant in exon 1 of the GNAS1 gene, not previously described. This substitution is predicted to disrupt the start codon (GNAS: p. Met1?). Heterozygous GNAS 1 inactivating variants cause pseudopseudohypoparathyroidism when paternally inherited. Further data is needed in order to establish the role of this novel variant in the clinical expression of the disease.

P2-P057

An Unusual Cause of Short Stature

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Objectives: Spondyloenchondrodysplasia with immune dysregulation (SPENCDI) is an immunoosseous dysplasia combining the typical metaphyseal and vertebral bone lesions with immune dysfunction and neurologic involvement which is caused by mutations in *ACP5* gene encoding tartrate resistant acid phosphatase 5.

Here, we report a three year old girl presented with primary hypothyroidism, developmental delay and thrombocytopenia and diagnosed as SPENCDI.

Case Report: A 3-year-old girl was referred to our department for primary hypothyroidism which was diagnosed during evaluation for growth and developmental delay at the age of 1 year with mildly elevated TSH and exaggerated response at TRH test. Brain MRI and tests for metabolic diseases which were done because of inability of talking and walking at two years of age were unremarkable. She was a product of consanguineous marriage of healthy parents with normal stature. She was born at 40 weeks of gestation and her birth weight was 3300 gr. Family history revealed treatment with rGH for short stature of her 8 year old brother.

On initial examination height SDS was -3,5 (85cm) and weight SDS -1,15 (13,3kg). She was noted to have spastic paraparesis, blue sclera and hepatosplenomegaly. Laboratory tests showed hrombocytopenia and autoimmune hemolytic anemia at the age of 4 year and fairly response to steroid treatment. The spine X-rays showed generalized platyspondyly with posterior vertebral bodies were irregularly ossified. A subsequent skeletal survey revealed generalized metaphyseal dysplasia with enchondromatous lesions. Findings were considered consistent with SPENCDI. Laboratory data showed normal levels of serum calcium, phosphate, ALP, intact PTH. A novel homozygous 19 bp deletion in the *ACP5* gene (c. [772-790del19]; [(772-790del19)]) was detected. Tests for immune dysfunction and neurological involvement revealed intense calcification in the bilateral basal ganglia and lateral ventricular frontal horns and a decrease in the number of CD4 + cells.

The older brother also had skeletal dysplasia with 160 cm final height and without any neurological abnormality and known immune dysfunction.

Conclusions: SPENCDI is a rare skeletal dysplasia characterized by enchondroma-like metaphyseal lesions in long bones and spondylar dysplasia with immune dysregulation and neurological symptoms. Here we desribed a case with full clinical picture of SPENDI and her less severely effected older brother with only short stature and bone dysplasia. SPENCD should be kept in mind in children with short stature and typical skeletal findings. Recognition of the disease is important for timely diagnosis and treatment of extraskeletal manifestations and for genetic counseling.

P2-P058

Validation of an Automated Method (BoneXpert) for the Determination of Bone Age in Paediatric Endocrinology – A Single Centre Experience

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Background: The BoneXpert method is an automated determination of bone age, which employs deformable models of each bone to locate the bones, and extracts the component of the bone appearance related to maturity in a holistic, statistical manner. The BoneXpert has been validated on normal children and children with diagnoses typical of pediatric endocrinology. Multiple clinical studies suggested that BoneXpert has adequate accuracy, precision, and efficiency to be clinically useful.

Objective: To investigate accuracy, precision and bias of conventional methods of bone age evaluation compared with BoneXpert.

Design: Comparison of bone age assessed using the method of Greulich and Pyle, Tanner-White-house (TW-RUS) or BoneXpert. 79 radiographs of the left hand were obtained from children with various diagnoses between the ages of 4.8 to 16.6 yr. The films were rated using the GP atlas method by two different raters, TW-RUS method by two different raters and BoneXpert. Results are evaluated using Rank and Intraclass correlation, and Bland-Altman analysis.

Results: Human GP (HGP) versus BoneXpert GP (BGP) score shows bias towards chronological age for HGP ratings, HGP scores being on average 0.3 years higher than BGP scores. We noticed similar results when comparing HGP with TW-RUS scores. There was no evidence of bias in TW-RUS scores towards chronological age. TW-RUS scores were on average 0.51 years higher than BGP scores. Rank and intraclass correlation stats showed high correlation between all methods. TW RUS showed higher correlation with BGP than HGP with BGP.

Conclusion: The results of our study suggest that BoneXpert has adequate accuracy, precision and efficiency. The automated method provides a reliable and efficient standard for bone age determination. Introduction of BoneXpert into clinical practice provides precise standardized bone age determination, vital for long term outcome and comparator studies of growth and growth interventions.

P2-P059

Arthrogryposis Multiplex Congenita Type II and Panhypopituitarism

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Aim: Arthrogryposis Multiplex Congenita type II is an autosomal dominant disease, characterized by multiple congenital contractures in the limbs without a primary neurological deficit. The most frequently observed clinical features are triangular face, palpebral fissures facing downwards, clarity in nasolabial folds, small mouth, high palate, adherent ear lobes, short stature, camptodactyly, ulnar deviations in the fingers, vertical talus and/or talipes equinovarus.

Case: A male patient who applied to the hospital complaint of his short stature was born with term 3000 gr and 50 cm. At the time of birth it was learnt that the arm, left leg, hand and neck had a curvature and limitation of movement and was diagnosed with Arthrogriposis Multiplex Congenita. In his physical examination chronological age: 5 years 10 months, height age: 2 years 8 months, bone age: 3 years 6 months, weight:12.7kg(<3p),height: 92.1cm(-4.49 SD) and he was prepubertal. In existence were triangular face, epicantus, micrognati, facial asymmetry, clearness in nasolabial folds, narrow mouth opening, high palate, long filtrum, ulnar deviation in fingers, abduction limitations in thumbs, tarsal fusion, short neck, asymmetry in shoulders and scoliosis. Hand, shoulder, elbow and neck joints were limited due to contractures. In hıs laboratory TSH: 2.4 mIU/ml, sT4: 0,55 ng/dl, IGF-1: <15 ng/ml (<-3SD),IGFBP3: 489 ng/ml (<-3SD) was observed. LT4 therapy was initiated for his central hypothyroidism after ACTH: 18.3 pg/ml, cortisol: 8.3ug/dl. The growth rate in 3 months after euthyroidism was 0.5 cm and IGF-1: <15 ng/ml (<-3SD) and IGFBP3: 570 ng/ml (<-3 SD). In the growth hormone stimulation tests results were in L-DOPA peak GH 0.66 ng/ml, in clonidine peak GH 0.84 ng/ml. After growth hormone treatment, the growth rate was 3 cm/3 months. The genetic analysis results is awaiting.

Conclusion: Half of the Arthrogryposis Multiplex Type II cases are caused by mutation in troponin I (TNN12),troponin T (TNNT3) and embryonic mysosin (MYH3) genes. In spite of short stature of syndrome features, only 2 cases of Panhypopituitarism have previously been reported in available literature.

Bone, Growth Plate & Mineral Metabolism P3

P3-P031

Growth Hormone Treatment of 2 Patients with X-Linked Hypophosphatemic Rickets Caused by *PHEX* Mutation: Effects on Linear Growth

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Background: Hypophosphatemic rickets (HR) is a group of rare disorders caused by an excessive renal phosphate wasting. X-linked HR (XLHR) is caused by mutation in *PHEX* (phosphate-regulating endopeptidase) gene and is characterized mainly by bone deformities, disproportionately short stature, dental anomalies and hypophosphatemia with coexisting low renal phosphate reabsorption. Early treatment with vitamin D and phosphate improves the patient's growth. Recombinant human growth hormone (rhGH) may also improve growth in XLHR through a direct effect on growth cartilage, and by increasing renal phosphate reabsorption and serum phosphate levels.

Objective: The aim of the study was to investigate the clinical phenotype and molecular background of HR in two patients in which XLHR was suspected as well as to analyze the effects of rhGH treatment on their growth.

Patients and methods: 2 patients, 8.25 years old girl and 6.75 years old boy were diagnosed with HR at the age of 2.25 years and then treated with alfacalcidol (73 and 69 ng/kg/d) and phosphorus (175 and 30 mg/kg/d). Due to the diagnosis of growth hormone deficiency rhGH therapy was initiated at the age of 6.75 years and 4.75 years, respectively (current doses of rhGH are 0,029 and 0.028 mg/kg/d). Molecular analysis was performed using total genomic DNA. *PHEX* gene was analyzed using standard PCR and direct sequencing method.

Results: The dominant clinical signs in both patients were bowing of legs and short stature. HtSDS at the time of diagnosis was -3.7 and -2.3, respectively. Current htSDS is -3.4 and -2.1, respectively and the height gain during rhGH therapy was +0.3 and +1.04 SD. In the patient 1, we found a known c.C716>T, p.T239M heterozygous polymorphism (rs7955866) in *FGF23* gene which was absent in the patient's affected father. We also found a novel heterozygous mutation c.326_327insCA, N110Ifs*7 in *PHEX* gene which was also present in the patient's father. *FGF23* in the patient 2 was intact, but we found a known hemizygous mutation c.1801_2250del in *PHEX* gene covering exon 17 to exon 22.

Conclusion: Early clinical and molecular diagnosis of HR, and early implementation of vitamin D and phosphorus is crucial to prevent severe bone deformities and to improve final height. rhGH therapy in patients with XHLR may be very effective in those with coexisting growth hormone deficiency. Genetic counseling in families with HR patients should be proposed.

P3-P032

A Novel Homozygous Mutation in the CASR Gene in a Neonate with Severe Primary Hyperparathyroidism; A Case Report

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Background: Neonatal severe primary hyperparathyroidism (NSHPT, MIM 23900) is a potentially lethal autosomal recessive disorder characterized by severe hypercalcemia, markedly elevated serum PTH levels and skeletal abnormalities that include multiple fractures, demineralization and erosions. It is secondary to biallelic loss of function mutation in the CASR gene that encodes the calcium sensing receptor.

Case presentation: We identified a 10 –day old baby boy born to first degree consanguineous Saudi parents who was hospitalized for poor feeding, lethargy and moderate dehydration. Found to have an incidental severe hypercalcemia 5.4 mmol/l (N:2.1-2.7), hypophosphatemia 0.76 mmol/l (N: 1-1.95) and markedly elevated PTH level 55.7 pmol/l(N:1.6-6.9), So the diagnosis of NSHPT was established. Medical treatment failed to restore eucalcemia so total parathyroidectomy with autotransplantation in the sternocleiodomastoid muscle was undertaken which resulted in resolution of clinical and biochemical picture. Molecular analysis of the CASR gene revealed a novel homozygous mutation " Gly695Val". Unaffected parents were heterozygous carriers.

Conclusion: We, hereby, report the identification of a novel pathogenic homozygous loss of function mutation in the CASR gene in this saudi neonate with severe hypercalcemia which has never been described before. functional studies are needed to examine the role of this mutation in CASR acitivity.

Key words: neonatal severe hyperparathyroidism, calcium sensing receptor, parathyroidectomy,autotransplantaion, parathyroid hormone.

P3-P033

A 13 Year-Old Boy Diagnosed As Osteogenesis Imperfecta With Normal Bone Mineral Density

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Osteogenesis imperfecta is a hereditary connective tissue disease developing based on the structure or synthesis impairment of type 1 collagen and proceeding with diffuse osteoporosis, fragility, fractures and deformities in bones. Bone mineral density can be at normal or even high levels particularly especially in type I and XIII. Here, a 13 year-old boy diagnosed as osteogenesis imperfecta with normal bone mineral density was presented and treatment results were shared.

A 13-year-old male patient was brought to hospital with complaint of frequent fracture in bones. It was discovered that there are fracture histories most times with minor traumas in arms and legs. He was born as term 3100 grams and there was no known other disease histories. It was stated that there are frequent bone fractures in father, uncle, aunt, grandmother and cousins.

In physical examination, his weight was 1.31 SDS, height was 0.57 SDS, puberty stage was 3 and there was no deformity finding in extremities. Other system examinations were normal. In laboratory, the following was determined; Ca: 10.1 mg/dl (N, 8.8-10.6), P: 4.8 mg/dl (N, 4-7), ALP: 376 U/l (N, 74-390), PTH: 38.5 pg/ml (N, 10-69) and 25(OH) D3: 19.2 ng/ml (N, 20-100).

In his bone densitometry (DEXA), corrected z score was identified as 1.5. In the genetic analysis, it was established that there was a p.1119T heterozygote mutation (known to cause disease) in COL1A2 gene. Hearing test was normal. In extremity graphics, no radiological finding that made us think osteogenesis imperfecta or skeletal dysplasia and compression fracture was determined in vertebra graphics. Due to recurrent bone fractures, alendronat sodium and vitamin D treatment were initiated. In the first month of the treatment, only minor fracture was developed in his finger and foot following the trauma. DEXA corrected z score taken in the first year following the treatment was established as 5.76 SDS. The aunt and uncle of the patient were found out to have osteogenesis imperfecta. The treatment has been continued since there is a clinical response to alendronat sodium therapy.

In osteogenesis imperfecta, while bone mineral density is usually determined low and it increases with the treatment, it can be normal in some types as type I and XIII. In the treatment of these patients, treatment plan should be performed by considering parameters like fracture number, pain, mobilization and quality of life.

P3-P034

A Rare Cause of Hypercalcemia in Childhood: Hypercalcemia Associated with Parathormon-Related Peptid

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Introduction: Parathormone-related peptide (PTHrP) regulates tissue calcium concentration by acting in paracrine or autocrine ways. It is mostly responsible for paraneoplastic hypercalcemia seen in adults. Paraneoplastic hypercalcemia in children is rarely reported in cancers such as ALL, medulloblastoma and hepatoblastoma (0,4-0,7 %). In experimental studies, PTHrP is shown to be synthesized apart from neoplastic tissue (glomerulus and tubule cells).

Case: A five-month-old male patient was consulted to us by Pediatric Nephrology due to hypercalcemia. It was learned that he was born on 29th gestational week as 1330 gr, peritoneal dialysis was performed owing to bilateral renal hypoplasia, vitamin D prophylaxis was applied and thiazide diuretic or another medicine was never used. In physical examination, his height was determined as -3,32 SDS and weight was -3,8 SDS. There was no subcutaneous fat necrosis or skeletal dysplasia. The examination of other systems was normal. In laboratory workups, the following was seen; urea: 43 mg/dL (N, 10-38), creatinine: 3,0 mg/dL (N,0,4-0,7), Ca: 14 mg/dL (N, 8,8-10,8), P:2,3 mg/dL (N, 4-7), Mg: 2,5 mg/dL (N, 1,8-2,6), ALP: 1631 U/L (N, 82-383), PTH:6,64 pg/mL (N, 10-69), 25(OH) D_3:97 ng/mL (N, 20-100), 1,25 $(OH)_2D_3$: 60 pg/mL (N, 16,4-81), pH: 7,38 (N, 7,35-7,45) HCO3:24 mmol/L (N, 22-26). Hypothyrodism and adrenal insufficiency were ruled out. Echocardiography was normal. Primarily, in the etiology PTH independent hypercalcemia were thought with these findings. Vitamin D poisoning or *CYP24A1* mutation was moved away in the patient with low phosphorus level, normal vitamine D metabolites. In direct radiograpies, Jansen's Metaphyseal Dysplasia was not considered in the patient with no metaphyseal dysplasia or rickets finding. PTHrP level was determined as 5,9 pmol/L (<2,0). In the workups of bone marrow examination and imaging, no malignancy evidence was established. Due to hypercalcemia not responding to hydration and furosemide treatment, pamidronate infusion was applied. Serum calcium level returned to normal after pamidronate and hypercalcemia did not recur in clinical observation.

Conclusion: Although hypercalcemia related to PTHrP mostly emerge as paraneoplastic, it can be rarely seen in renal developmental pathologies. Hypercalcemia related to PTHrP should be thought in the differential diagnosis of cases followed up with hypoplasia/dysplasia and those in whom hypercalcemia has developed in their clinical observation.

P3-P035

Our Treatment Experience with Nocturnal Continuous Enteral Calcium Infusion in a Case with Vitamin D Resistance Rickets Type II

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Introduction: Vitamin D resistant rickets type II (VDDR-II) is a disease with a difficult treatment developed as a result of mutations in VDR gene. Despite high dose active vitamin D and oral calcium treatments, sufficient recovery cannot be achieved mostly. Successful results with intravenous calcium infusion that is an alternative treatment have been reported; however, serious restrictions and complications such as hospitalization, catheter infection, thrombosis, skin necrosis.

Aim: It presents the results of nocturnal-continuous enteral calcium infusion in a case not responding to conventional treatment.

Case: A 19-month-old male patient was guided with findings; caput quadratum, rachitic beads, enlargement in wrists and O-leg deformity. The height of patient whose parents are relatives was -3,2 SDS, weight was -1,47 SDS; he had no alopecia. Biochemical and radiological findings were compatible with stage 3 rickets. VDDR-II was considered when not having response to stoss therapy applied with nutritional rickets diagnosis and determining high 1,25 $(OH)_2D3$ level. R158L (c.473 >T) homozygote response mutation was identified in *VDR* gene. Upon not having response to conventional treatment, nocturnal-continuous enteral calcium gluconate infusion (100 mg/kg/12 hour with naso-gastric catheter) was initiated by taking consent to avoid complications of intravenous calcium treatment. 20 days later, he applied to us with brain fog and severe metabolic acidosis with increased anion gap. Despite all examinations carried out, the cause of acidosis could not be clarified. Dialysis was applied to the patient who did not respond to NaHCO3. After being discharged from the hospital, the patient referred to us on the 30th day of the treatment with consciousness change. Scan tests performed in terms of neurometabolic diseases were normal. Metabolic acidosis attacks of the patient recovered with support treatment did not recur after discontinuation of enteral calcium gluconate treatment. The patient is still 4 years old and he periodically receives intravenous calcium gluconate treatment.

Conclusion: Difficulties experienced in the treatment of cases with VDDR-II direct physicians to alternative treatment search. A case with severe metabolic acidosis thought to be related to enteral calcium gluconate infusion was presented in this case report. While calcium gluconate treatment does not lead to metabolic acidosis when applied intravenously, it is unclear why it causes this situation when applied enterally.

P3-P036

A novel *COL1A2* gene mutation in a Turkish family with Osteogenesis İmperfecta

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Background: Osteogenesis imperfecta (OI) is a rare congenital bone disease associated with defects in type I collagen synthesis resulting increased bone fragility, low bone mass, connective tissue manifestations and short stature. The majority of the types of OI are caused by autosomal dominant mutation in *COL1A1* and *COL1A2* genes. Here we showed the new, novel *COL1A2* gene mutation at the heterozygous state in a family with OI.

Case: A 5-years-old boy was presented with short stature. His medical history revealed that the patient was the first child of the nonconsanguineous parents, his birth weight and height were normal, and had no bone fracture history to date. Family history revealed that his mother had also blue sclera and her arm and leg were broken ten years ago. On physical examination, his height was 98 cm (-1,42 SDS), weight was 15 kg (-1,07 SDS)**,** he had mild blue sclera, normal teeth and had no bone deformity. On admission, the laboratory evaluation were normal, however Z score of bone mineral density of lumbar spine was -2,8. The clinical and radiological criteria supported OI type 1. The entire coding region of the *COL1A1* and *COL1A2* genes were analyzed by PCR-DNA direct exome sequencing. A new variant, p.Gln133Asp (c.398G>A) was found in the 9th exone of *COL1A2* gene at the heterozygous state as a cause of OI. The same mutation was identified in heterozygosity in the *COL1A2* gene of the patient's mother.

Conclusion: Growth retardation is a notable symptom of OI, and additional extra-skeletal features also may manifest to a variable degree. The novel mutation reported here is a pathogenic mutation that result in OI type 1. Genotype-phenotype databases are beneficial for better genetic counselling.

P3-P037

Hypophosphatemic Hypercalciuric Ricket: 3 Brothers with Dent´s Disease

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Brother 1: 7 years old boy, with right genu valgum and short stature (-2,11 DS); X ray shows rickets features. Plasmatic Calcium 9,3 mg/dl; phosphate 2,5 mg/dl; Alkaline phosphatasas 460U/L; Parathyroid hormone 83 pg/ml; 25OH Vitamin D 24 ng/ml. Urine calcium 159 mg/24h (9,2 mg/K/day); Urine phosphate 870 mg/24h; TmP/GFR 2,6 (NV:3,8 -5,0); proteinuria 100 mg/dl.

Brother 2: 4 y.o boy with frequent respiratory diseases in infant period. Genu valgum from 3 years old. Short stature (-3,08 DS) and

BMI p16. Rachitic rosary and wide metaphysis. Normal calcium; Phosphate 2,8 mg/dl; Alkaline phosphatasas 742 U/L; Parathyroid hormone 155 pg/ml; 25OH Vitamin D 5,4 ng/ml. Urine calcium 210 mg/24h (17 mg/K/day) – Urine phosphate 670 mg/24h – TmP/GFR 1,9 (NV:3,8 -5,0); proteinuria 110 mg/dl. Renal ultrasound with nephrocalcinosis.

Brother 3: Healthy boy until 10 y.o when start genu valgum. He has mild hypophophatemia and hypercalciuria.

The initial treatment of Colecalciferol normalized PTH. Then, they receive phosphate and citrate salts and thiazide diuretics until now; plasma Phosphate increased. Genu valgum partially improved. They still had good renal function.

The genetic study identified the mutation c.731C>T (p.S244L) in CLCN5 gen in the 3 brothers. The mother is an asyntomatic carrier. The father has not the mutation.

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Discussion: Dent´s Disease is a X-linked inherited renal tubular disorder characterized by manifestation of proximal tubular dysfunction, including proteinuria, hypercalciuria, nephrolitiasis, nephrocalcinosis and progressive renal failure. Rickets occur in a minority of patients. The disease is found in males, generally in early childhood. Female carriers are asyntomatic or show a very mild phenotype. It´s caused by mutations in either CLCN5 (Dent´s disease1) or OCRL1 (Dent´s Disease2) genes located on chromosome Xp11.22 and XQ25 respectively.

CLCN5 encodes the electronic CL-/H+ CIC-5 and it´s inactivation is associated with severe trafficking defect in tubular cells.

Treatment is supportive, with focus on prevention of nephrolithiasis. Thyazides diuretics are used to treat hypercalciuria. In case of rickets must use phosphate suplements and Vitamin D must be used with caution since it may increase hypercalciuria. High citrate diets seem to delay progresión of renal disease.

P3-P038

Infantile Hypophosphatasia

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Hypophosphatasia is characterized by defective mineralization of bone and/or teeth in the presence of low activity of serum and bone alkaline phosphatase. Clinical features range from stillbirth without mineralized bone at the severe end to pathologic fractures of the lower extremities in later adulthood at the mild end. Although the disease spectrum is a continuum, six clinical forms are usually recognized based on age at diagnosis and severity of features: Perinatal (severe) hypophosphatasia characterized by respiratory insufficiency and hypercalcemia. Perinatal (benign) hypophosphatasia with prenatal skeletal manifestations that slowly resolve into one of the milder forms. Infantile hypophosphatasia with onset between birth and age six months of rickets without elevated serum alkaline phosphatase activity.

Here we will discuss a 15-month-old girl patient who has been referred to for the reason of delaying teeth

Case: A 15-month-old girl applied for the delay in tooth extraction. She was born at the 40th week of gestation by Caesarean section with a birthweight of 3200 g as the first child of consanguineous parents. On her physical examination at one month old, her weight was 10,2 kg (50^{th} -75^{th} centile), her height was 74.5 cm (25^{th}-50^{th} centile), and her head circumference was 35.5 cm (10^{th}-25^{th} centile).

On laboratuary examination: Ca:11,3 mg/dl, P:5,8 mg/dl, ALP: 59 IU/L(alt sınır 125 IU/L).

25OH vit D:32,3 ng/ml,PTH:8,82 pg/ml, 1,25 OH vit D:55 pg/ml, Urinary calcium excretion was normal with a calcium/creatinine ratio of 0.16 Pyridoksal 5 phosfate: 68,40 µg/L (5-50),urine phosphoetanolamin:895,20 µmol/g kre (33-342).

Genetic analysis: A heterozygous p.S181L (c.542C>T) mutation was detected in ALPL gene.

Conclusion: The clinical characteristics of infantile type of HPP are respiratory complications, premature craniosynostosis, demineralization, rachitic changes in the metaphyses, hypercalcemia, short stature, and premature loss of primary teeth. Clinical features, age, bone mineralization, elevated serum concentrations of calcium and phosphorus, and low serum ALP enzyme activity helps differentiate HPP from other conditions. In the presented patient, HPP was considered with onset after 15 months of age delaying teeth, hypercalcemia, remarkably low level of ALP, and normal PTH level.

P3-P039

Carbonic Anhydrase Deficiency: Three Siblings

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Introduction: The carbonic anhydrase II (CA II) deficiency syndrome is a rare autosomal recessive disorder associated with osteopetrosis, renal tubular acidosis(RTA), and cerebral calcification(CADS;autosomal recessive osteopetrosis type 3).Other features include visual and auditory impairment, short stature, a large cranial vault, history of multiple skeletal fractures, developmental delay and cognitive defects, anemia, splenomegaly and secondary erythropoiesis.

We report here, three siblings of CAII deficiency syndrome presenting with short stature, distal renal tubular acidosis and cerebral calcification. This is the first report of the disease occurring in three successive generations with a homozygous mutation on 8q22.

Cases: Two sisters (aged 16,5 years and 13.5 years,respectively) were referred to pediatric endocrinology department due to the history of recurrent long bone fractures (sister 1 1:3 fractures,sister 2:2 fractures).They were born to third degree consanguineous parents. Their 3 years old brother was invited for medical examination as the parents had reported him to have develeopmental delay.

Birth lengths and weights of the three siblings were within normal ranges, but growth parameters of two sisters were below the 3rd percentile after 1 year of age. Motor milestones and speech development were also delayed for all of them. At presentation, the height age and bone age of sister 1 were 11 years and 16 years and of sister 2 were10.3 and 12years, respectively.Their brother's height

(92cm,25 p) and weight (14,5 kg,50p) were in normal ranges at presentation. They all had a broad head with prominent forehead, a long bulbous nose, a relatively thin upper lip, dental carries, dental malalignment and malocclusion. The laboratory investigation of all revealed renal tubular acidosis with metabolic acidosis associated with hypokalemia, hyperchloremia and persistently positive urine anion gap without renal failure and the urinary pH of >5.5 indicating distal renal tubular acidosis. The patients were found to be homozygous for the mutation in CA II gene and parents were heterozygous for the same mutation. They were started on potassium chloride and sodium bicarbonate.

Discussion: Carbonic anhydrase II deficiency syndrome is a rare disease that can be missed due to a lack of clinical suspicion. It is important that treatment be introduced at an early stage, and serious complications can be avoided with regular follow up. The corner stone of the management of the disorder is alkali therapy to correct the condition, allowing normal growth and decreased stone formation and potassium loss.

P3-P040

A Novel P.Gly775Glu Missense COL1A2 Mutation Causes Severe Osteogenesis Imperfecta in a Prepubertal Girl

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Background: Osteogenesis imperfecta (OI) due to COL1A1 and COL1A2 mutations is the most common cause of primary osteoporosis.

Case Presentation: We present a 10-year-old girl with a history of skeletal fragility, starting in the perinatal period. Her parents are not consanguineous and there is no family history of early osteoporosis. To date, she has sustained nineteen low-energy, long bone fractures and she has skeletal deformities (leg length discrepancy, genu varum and scoliosis), blue sclerae and grey teeth. Her cardiac function and hearing are normal. Her baseline bone mineral density at the age of 2.5 years was low (Z-score L2-L4= -3.4), but normalized while on treatment with IV bisphosphonates, which started at the age of four years. Her orthopaedic management has been challenging, including a right tibial osteotomy and two Ilizarov's procedures for right tibial pseudarthrosis, which was diagnosed while she was on IV pamidronate; femoral fractures treated with flexible intramedullar nails; double open osteotomies of bowed femoral bones with expandable Duvet Fassier nails. Currently she is on a weight bearing procedure after the union of her femoral osteotomies and out of bisphosphonate treatment.

Methods: Sanger sequencing of *COL1A1*/*COL1A2* was reported as negative initially. However, the strong clinical suspicion of OI led to further investigations. Therefore, whole-genome sequencing (WGS) was performed on the index patient and her healthy parents and brother to identify the genetic cause of the disease.

Results: WGS analysis revealed a novel missense mutation in exon 38 of *COL1A2*, NM_000089.3: c.2324G>A (p.Gly775Glu), which was further validated by Sanger sequencing. This genetic finding correlated well with the skeletal phenotype of the patient and was thus classified as pathogenic.

Conclusion: This case provides more insight into the molecular background of OI and the association between genotype-phenotype in this rare disease. It also highlights the possibility of pseudarthrosis in OI under treatment, which is a relatively uncommon, poorly described complication of the disease. Finally, perseverance in solving a diagnostic dilemma is of paramount importance. The possibility of falsely reassuring genetic results should always be taken into account and should lead to further investigations when the clinical suspicion is strong.

P3-P041

SHOX Gene Deletion Screening by FISH in Children with Short Stature and Characteristics of Patients

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Background: Short stature homeobox-containing *(SHOX)* gene that strongly affects height. Due to high prevalence of *SHOX* gene mutations, in all children with unexplained short stature should be investigated to benefit from early growth hormone (GH) treatment. The aim of this clinical study was to determine the rate of *SHOX* haploinsufficiency in short stature patients and describe their anthropometric measurements.

Methods: Between 2010 and 2017, we evaluated eighty six patients (female: 70, male: 16; aged 4.3-18 years) with a clinical diagnosis of short stature, based on inclusion criteria. Clinical abnormalities were presented for patients with SHOX haploinsufficiency.

Results: Three children (three females) out of 86 patients (70 females) had one copy number of the *SHOX* gene, and 83 patients had 2 *SHOX* gene copy numbers, resulting in a rate of 3.6%. 2 of them were were born small for gestational age (SGA). All cases were shorter than the target height, and one of them presented with madelung deformity in clinical examination. Madelung deformity was detected in 3 children, when they were evaluated radiologically. The sitting height/height ratio was found to be within the normal range, while the mesomelia (the diference in arm span and height) was abnormal. Madelung deformity and mesomelic limb shortening were the pronounced clinical features. GH therapy was initiated at a dose of 0.35 mg/kg/week when one individiual was at 7.3 years of age with a height of 107 cm, a height SDS of -3.2, and an annual growth rate of 4.3 cm. Under growth hormone therapy, the growth was 10.2 cm in the first year and 6.2 cm in the second year. The patient responded well to GH treatment for the first two years. Despite the reduction of GH treatment doses,

persistent elevated insulin like growth factor (IGF-1) levels cause the treatment to be stopped.

Conclusion: It is likely that the frequency of Madelung deformity would be even higher if patients were evaluated radiologically. Although SHOX alterations and SGA could overlap due to their high prevalence, SHOX mutations must be taken into consideration at children who did not catch up. Since GH treatment was not well tolerated due to persistent elevated IGF-1, it needs long term evaluations of patients with *SHOX* deficiency.

P3-P042

Pseudoachondroplasia

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Aim: Pseudoacondroplasia is a short extremity dwarfism characterized by lifelong arthralgia and early onset osteoarthritis. At birth there is a normal height and face appearance. At the beginning of walking, first symptom is a swaying walking nature. Typically, at second year of life, short height becomes apparent and leads to a disproportionate short-limb appearance. In childhood, joint pain in the broad joints especially in the lower extremities is common. Degenerative joint disease is progressive.

Case: Ten-year and six-month old male patient admitted to our clinic due to short stature, his knee and hip pain Before admission, he was diagnosed with achondroplasia and given growth hormone treatment, it was learned that after 3 months of growth hormone treatment, it was stopped because of Pertes disease. in his natal history he was a 36-week, 2800 gram born. The mother of patient showed similar characteristics. There were no other short stature history in the family. His chronological age: 10 years 6 months, height age: 5years 3months, bone age: 10 years, weight: 27.9kg(10p),heigth (<3p, -4.65 SD), at physical examination, axilla(-), pubis stage 2, testis volume: 3/3ml. Upper arm: 21.5cm, forearm: 24.5cm, head-pubis: 61cm, pubis-heel : 50.8cm were measured. Brachydactyly, rhizomelia, scoliosis, sway walking, genu varum and lumbar lordosis were present. Previously performed FGFR3 gene analysis revealed normal. On the bone radiography of the patient, irregular epiphysis and metaphysis of long bones, delayed epiphyseal ossification, smallness on femoral head epiphysis, brachydactyly, short metacarpal bones, irregular carpal bones were detected and diagnosed as pseudoachondroplasia. The result of the COMP gene analysis is awaiting.

Conclusion: The diagnosis of Pseudoachondroplasia due to mutations in the cartilage oligomeric matrix protein (COMP), which is autosomal dominant, can be made based on clinical findings and radiological features. The appearance of normal craniofacial appearance, joint hyperlaxity and characteristic radiological findings is separated from achondroplasia. Pseudoacondroplasia should be kept in mind in cases with achondroplasia but with joint aches and hyperreactivity.

P3-P043

Low Level of Vitamin D in Children Increases the Risk of Bone Fractures

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Introduction: The physiological process by which vitamin D regulates calcium and phosphorus metabolism, the major mineral constituents of bone tissue, is by far very well understood. However, the clinical implementation of vitamin D deficiency on bone fragility in childhood remains controversial.

Objective: The aim of this case-control study is to investigate the prevalence of vitamin D deficiency among Lebanese children who experienced a "low-energy" fracture in our center.

Materials and Methods: A total of 38 cases and 70 control patients were included in this study. All healthy children admitted to the emergency department between 1 and 15 years of age were potential candidate for this study. Fracture was confirmed by conventional X-ray radiography and 25-HydroxyVitamin D level of the same candidates was measured.

Results: A total of 20 patients out of the 38 cases were suffering from vitamin D deficiency (25-hydroxyVitamin D < 20 ng/ml), whereas only 13 out of the 70 control candidates were found to have deficiency in vitamin D. A statistically significant relationship between D hypovitaminosis and low energy fractures has been noticed among children between 1 and 15 years of age who presented to the emergency department of Notre-Dame des Secours University medical Center (OR: 4.63; 95% CI: 1.92–11.18; X^2: 12.41, P-value: 0.000428).

Conclusion: A relation has been established between vitamin D deficiency and low energy fractures in Lebanese children. However, the reasons behind D hypovitaminosis, despite sufficient amount of sun light exposure, in Lebanese pediatric population are still to be considered. Furthermore, a larger sample and multicenter study will be needed to determine if a relationship exists between the severity of vitamin D deficiency and the frequency of fractures and their complications.

Key Words: Vitamin D, Low energy fracture, Children

P3-P044

Clinical Evaluation of Eight Patients with Parathyroid Adenoma

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Objective: According to the etiology of hyperparathyroidism, it is divided into primer and secondary (uremic). It usually develops due to CaSR mutation in the infancy period. On the other hand, it usually emerges secondary to a parathyroid adenoma in ado-

lescents. Parathyroid adenomas seen in childhood are commonly associated with familial multiple neoplasia syndromes(MEN). Patients may present with bone pain, proximal myopathy, fractures, renal stone, pancreatitis or they can also be completely asymptomatic. Herein, clinical features of 8 patients with primary and secondary parathyroid adenomas diagnosed in our clinic in the last 2 years are presented and treatment approaches are shared.

Case: Eight children who have been treated with hyperparathyroidism for the last 2 years and who are taking follow-up care have been evaluated. The reasons for referral, hormonal and biochemical evaluation of the patients, and the treatments applied were evaluated. The M/F ratio of the patients is 3/5, and the age ranges are 8-15 years. Attending symptom was abdominal pain in one patient. Three of the cases had secondary hyperparathyroidism due to treatment of hypophosphatemic rickets. The other five were sporadic. None of them had family history or MEN-related clinical findings. All patients had localized adenomas and all but two of them underwent surgery The pathological evaluations were compatible with the adenoma.

Result: Parathyroid gland disease is a rare condition in children, usually present with primary hyperparathyroidism due to a parathyroid adenoma as in our cases. The disease was more common in girls. Most of the patients were asymptomatic. There were no MEN-related findings or family history in presented cases. We tried to take attention to the issue by sharing the experience of our clinic in this rare disease

Keywords: parathyroid adenoma, hyperparathyroidism, hypercalcemia

P3-P045

Idiopathic Hypoparathyroidism in a 10 Year-Old Girl with Concomitant Epilepsy, Long Q-T Syndrome (LQTS), Pericarditis and Pneumonia

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Introduction: PTH is one of the principal regulatory hormones for calcium and phosphate homeostasis. Hypoparathyroidism, caused by reduced parathyroid hormone (PTH) concentration is characterised by hypocalcemia and hyperphosphataemia. Hypoparathyroidism in children can occur either as part of a genetic syndrome, autoimmune disorder, be acquired secondarily to thyroidectomy or some destructive process of the glands. If the reason for decreased PTH concentration is unknown, it is called idiopathic hypoparathyroidism.

Case Presentation: We present a ten-year-old girl who was initially presented to the Department of Paediatric Neurology and Rehabilitation, Medical University of Białystok with convulsions but then after hypocalcaemia was confirmed admitted to the Department of Paediatrics, Endocrinology, Diabetology with Cardiology with suspected hypoparathyroidism. There was no history of candidiasis. In the family history mother had epilepsy and arrhythmias. She was admitted severly unwell with drowsiness and confusion. The physical examination revealed rash on the whole body (propably an allergic reaction to oxcarbazepin), caries, mild dysmorphic features - hyperthelorism. Because of the low PTH concentration (<3 pg/ml) and typical biochemistry (total calcium blood concentration 0.8 mmol/L, plasma phosphate 4.1 mmol/L) hypoparathyroidism was confirmed. Other hormonal analyses showed no thyroid or adrenal gland disorders (TSH, fT4, cortisol, ACTH level normal). Liver and kidney function were normal. Ultrasonography of the thyroid and parathyroids showed a hyperechoic area in the thyroid left lobe (hard in elastography), but no parathyroid pathology. Ultrasonography of abdomen and echocardiography were normal. Long QTc (over 0.5 seconds) was present in the ECG. Hypocalcaemia was initially treated with intravenous and oral calcium, vitamin D_3 and the synthetic precursor of active form of the vitamin D_3 - alfacalcidol. Hyperphosphataemia was treated with sevelamer, - a phosphate-binding drug. She was also treated with valproic acid for epilepsy and hydrocortisone to reduce her allergy symptoms. Calcium remained low and phosphate raised initially despite treatment until sevelamer was added after which calcium and phosphate normalised. During hospitalisation she developed intermittent fever, raised CRP, features of pneumonia and pericardiam effusion. Despite negative blood cultures and no evidence of viral infections, including HIV, B19 parvovirus, influenza virus, many zoonoses and tuberculosis she was treated empirically with antibiotics. PET MRI didn't reveal any pathology.

Conclusions: Coexistence of hypoparathyroidism with pericarditis and pneumonia is unusual. Sevelamer proved useful in correcting the plasma calcium more rapidly than alfacalcidol alone. A diagnosis of idiopathic hypoparathyroidism may sometimes be modified after other typical symptoms following initial presentation.

P3-P046

The Level of the Vitamin D and Bone Mineral Density in Children with Obesity

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Objective: To evaluate bone mineral density (BMD) and its relationship with vitamin D in children with obesity.

Methods: We examined 110 children in the University Hospital (Minsk) from 2015 to 2018 yrs.

Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Body composition with evaluating of mineral component were made by dual energy X-ray absorptiometry with the calculation of feet, hands, spine, ribs, hips BMD (g/cm2), Z-test. The levels of vitamin D were determined.

All children were divided into 2 groups: group 1 - children with obesity (n=75, boys(B)/girls(G)=47/28, age 14,24±2,02 yrs,

BMI 32,7±5,3 kg/m²; group 2– normal-weight control (n=35, B/G=17/18, 14,08±2,47 yrs (p=0,3), 19,4±2,4 kg/m² (p=0,0001)).

Results: Legs BMD were increased in boys with obesity (0,94±0,11g/cm^2 vs 1,13±0,17g/cm^2 (p=0,03)) compared to control group without significant differences in G (1,29±0,12g/cm^2 vs 1,23±0,02g/cm^2 (p=0,5).

Ribs BMD were higher in group 1 children compared to group 2 (B 0,72±0,08 g/cm^2 vs 0,59±0,06 g/cm^2 (p=0,02); G 0,71±0,05 g/cm^2 vs 0,65±0,06 g/cm^2 (p=0,05)).

There were no significant differences in spine BMD (G 1,09±0,11 g/cm2 vs 0,98±0,14 g/cm^2 (p=0,084), B 1,0±0,11 g/cm^2 vs 0,87±0,24 g/cm^2 (p=0,39)); pelvis (G 1,22±0,13 g/cm^2 vs 0,98±0,14 g/cm^2 (p=0,12); B 1,19±0,15 g/cm^2 vs 1,04±0,21 g/cm^2 (p=0,09)); total (G 1,18±0,09 g/cm^2 vs 1,11±0,13 g/cm^2 (p=0,29); B 1,17±0,13 g/cm^2 vs 1,06±0,14 g/cm^2 (p=0,21)) in obese children compared to control.

A significant decrease in vitamin D levels were in obese B compared to control (29,48±4,7ng/ml vs 33,41±2,1ng/ml (p=0,05)); G (24,59±5,7 vs 34,41±3,2 ng/ml (p=0,04)).

Conclusions: A significant increase in ribs and legs BMD and decrease in vitamin D levels were found in children with obesity.

P3-P047

Evaluation of Bone Mineral Density and Bone Metabolism Markers in Hicldren Diagnosed as Celiac Disease

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Introduction and aim: Metabolic bone disorders due to calsium and vitamin D deficiency are one of the most frequent extraintestinal symptoms in Celiac disease. In this study it is aimed to evaluate bone mineral density in patients with Celiac disease during diagnose and evaluate the factors related to bone mineral metabolism.

Material and Method: The study included 43 children diagnosed as Celiac disease between December 2015 and December 2017. Clinical, anthropometric, patological and laboratory (calsiyum, phosphor, alkalenphosphataz (ALP), parathormon (PTH), 25OHvitamin D levels) properties of patients were detected retrospectively. Lumbal (L1-L4) bone mineral density levels measured via DEXA (Dual Energy X-Ray Absorptiometry) were evaluated and Z scores due to cronological age and height age were calculated.

Results: Mean age of 43 patients (34 girl/9 boys) was 9.9±4.8 (2.5-17.7) years. 46.5% of patients were pubertal during diagnose. 30.2% (n=13) was 0-6 years old, 30.2% (n=13) was 7-11 years and 39.5% (n=17) was over 11 years. BMD Z score due to chronological age was -0.83±1.1 (-3.6-1.6) and -0.18±1.1 (-3.6-1.8) due to height age. There were no difference in BMD Z scores due to chronological and height ages (p=0.150, p=0.225, respectively). BMD Z scores due to chronological age was >-1 in 51.2% of the patients (n=22), between -1 and -2 in 34,9% (n=15) and <-2 in 14% (n=6). BMD Z scores due to chronological age <-2 in over 11 age was statistically high (p<0.001). Mean vitamin D level was 13.5±7.7 (4.6-35.1)ng/ml and no relation between BMD Z scores and plasma vitamin D, Ca, P, ALP and PTH levels (p>0.050). There was positive correlation between BMD Z scores due to chronological age and body weight, height and BMI Z scores (p<0.001, p=0.005, p=0.015, respectively).

Conclusion: Higher diagnose ages effects bone mineral density negatively in Celiac disease. Diagnose in early ages decreases bone mineral leak and decreases morbidity in patients with osteopeni and osteoporosis via treatment posibilities.

P3-P048

Comparison of Serum 25-Hydroxy Vitamin D Levels Among Children & Adolescence with Attention Deficit Hyperactivity Disorder and Healthy Iranian People

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Background: Attention Deficit Hyperactivity Disorder (ADHD) is the most prevalent chronic behavioral disorder among children. No definite pathology is yet defined for this disorder and findings are in favor of multifactorial hypothesis.

Aims: This study was performed with the aim of determining the association between vitamin D serum levels and ADHD among 6-14 year-old children referring to Imam Khomeini Hospital Complex during 2014-2015 in Tehran, Iran.

Measurements & methods: This case-control study was performed on 50 healthy and 50 ADHD children. Data was collected in a researcher-made questionnaire. 25-Hydroxy vitamin D levels were measured and documented. Data was analyzed using Chi-square test, independent T-test and Regression by SPSS 19 software.

Results: Mean 25-Hydroxy vitamin D level was 16.57±9.09 ng/ml among ADHD patients and 22.24±12.76 among healthy children. Mean 25-Hydroxy vitamin D level was significantly lower among the case group compared to the control group (p=0.012). Severe Vitamin D deficiency was significantly more prevalent among the case group (p=0.0001). Adequate 25-Hydroxy vitamin D level was significantly more prevalent among the control group (p=0.002)

Conclusion: Hypovitaminosis D is more prevalent among Iranian ADHD children compared to healthy ones. It seems that Hypovitaminosis D is associated with ADHD symptoms as an independent background variable.

Keywords: Vitamin D Deficiency; Attention Deficit Hyperactivity Disorder; Children & adolesence.

P3-P049

Evaluating the Effect of Zoledronic Acid on Treatment of Primary and Secondary Pediatric Osteoporosis at Children's Hospital 1 in Vietnam

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Background: Osteoporosis is a condition of skeletal disorders characterized by compromised bone strength that predisposes to an increased risk of fracture. Osteoporosis is a common disease in adult, especially in postmenopausal women. Nevertheless, pediatric osteoporosis seems to be a rare disease, which increases risk of fracture not only in childhood period but also reach adulthood. Therefore, the role of diagnosis correctly and appropriate treatment at this age group are very important. Treatment of bisphosphonates has been shown to be effective in improving adult bone mineral density (BMD) for more than 25 years, and has been used in pediatric treatment for about 15 years. In this study, we aim to evaluate the effect and safety of Zoledronic acid (ZA) in treatment of primary and secondary osteoporosis in children.

Objectives: To assess the effect and safety of ZA in improving BMD, height, clinical signs and the rate of fractures.

Subjects and method: this is a retrospective case series of 13 children and adolescents diagnosed with osteoporosis at Children's Hospital 1. These patients were followed by checking BMD by Dual-energy X-ray absorptionmetry (DXA) before, during and after treating with ZA every 6-12 months. Height Z-score is calculated base on CDC reference.

Results: Our study included 13 cases, in which there are 6 cases of primary, 7 cases of secondary osteoporosis. The mean patient age was 10.47 years, the youngest was 1 month old and the oldest was 15 years old. There was a significant improvement in BMD after treatment ZA with BMD Z-score before and after was -3.8 and -1.7, respectively (P= 0.03). There weren't any new fractures after treatment. About side effect of ZA, we haven't recorded any side effects during and after ZA infusion. Life quality has been improved significantly; most children no longer complained about bone pain, back pain or limited movement compared to before treatment. However, ZA hasn't show the clearly effect on height with height Z-score before and after treatment was -2.3 and -1.9, respectively (P= 0.89).

Conclusion: Zoledronic acid appears to have some favorable effects in the treatment of primary and secondary osteoporosis in children and adolescents. Intravenous ZA improved BMD, life quality and protected bone from new fractures in both groups of pediatric osteoporosis.

Key words: pediatric osteoporosis, zoledronic acid, BMD

P3-P050

Hypocalcemia Secondary to Maternal Vitamin D Deficiency

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Background: 28 days old baby girl presented to ER with seizure like activity for the last two weeks, breast feeding well and thriving. pasr history full term normal delivery, no neonatal complications and no maternal history apart from iron deficiency anemia.

Case presentation summary :Examination unremarkable, vitals and sugar were stable.intermittent jerky movements of the limbs with no stiffness.

Investigations: calcium 7.4mg/dL,Magnesuim(Mg)0.52mg/dL,phosphate 8.3mg/dL,glucose 90mg/dl.alkpo4 raised and iPth normal.

The bay was initially treated with a loading dose of phenobarbitone and oral calcium.Within 24 hours the serum calcium starts normalizing. The Mg level remained below normal. Serum 25 hydroxyl vitamin D reported less then 12ng/ml.urinary electrolytes were in the normal ranges.renal and cranial ultrasounds reported normal.metabolic and genetic studies were in progress.Maternal vitamin D reported less then 8ng/ml.

Within 24 hours the seizures stopped.serum calcium including the ionized calcium and phosphate levels starts normalizing, the Mg level still low and a mild response to a state dose of magnesuim. The baby was started on the third of the treatment with cholecalciferol and the magnisuim starts normalizing.The mother was started on vitamin D.

Conclusion/ Learning points: This case of hypocalcemia secondary to maternal vitamin D deficiency responded to oral calcium supplements, the Magnesuim starts normalizing after starting the baby on cholecalciferol.The magnesuim levels were not responding to calcium and bolus dose of magnesuim.The vitamin D was started on the third day of treatment because of the risk of bone resorption.

P3-P051

Clinical and Genetic Evaluations of Three Patients with Vitamin D Dependent Rickets Type 1A

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Vitamin D dependent rickets type 1A (VDDR-IA) is inherited in an autosomal recessive pattern and caused by mutations in CYP27B1 gene encoding enzyme 1α-hydroxylase. Deficiency of 1α-hydroxylase leads to decrease of 1,25(OH)2 vitamin D production. VDDR-IA usually manifests clinically during the 1st year of life. Clinical features of VDDR- IA include progressive growth retardation, hypotonia, rachitic skeletal deformities, hypocalcemic seizures in early infancy. Serum profiles show hypocalcemia, hypophosphatemia, secondary hyperparathyroidism and increased alkaline phosphatase activity, the serum levels of 25(OH) vitamin

D are normal or raised while the levels of 1,25(OH)2D are low or undetectable.

We presented here three patients with different features of VDDR- IA. One baby had of lower limb deformities and hypotonia. A 9-month-old male who presented with severe muscle weakness, failure to thrive and skeletal deformities, including multiple fractures and seizures.

A 12 years old girl presented only low body weight and a muscle pain, however, bone deformities were absent.

All patients had classical biochemical data of rickets: hypocalcemia, hypophosphatemia, high serum ALP and elevated PTH. Radiological findings included cupping and fraying of the radial and ulnar metaphyses. A targeted next generation sequencing approach (Ion Torrent platform) was used for sequencing of rickets candidate genes. In all patients were identified mutations in the CYP27B1 gene. DNA sequencing of the patients revealed compound heterozygosity mutations: F80LfsX79 [c.240delT] and N310D [c.928A>G]; R389H [c.1166G>A] and H240PfsX93 [c.718dupC];P74L [c.221C>T] and Q479X [c.1435C>T]. The exon 7, p.R389H mutation has previously been described and identified as disease causing, others were novel. Once alfacalcidol therapy was initiated, the patients showed significant improvement of condition and a correction of deformations. Serum calcium, phosphorous, alkaline phosphatase and parathyroid hormone returned to normal range. In conclusion, we presented patients whith different phenotype of VDDR- IA caused by 1alpha-hydroxylase gene mutations.

P3-P052

A Rare Case of Familial Hypocalcemia

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Objectives: Familial hypocalcemia is a rare autosomal dominant disease characterized by hypercalciuric hypocalcemia. The disorder is caused by heterozygous mutation in the *CASR* gene that encode a calcium-sensing receptor in parathyroid glands and kidney tubules.

Clinical case: The boy was born at term from non-consanguineous parents with normal length and weight. On the second day of life he was admitted to an intensive care department with convulsions. Calcium level was not checked, anticonvulsant drugs were prescribed. Treatment was not effective and generalized convulsions repeated every month. After he turned 2 years old generalized convulsions stopped, but muscle cramps, headache and urinary incontinence persisted. Hypocalcemia (1.62 mmol/l), hyperphosphatemia (3.41 mmol/l) and low PTH (0.57 pm/l) were detected at the age of 6 for the first time. Hypoparathyroidism was diagnosed and alfacalcidol was initiated. At the age of 6.5 he was admitted to our hospital. Chvostek's sign, mild mental retardation, mild growth delay (SDS – 1.69) were observed at the examination. Signs of nephrocalcinosis were found by ultrasound. He had mild hypocalcemia (total calcium 1.96 mmol/l, ionized calcium 0.96 mmol/l), and hypercalciuria (calcium/creatinine ratio was 1.05). Autosomal dominant hypocalcemia was suspected.

The patient's mother didn't have a history of convulsions, but she had mild muscle cramps of arms and legs and episodes of lockjaw. She was found to have hypocalcemia, low PTH and nephrocalcinosis.

Previously undescribed heterozygous deletion c.344-358del in *CASR* was detected in both, the boy and his mother.

Grandparents of the boy had normal levels of calcium and phosphate. Maternal grandmother had a history of kidney stone disease, but the mutation in *CASR* was not found.

Conclusion: Familial autosomal dominant hypocalcemia due to mutations in *CASR* gene is a rare cause of hypocalcemia. Clinical presentation of the disease could be variable within one family.

P3-P053

HDR Syndrome: A Case Report of Hypoparathyroidism, Hearing Loss and Renal Agenesis

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Background: Hypoparathyroidism, sensorineural deafness, and renal disease (HDR syndrome, Barakat syndrome) is a rare condition, caused by a mutation on chromosome 10p which affects the *GATA3* gene. *GATA3* encodes a transcription factor important for the embryonic development of the parathyroid gland, the auditory stem, and the kidneys. Its expression has also been found in the thymus and the central nervous system. A wide range of renal involvement has been reported in the literature - agenesis, hypoplasia, cystic kidneys, vesicoureteral reflux, nephritic syndrome, hematuria, chronic kidney disease and renal failure.

Clinical Case: A 14-year old boy was admitted to Endocrinology department with history of a bilateral sensorineural hearing loss, tic disorder at the age of 11 years, 2 generalized epileptic seizures in the last month, calcification in the basal ganglia imaged on cranial CT. Chovestek's sign was positive. Biochemical tests revealed hypocalcemia: total Ca 5.01 mg/dl (8.6 -10.2), ionized Ca 2.60 mg/dl (4.8–5.5), hyperphosphatemia: 10.04 mg/dl (2.7 - 4.5), parathyroid levels not consistent with hypocalcemia: 20 pg/ml (15-65), levels of ACTH, cortisol rhythm, TSH and fT4 in the reference range. Liver and renal function were normal. Urinalysis did not show proteinuria and hematuria. Urine volume in 24 hours was 1500 mL with normal urine calcium, phosphorus, and creatinine levels. No chromosomal abnormalities were detected on standard G-banding analysis.

Ultrasound of the kidneys revealed absence of the right kidney with a compensatory hypertrophy of the left one. Renal agenesis was subsequently diagnosed by DMSA scintigraphy. Echocardiogram showed normal heart function.

Initial treatment was with parenteral calcium gluconate infusion followed by peroral calcitriol and calcium supplementation. The patient was receiving valproic acid for symptomatic epilepsy.

He was discharged with peroral dihydrotachysterol and a high-calcium, low-phosphorous diet.

Conclusion: HDR syndrome is a genetic disorder with phenotypic variability. Diagnosis is based on the clinical finding. In conclusion, we recommend that, a patient presenting with seizures associated with deafness, should undergo determination of serum calcium, phosphate and parathyroid hormone, as well as renal imaging.

P3-P054

Growth in the Coeliac Disease of the Child

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The aim of the present study was to evaluate growth of celiac disease (CD) patients.

Subjects and methods:

Growth was assessed by:

-Longitudinal study of growth CD patients compared with the subjects studied by Sempé, Pédron.

-Semi longitudinal case-control study. Controls were the brothers and sisters CD patients.

Results:

1. Growth was significantly more delayed in CD patients (103 girls,92 boys) than in Sempé, Pédron subjects. However, evident catch-up growth was noted between 18 and 21 years age.

2. The growth speed was less important during puberty compared to Sempé, Pédron subjects. After 18 age, our CD patients was continued their growth in time where Sempé, Pédron subjects finished their growth.

3. When CD was associated with Diabete type 1, growth was significantly more delayed than in the CD isolated or diabetes patients isolated.

4. The semi-longitudinal study: The mean adult height was: 158, 42 ± 6, 3 cm (269 women CD) vs 162, 17 ± 6, 3 cm (193 controls :p<0, 0001). The mean adult height was 170, 28 ± 7, 5 cm (194 men CD) and 172, 53 ± 6,8 cm (200 controls: p < 0.09).

Conclusion: growth,and adult Height are delayed especially in the CD girls. Among the factors influencing growth, there the auto immuns diseases associated.

P3-P055

The British OsteoNEcrosis Study: A Multi-Centre Prospective Study

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Introduction: Osteonecrosis can be a debilitating consequence of treatment for acute lymphoblastic leukaemia (ALL), most commonly affecting patients aged between 10 and 20 years at diagnosis of malignancy. Patients may have asymptomatic lesions that spontaneously regress, and little is known about the natural history of lesions. There is also limited understanding of the relationship between osteonecrosis and other markers of bone health.

Aims: The aims of the British OsteoNEcrosis Study (BONES) are to determine:

- The incidence of symptomatic and asymptomatic osteonecrosis in patients aged between 10-25 years undergoing treatment for acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma, and variation in incidence at different time points in their treatment
- Risk factors for progression and development of symptomatic osteonecrosis in this population
- Specific radiological features predicting for progression or regression of osteonecrosis, with validation of a classification system for osteonecrosis
- Vertebral fracture incidence and bone mineral density in these patients

Study Design: BONES is a multi-centre prospective, longitudinal cohort study based at tertiary children's hospitals around the UK.

Research Population: Patients aged 10 to 25 years with a first diagnosis of acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma.

Anticipated recruitment: 50 patients over 2 years

Methodology: Magnetic resonance imaging of lower limbs for assessment of osteonecrosis within 4 weeks of diagnosis, at the end of delayed intensification, and 1, 2 and 3 years after the start of maintenance therapy. Physiotherapy assessment will occur at the same time-points, with completion of the child health assessment questionnaire. Additional collection of clinical and biochemical data will include demographic information, prognostic and diagnostic data, BMI and phase of puberty, bone and lipid profile, PTH and vitamin D status.

Bone mineral density and lateral vertebral assessment will be assessed at diagnosis and annually thereafter to a total of 4 assessments.

Data analysis: A central review panel will assess MRI and DXA assessments. Vertebral fracture prevalence will be assessed using the Genant semi-quantitative method.

Chi squared tests will be used for categorical variables to compare baseline characteristics between patients with and without osteonecrosis. The two sample t-test will be used for continuous variables with a normal distribution and the Mann-Whitney U test will be used for continuous variables with a skewed distribution. We will examine effect modification by risk factors such as age, sex, ethnicity and risk group by performing stratified analyses.

Ethics: ethical approval has been obtained: REC ref: 16/YH/0206

P3-P056

Response to Pamidronate Therapy and Pharmacogenetics in Patients with Osteogenesis Imperfecta

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Introduction: Osteogenesis imperfecta (OI), is a genetically heterogeneous connective tissue disorder associated with skeletal fragility, deformity, and growth deficiency. Intravenous bisphosphonate therapy is the mainstay of medical treatment of this condition. Given the paucity of data from Asia we sought to evaluate the genetic epidemiology and the response to pamidronate therapy in a cohort of Malaysian patients.

Method: Genetic analysis was performed in 29 children with OI [Type I n = 4, Type III n = 16, Type IV n = 4 and Type V n = 3) from the UKM Medical Centre (UKMMC) and Putrajaya Hospital. 25 patients were on pamidronate treatment. Clinical, biochemical and radiological data was collected prior to and at several times during treatment. Targeted sequencing of genes was performed using the Ion AmpliSeq in the Ion Torrent^{TM} semiconductor sequencer to identify the mutations. The identified mutations were validated using Sanger sequencing and *in silico* analysis was performed to evaluate the effects of the candidate mutations at protein level.

Results: Genetic analysis revealed that 62% of patients had mutations in collagen genes, 48% (n=14) in *COL1A1* and 14% (n=4) in *COL1A2*. 8 had mutations in *IFITM5*, *BMP1*, *P3H1* and *SERPINF1* and no mutations were discovered in 3 patients. Treatment was started at a median age of 4.8 [1.9–7.6] years. At the end of the observation period, the median duration of therapy was 5.3 [3.9–7.2] years. The fracture rate was reduced for all OI types during treatment ($p < 0.05$). Height SDS scores did not significantly change during pamidronate therapy. Patients with haploinsufficiency mutations had a milder phenotype as compared to those with qualitative mutations. In the group of patients with helical mutations, the type of alpha chain affected did not influence the fracture rate.

Conclusion: Cyclic pamidronate administration reduced the fracture rate effectively in patients with all types of OI. Patients with qualitative mutations had a more severe clinical course.

P3-P057

Results of 22 Weeks of Burosumab Therapy in a Patient with Severe Bone Deformities Due to XLH

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X-linked hypophosphatemic rickets (XLH) is the most common form of hereditary rickets. It is caused by inactivating mutations in the PHEX gene (phosphate-regulating-endopeptidase-analog, X-linked), leading to increased fibroblastic growth (FGF-23) levels, responsible for the renal phosphate wasting. This results in hyperphosphaturia and hypophosphatemia, and altered bone mineralization, in the absence of vitamin D deficiency. Classical treatment consists on oral supplementation of phosphate and bioactive forms of vitamin D. Recently, the European Medicines Agency approved the use of Burosumab, an anti-FGF-23 monoclonal antibody, in patients older than one year with radiographic signs of bone disease.

We present the case of a 6-year-old male patient, attended initially at the age of 21 months, for severe genu varum and radiographic signs of rickets.

The tests performed revealed normocalcemia and normomagnesemia, with hypophosphatemia (2.2mg/dl, NV 3,8-7,5), hyperphosphatasemia (539 U/l, NV 40-462) and decreased tubular phosphate reabsorption (TPR) in 24-hour urine (70%; NV >85%), without hypercalciuria (3mg/kg/day, NV <4 mg/kg/day), increased levels of intact PTH (77pg / ml, NV 15-65) and $1,25(OH)_2$-Vitamin D (106 pg/ml; VN 16-56) with normal 25 (OH)-vitamin D (24.9) ng / dl; VN 21-100), and normal lumbar bone densitometry (Z score -0.1 SDS).

Plasma FGF-23 levels were markedly increased (>427 RU/ml; NV <145), and genetic testing confirmed the clinical diagnosis, showing a mutation in exon 6 of PHEX gene in hemicigosis.

He received conventional therapy for 4 years, with adequate adherence, with no clinical or biochemical response, requiring hemiepiphysiodesis of the distal femur and bilateral proximal tibia due to significant deformity, which rendered no positive results and were eventually removed.

He started burosumab therapy at 0.8 mg/kg every 15 days due to an early access program. No local or systemic adverse events appeared. He has now completed 22 weeks of therapy and there has been an improvement in phosphorus levels (3.5 mg/dl), phosphatases (326 U/L) and TPR (98%), correction of hyperparathyroidism, as well as an improvement of the lower limbs deformities and bone density gain (Z-score 1.8 SDS).

In addition, the family refers improvement in quality of life, with greater mobility and less effort to perform physical exercise.

In our case, burosumab therapy has been effective clinically and biochemically, with no adverse events up to date. However, the follow-up is still too short to evaluate long term benefits and clinical outcome.

P3-P058

Severe Neonatal Hypercalcemia: A Challenging Case

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Neonatal severe hyperparathyroidism (NSHPT) is a rare autosomal recessive disorder due to inactivating mutations of calcium-sensing receptor. These receptors are vital in calcium homeostasis and are expressed in a number of tissues such as parathyroid glands, renal tubules and bone. Homozygous mutations lead to severe hypercalcemia and life-threatening bone demineralization if untreated.

A neonate born to 2nd degree consanguineous parents presented with poor feeding and low-grade fever at day 10 of life. At presentation, he had 30% weight loss and moderate dehydration. He was lethargic and hypotonic. His perinatal period was uncomplicated. A negative septic screen prompted evaluation for electrolyte abnormalities, which revealed an albumin-corrected calcium (Ca) of 7.4 mmol/L (normal: 2.2-2.7 mmol/L). Further, serum phosphate was low and alkaline phosphatase normal. In the absence of subcutaneous fat necrosis, and a typical presentation, NSHPT was clinically suspected, which was supported by an elevated PTH (403 pg/ml, normal 4-72 pg/ml) and radiological evidence of periosteal erosions. Family screening revealed normocalcemia and normocalciuria.

Immediate management involved hyper-hydration and intravenous furosemide, following which Ca dropped to 6.8 mmol/L. Calcium dropped dramatically to 4.8mmol/L after the administration of 0.75mg/kg intravenous pamidronate in divided doses.

At 6 weeks of age, Cinacalcet was started at 5mg daily due to persistent hypercalcemia and gradually increased to 20mg bid (12mg/kg/d). There was negligible response to cinacalcet and a 2nd dose of pamidronate was required. Due to symptomatic severe hypercalcemia, total parathyroidectomy with re-implantation of half a gland under the left biceps muscle was performed at 3 months of age. Perioperative frozen sections helped to identify the parathyroid glands. Histology revealed parathyroid hyperplasia. Intravenous calcium was started during the perioperative period. Calcitriol and calcium carbonate was added once oral feeds were commenced.

Preoperative PTH was 1744pg/ml and post-op PTH on D1 was undetectable. One month after surgery PTH had increased to 9pg/ml and regular PTH testing showed a steady increase. Calcium supplements were gradually tailed off and omitted 6 months after surgery.

Twelve months after surgery PTH is 34 pg/ml and there is no evidence of hyperplasia of the re-implanted gland. The 16-month infant is currently having normal growth and neurodevelopment without the need for any medications.

This case of NSHPT awaits genetic confirmation. NSHPT is a rare cause of a common neonatal presentation. It can be fatal if not promptly recognized and treated.

P3-P059

Assessment of Vitamin D Status in Healthy Pre-Pubertal Egyptian Children

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Background: Despite a shining sun all through the year, vitamin D deficiency is still prevalent in Egyptian children which suggests a relative resistance to vitamin D in Egyptian population.

Aim: To assess 25(OH)D status in healthy pre-pubertal Egyptian children and to relate its levels to anthropometric parameters in these children.

Methods: Sixty healthy children aged between 3 and 10 years coming to the Outpatient clinic, Children's Hospital, Ain- Shams University for minor complaints were randomly recruited in the study. Children having any form of rickets, or any chronic illness, those receiving any medications that might interfere with vitamin D absorption or those receiving calcium and/or vitamin D therapy in the last 6 months prior to study were excluded. All were subjected to history taking, anthropometric measurements and measurement of serum calcium, phosphorus, alkaline phosphatase, 25(OH)D and parathyroid hormone.

Results: The median hours of sun exposure per week was 7 hours/week. Forty five cases (90%) had 25(OH)D deficiency, 4 (6.7%) had insufficiency and only 2 (3.3%) had adequate 25(OH) D levels. Vitamin D levels were not affected by the duration of exclusive breast feeding (p= 0.617). There was a significant positive correlation between serum 25(OH)D and hours of sun exposure per week and percentage of body exposure to the sun.

Conclusion: Vitamin D insufficiency and deficiency are common among Egyptian pre-pubertal children which may be due to vitamin D receptor polymorphism.

P3-P060

Are Caucasian Children at Risk of Sub-Optimal Vitamin D Levels?

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Background: Low vitamin D levels have been linked to stunted growth and lower bone mineral density. Vitamin D insufficiency is a recognised condition in children in the UK. However, optimal levels of vitamin D are not adequately defined and guidance regarding supplementation is also limited.

Aim: To identify vitamin D levels in a select cohort of Caucasian children aged 0-16 years, and describe how preterm birth, obesity, age and malabsorptive conditions correlate with sub-optimal levels.

Methods: We obtained 368 25(OH)D test results conducted over 8 months from electronic records at Royal Cornwall Hospital. 314 results were screened for demographic and clinical factors, and vitamin D status. The vitamin D levels are defined as deficient at

<25 nmol/l, insufficient between 25 and 50 nmol/l and sub-optimal between 50 and 75 nmol/l.

Results: Insufficient vitamin D levels or lower were identified in 40.46% of the cohort and 75.19% had sub-optimal levels or lower. The mean vitamin D level across the cohort was 58.27 nmol/l. Mean vitamin D levels were 70.41 nmol/l in children aged 0-4, 58.30 nmol/l in children aged 5-10 and 50.26 nmol/l in children aged 11-16 (p<0.001). In overweight children, there was a weak negative correlation of -0.2 between BMI and vitamin D levels. 9.68% of children born preterm had vitamin D deficiency compared to 4.17% of children born at term. Optimal levels were found in 35.48% of preterm children and 24.31% of those born at term. There was no significant difference in insufficient or lower vitamin D levels between children with (36.98%) and without (43.27%) malabsorptive conditions. A high prevalence of sub-optimal vitamin D levels or lower (82.35%) were noted in children with cystic fibrosis in spite of supplementation.

Conclusions: The prevalence of insufficient and sub-optimal vitamin D levels in Caucasian children was higher than previously reported. Our study found that adolescents and overweight children are at risk groups for sub-optimal or lower vitamin D levels. Lower levels in patients with cystic fibrosis may be explained by non-compliance to supplementation. Supplementation with regular review could be extended to these groups.

P3-P061

Incidence Rate of Vitamin D Deficiency in 12-Year Old Children in Japan

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Back ground: The incidence rate of vitamin D deficiency is increasing throughout the world in recent years, but the rate of vitamin D deficiency in Japan is unknown.

Aims: We measured the incidence rate of vitamin D deficiency in 12-year old children in Japan.

Methods: A total of 492 children (247 boys and 245 girls) from one Japanese community enrolled in this study. At age 12, 25 hydroxyvitamin D (25OHD) were measured in all children by using radioimmunoassay. The levels of intact parathyroid hormone (iPTH), calcium (Ca), phosphorus (P), albumin (Alb), alkaline phosphatase (ALP) and fibroblast growth factor 23 (FGF23) were also measured in the subjects who shows low 25OHD level (≦20 ng/ml).

Results: 25OHD levels were significantly lower in girls (20.9±3.1 ng/ml) than in boys (22.2±3.3 ng/ml) (p<0.0001). The number of subjects who showed vitamin D deficiency (<20mg/ml) were 74 (30.0%) in boys and 111 (45.3%) in girls and severe vitamin D deficiency (<15ng/ml) were 3 (1.2%) in boys and 8 (3.3%) in girls. The levels of iPTH, Ca, P, Alb, ALP and FGF23 in subjects who showed vitamin D deficiency were 22.3±8.9 pg/ml (range 4~74 pg/ml), 9.5±0.4 mg/dl (8.3~10.7 mg/dl), 4.7±0.6 mg/dl (3.3~6.1 mg/dl), 4.6±0.3 g/dl (3.5~5.2 g/dl), 918.3±340.1 U/l (200~1834 U/l) and 46.5±58.2 pg/ml (12~740 pg/ml), respectively. Only one subject whose 25OHD level was 16 ng/ml showed some little higher levels of iPTH (74 pg/ml) and ALP (1484 IU/L), but normal levels of Ca and P.

Conclusion: We show that 38% of Japanese 12-year old early adolescents suffer from vitamin D deficiency. Findings from this study indicate that vitamin D deficiency requires close oversight in public health during adolescence.

P3-P062

Idiopathic Juvenile Osteoporosis: Common Symptoms in an Uncommon Condition

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Introduction: Osteoporosis in children and young people can be primary due to Osteogenesis Imperfecta (OI) or secondary to chronic disease. We report 2 patients with Idiopathic Juvenile Osteoporosis (IJO), a rare primary osteoporotic disorder

Case 1: A 12 year old boy presented with 12 months of lower back pain and stiffness, against a background of chronic pain in knees, wrist and ankles. There was no history of fractures or systemic disease. Examination revealed normal anthropometry [height 154.1cm (+0.42SDS), weight 38.3kg (+0.09SDS)] and prepubertal status. He had mild tenderness over the thoracolumbar spine, knee and ankle joints but no limitation of movement. He had no skeletal/extra skeletal manifestations of OI. X-ray and MRI of the spine revealed multiple thoracic vertebral compression fractures [T6-T10]. DEXA scan revealed a low lumbar spine bone mineral density (BMD) Z-score of -3.2. Further investigations ruled out secondary causes of osteoporosis. Iliac crest bone biopsy showed high turnover osteopenia, increased osteoid surface with no definite mineralization defect and was predictive of responsiveness to bisphosphonate therapy. He was commenced on intravenous zoledronic acid.

Case 2: A 14 year old boy was referred with severe back pain of subacute onset. He had several childhood fractures (wrist, ribs and navicular bone) and limb pains for 6 years prior to presentation. Examination revealed normal height [158 cm, +0.3SDS), excessive weight [100kg, +2.9 SDS) and signs of early puberty. MRI spine showed loss of height of T7 to L1 vertebrae. DEXA scan showed a lumbar spine BMD Z-score of -2.8. Investigations for secondary osteoporosis were normal and genetic testing was negative for common mutations in *COL1A1/COL1A2*. Bone biopsy showed adynamic bone with reduction in thickness of the cortices, osteoblast and osteoclasts. He received intravenous pamidronate therapy with symptomatic relief. Repeat DEXA scans after 1 and 3 years showed improvement in BMD Z-scores to -1.1 and +0.4 respectively. He is maintained on oral risedronate therapy.

Conclusion: IJO is a diagnosis of exclusion based on clinical and histological findings. Non-specific symptoms can lead to delay in the diagnosis. It should always be considered in the differential

diagnosis of pre- and peri-pubertal adolescents with chronic back/bone pain in the absence of other causes. Bone biopsy is an important part of the diagnostic workup, however histology can be variable. Early diagnosis and appropriate therapy with bisphosphonates can promote bone remodelling thereby alleviating chronic pain and morbidity.

P3-P064

Hypercalcemia Associated with Increased Parathyroid Hormone-Related Protein(PTHrP) in a Patient with Medulloblastoma Successfully Treated with Pamidronate

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We report a patient with medulloblastoma showing severe hypercalcemia and a raised PTHrP serum level. He was a 19-year-old with a history of recurrent medulloblastoma. He developed constipation, lethargy and altered mentality for 3 weeks. There was no family history of hypercalcemia. Laboratory test revealed hypercalcemia of 18.2 mg/dL. PTHrP increased to 10.7 pmol/L (normal range: < 1.1 pmol/L), whereas serum level of intact parathyroid hormone was suppressed to 5 pg/mL (normal range: 15-65 pg/mL). Intoxication of 25-hydroxy-vitamin D3 and 1,25-dihydroxy vitamin D3 was also excluded. After the diagnosis of humoral hypercalcemia was made, single dose of intravenous pamidronate (1mg/kg) was injected to patient with massive hydration. After 3 days, level of serum calcium was normalized. After 7 days hypocalcemia which was one of the complications of bisphosphnates developed. Although long-term efficacy and safety data are insufficient, bisphosphonates can be effective treatment for humoral hypercalcemia associated with malignancy.

P3-P065

A Novel Deletion Mutation in the GLUT 2 Gene in a Patient with Fanconi Bickel Syndrome

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Glucose transporter 2(GLUT2), a transmembrane carrier protein that facilitates glucose movement across cell membranes, is an essential protein in carbohydrate metabolism. Mutation of SCL2A2 gene, which encodes this transporter, leads to a rare well-defined entity called glycogen storage disease type XI (GSD XI) also known as Fanconi Bickel syndrome. The result of this defect is hepatomegaly, proximal tubular dysfunction, fasting hypoglycemia, glucose intolerance, failure to thrive and rickets. In this report, we describe a 4 year old Iranian boy who presented dramatic exacerbation of these conditions as noted.

Since this syndrome is caused by mutations to the *SLC2A2* gene and is inherited in an autosomal recessive mode, Informed consent for genetic analysis was obtained from the patient. Genomic DNA was extracted from peripheral blood samples of the patient and was used for PCR direct sequencing analysis of all of the coding regions and of the exon/intron boundaries of the SLC2A2 gene. This analysis showed in frame deletion of 3 bp in exon 3 (c.115_117delATA: p.Ile39del). In order to give accurate genetic counselling, cosegregation analysis of this variant in all the family members and Sanger sequencing in 100 ethnicity- matched control subjects were performed. The result revealed that this variant more likely to be pathogenic. As we know this Single Nucleotide Polymorphism (SNP) has been reported with no clinical significance in database and literature.

P3-P066

A Case of Turner Syndrome with Graves' Disease and Primary Hyperparathyroidism

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A 12-year 8-month-old girl visited our hospital due to short stature. Her height was 130.7cm (-3.6SD), and her weight was 42 kg (-0.24 SD). She had cubitus valgus and breast budding (Tanner stage II) without a webbed neck, congenital heart anomaly, exophthalmos, or goiter. Laboratory results in serum were as follows: Ca 10.3 mg/dL, LH11.7 mIU/mL, FSH37.7 mIU/mL, estrogen 18.6 pg/mL, IGF-1 304 ng/mL, and bone age 12 years and 0 months. All other laboratory findings including thyroid function testing were normal. Peripheral lymphocyte analysis using the G-band technique revealed the following karyotype: 46,X, del(X)(p11.1).

When the patient was 13 years old, she was treated with growth hormone(GH) for 3 years and 9 months. Her height reached 146.6 cm (-2.2 SD). Menarche began spontaneously at the age of 14 years and 2 months, but her cycle was irregular and gradually disappeared. At the age of 17 years and 1 month, she was given Kauffman therapy. At the same time, she showed slight bilateral exophthalmos and a moderately sized goiter. The diagnosis of Graves' disease was established by serum findings as follows: TSH < 0.005 μIU/mL, (fT_4 3.49 ng/mL) T_3 3.00 ng/mL, and TSAb 624%. Upon treatment with methimazole, her laboratory findings fell within normal limits. At the age of 20 years, her laboratory data in serum were as follows: Ca 10.6 mg/dL, P 3.3 mg/dL, intact parathyroid hormone (iPTH) 105 pg/mL; she had no symptoms of hyperparathyroidism. We followed her condition closely and noted an increase in serum Ca and iPTH to 11.1 mg/dL and 103 pg/mL, respectively. Swelling of a tumor involving the upper left parathyroid gland was identified by cervical ultrasonography and scintigraphy. The tumor(399mg in weight) was resected and pathological analysis revealed an adenoma. She was diagnosed with primary hyperparathyroidism (PHP). After parathyroidectomy, her serum Ca and iPTH levels normalized.

There have been no reports of Turner syndrome with Graves' disease and PHP. In our case, Graves' disease developed after treatment with growth hormone, and associated PHP was subsequently confirmed.

PHP can sometimes present as part of multiple endocrine neoplasia type 1 (MEN1). Our case is not concomitant with MEN1 presentation. Moreover, there was no history of endocrine disorders associated with MEN1 in our patient's family.

P3-P067

Neonatal Hypocalcemia Revealing a Malignant Osteopetrosis

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Background: A one-month girl was referred to our unit for hypocalcemia. She was the first child of healthy non-consanguineous parents. Her family history was unremarkable except a miscarriage in the mother and oligoasthenospermia in the father that justified a medically assisted reproduction. She was born eutrophic at term after a pregnancy marked by a moderate gestational diabetes. On day 3, a routine neonatal screening revealed a severe asymptomatic hypocalcemia (total calcium: 1.6 mmol/l). According to neonatal unit protocol, an oral treatment with calcium gluconate 200 mg/d and calcitriol 10 drops/d was started.

Laboratory investigations on day 7 showed persistent hypocalcemia (total calcium: 1.89 mmol/l), phosphatemia at lower limit (1.4 mmol/l), normal alkaline phosphatase levels (223 UI/l), and low urinary calcium/creatinine ratio. Serum PTH levels were high (429 pg/ml), consistent with secondary hyperparathyroidism, and were associated with normal 25-hydroxyvitamin D (25OHD) level (30 ng/ml), and high 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) level (342 pg/ml).

Skeletal survey revealed the association of rickets with metaphyseal impairment and focused osteocondensation lesions on skull basis, limbs, and vertebrae, suggestive of osteopetrosis.

Genetic analysis found combined heterozygous mutation in the TCIRG1 gene, confirming a malignant neonatal osteopetrosis.

Evolution and management: Given the high levels of $1,25(OH)_2D$, calcitriol treatment was stopped and substituted by colecalciferol.

On day 45, asthenia, pallor, and purpuric lesions were noted and CBC confirmed bicytopenia with anemia (9.2 g/dl) and thrombocytopenia (17 G/l).

Moreover, because of eye tracking defect, investigations are underway to rule out an optic nerve compression.

As TCIRG1 encodes a proton pump and cause osteoclast dysfunction, stem cell transplantation has been shown to be an effective treatment and was performed in our patient at 3 months of age.

Conclusion: Malignant osteopetrosis is a rare disease (estimated incidence of 1/200,000 live births) due to defective resorption of immature bone by osteoclasts. Paradoxal hypocalcemia can be the first sign of the disease as osteoclasts are unable to release calcium from bone. Without stem cell transplantation, the evolution can be fatal. Early diagnosis is required to perform stem cell transplant before neurosensorial impairment.

P3-P068

Frontal Behavior Dysfunctions Revealing a Dramatic Progression of Complex Cranial Base Abnormalities in a Severe Osteogenesis Imperfecta

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Background: In our bone unit, we were following since their younger age, two brothers with a severe osteogenesis imperfecta. We had no genetic confirmation but the severity of the disease combined with unaffected consanguine parents argues for a recessive autosomal transmission. Both present with highly severe form of osteogenesis imperfecta: repeated vertebral and peripheral fractures, long bone deformations, centromedullary nails on the lower limbs, major motor handicap and disability (wheelchair), cyphoscolisois and severe growth retardation below – 3 standard deviation score.

Our Case: The younger boy had received treatment with bisphosphonates since the first year of life, associated with vitamin D supplementation, and with intensive physical rehabilitation. At fourteen years old, bisphosphonates reached their limits: repeated untraumatic fractures, delayed fracture healing, osteosynthesis material loosening. We confirmed a growth hormone deficiency. The cerebral MRI showed pituitary hypoplasia and asymptomatic craniocervical junction abnormalities. Basilar impression was associated to clivus malposition and brainstem deformation. The medullar MRI showed known vertebral fractures and scoliosis. We stopped bisphosphonate and started nocturnal enteral nutrition and growth hormone treatment in order to improve bone mass and strength.

Evolution: During 2 years, no fracture occurred. Nutritional status was better. At the age of sixteen years old, he presented behavioral troubles: disinhibition, motor instability, stereotypies, sphincter dysfunctions. Neurological examination was normal, especially without headache, or visual impairment, no sign of cranial hypertension, or pyramidal syndrome. However ophthalmologic examination revealed papilledema.

TDM survey: The cerebral TDM showed an important triventricular hydrocephalia and basilar impression.

Treatment: We stopped growth hormone treatment. A ventriculostomy was performed. It was well tolerated and improved the frontal behavior.

Conclusion: In that family, the phenotype concerning the skull basis seems different. While treated earlier, the younger boy had a worst evolution curse and more complex abnormalities. Usually phenotype is the same in the same family. Early bisphosphonate treatment did not protect that child from such a complex and unusual cranial base abnormalities. Neurological examination and behavioral evaluation are essential in severe osteogenesis imperfecta. Ophtalmologic examination and cerebral imaging must be performed in frontal behavior dysfunction.

P3-P069

Ionized Calcium and 25-Hydroxyvitamin D_3 in Children with Steroid-Sensitive Nephrotic Syndrome

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Introduction: Nephrotic syndrome (NS) is one of the most frequent glomerular pathological conditions seen in children. The International Study of Kidney Disease in Childhood (ISKDC) reported that 84.5% of children with idiopathic nephrotic syndrome (INS) had minimal-change nephrotic syndrome (MCNS). Complications of INS may arise as a result of the disease itself or secondary to treatment. The chief complications of NS are infection, followed by thromboembolic events. Other disease-associated complications include hypovolemic crisis, cardiovascular complications, acute renal failure and hormonal and mineral alterations (e.g. hypothyroidism, and bone disease).

Objective: To study the level of serum ionized calcium during the active stage and after remission in steroid-sensitive nephrotic syndrome (SSNS) patients and 25-hydroxyvitamin D_3 (25-OHD) and parathyroid hormone (PTH) during the active stage of the disease.

Subjects & Methods: Twenty children with first episode of SSNS attending Alexandria University children's hospital were investigated, compared to 20 healthy children as a control group. Serum ionized calcium, serum 25-OHD, PTH, phosphorus, alkaline phosphatase (ALP) were measured during the active stage of the disease and serum ionized calcium was repeated after remission.

Results: Children with active SSNS had low ionized calcium and low serum 25-OHD levels, with high PTH, high phosphorus and low ALP levels versus controls. All patients had 25-OHD deficiency of which 80% were severely deficient. Both serum ionized calcium and 25-OHD had a significant negative correlation with PTH ($r = -0.655$, $p = 0.002$) and ($r = -0.575$, $p = 0.008$) respectively. Serum ionized calcium was negatively correlated to spot protein/creatinine ratio in urine ($r = -0.565$, $p = 0.009$). Levels of serum ionized calcium during the active stage of the disease were markedly lower than that after remission. However, both were significantly lower than the control group.

Conclusion: Children with SSNS are at risk of vitamin D deficiency and hypocalcemia, therefore further studies will be needed to prove the need of vitamin D supplementation to prevent the occurrence of possible complications, e.g tetany or bone abnormalities.

P3-P070

Hypercalcemia Due to Six Newly Identified Inactivating Mutations in the CaSR Gene

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Introduction: Heterozygous inactivating mutations that occur in the calcium sensing receptor (CaSR) gene often lead to benign mild to moderate and parathormone (PTH) dependent familial hypocalciuric hypercalcemia (FHH). Neonatal severe hyperparathyroidism is a clinical condition that develops due to homozygous inactivating mutations in the CASR gene and results in severe, life-threatening hypercalcemia. In this study, we aimed to discuss the differences in clinical, genetic, laboratory findings and treatment needs of six cases in which we detected inactivation mutations in the CASR gene in the etiology of hypercalcemia.

Patients and Methods: There were no reports of drug use in six cases referred to the endocrinology polyclinic because of hypercalcemia. In these cases, hypocalciuria was detected and familial hypocalciuric hypercalcemia was considered. Novel mutations were detected in six patients. Parathyroidectomy was performed on the patient with severe hyperparathyroidism in the newborn due to continued hypercalcemia despite intravenous hydration, bisphosphonate and cinacalcet administration Pamidronate disodium was given to two patients for a short time and mild hypercalcemia was observed in their follow-up In the other three cases, there was mild hypercalcemia and no bisphosphonate treatment. The general and clinical characteristics, laboratory and genetic results of the cases are shown in table 1.

Conclusion: Neonatal severe hyperparathyroidism can lead to life-threatening clinical and laboratory findings. Inactivated homozygous mutations in the CASR gene is resulted, severe hyperparathyroidism in the newborn, and the response to medical treatment may vary according to the mutation type. In our case, the newly identified mutation was clinically severe and parathyroidectomy was performed. Surgery should be performed at experienced centers without delay when medical treatment is ineffective. All of the mutations detected in six cases with familial hypocalciuric hypercalcemia were identified newly. Clinical findings and medical treatment needs of the cases were observed to vary according to the type of mutation.

Table 1. (for Abstract no P3-P070)

Age at diagnosis	Gender	Ca (mg/dl)	P (mg/dl)	ALP (U/L)	PTH (pg/mL)	25(OH)D3 (ng/mL)	Urine Ca/Cr	Mutation	Treatment
7 day	M	24.2	3.6	282	1043	33	0.01	p.N207Kfsx42 (Homozygous)	Bifosfonat, cinacalcet, parathyroidectomy
4 month	F	14.6	3.8	187	41	13.6	0.02	p.N867S (Heterozygous	Bifosfonat
11 month	F	11	3.9	211	90	33.7	0.15	p.Glu612del (Heterozygous)	Diet
22 month	F	11.3	4.4	227	24	23	0.076	p.Leu655pro (Heterozygous)	Diet
33 month	F	13.9	3.4	199	60	35.4	0.008	p.Glu612del/ p.Asn90Thr (compaund heterozygous)	Bifosfonat
13 year	M	11.7	3.6	308	108	26	0.02	p.602delE (Heterozygous)	Diet

Diabetes & Insulin P1

P1-P040

Poor Metabolic Control in Children and Adolescents with Type 1 Diabetes and Psychiatric Comorbidity

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Objective: Type 1 diabetes in childhood is associated with an increased risk of psychiatric morbidities. We investigated predictors and diabetes outcomes in a pediatric population with psychiatric comorbidities.

Research Design and Methods: Nationwide pediatric registerbased study. Data from the Danish national childhood diabetes register (DanDiabKids) and The National Patient Register were collected (1996–2015) for this population-based study. We used Kaplan–Meier plots to test whether age at type 1 diabetes onset and glycated hemoglobin (HbA1c) levels during the first 2 years following onset were associated with the risk of psychiatric disorders. Mixed-effects linear and logistic regression models were used with HbA1c, BMI, severe hypoglycemia, or ketoacidosis as outcomes and psychiatric comorbidities as explanatory factors.

Results: In total 4,730 children and adolescents (52.1% boys) with type 1 diabetes were identified in both registers. The mean age at onset of diabetes was 8.98 years (3.81 SD), birth year ranged from 1979–2013, mean duration of diabetes at last visit was 5.95 years (3.65), 93.85% were of Danish ethnicity, and 5.37% were immigrants or offspring of immigrants.

Among children and adolescents with type 1 diabetes, 1035 (21.9%) were also diagnosed with a psychiatric disorder within the observational period. High initial HbA1c levels predicted higher risk of psychiatric morbidity. Patients with psychiatric comorbidity had higher HbA1c levels (0.21% [0.14; 0.28] (2.32 mmol/mol [1.56; 3.08]) ($p < 0.001$)) and an increased risk of hospitalization with diabetic ketoacidosis 1.76 [1.17; 2.65] ($p = 0.007$). HbA1c levels were highest in patients with potentially reactive psychiatric disorders, e.g., anxiety, mood, behavioral, and eating disorders (0.28% [0.19; 0.36] (3.06 mmol/mol [2.12; 3.99]) ($p < 0.001$)). Children with neurodevelopmental/constitutional psychiatric disorders were not found to have higher HbA1c levels. We found no associations with BMI or hypoglycemia.

Conclusions: We found that high HbA1c levels in the period immediately after type 1 diabetes onset was a possible indicator for subsequent psychiatric disorders, and that having a psychiatric disorder was associated with an increased risk of poor metabolic outcomes, especially in patients with potentially reactive disorders. An increased focus on the disease burden might improve outcomes as reactive psychiatric disorders might be prevented if symptoms are targeted early.

P1-P041

Concealment of Type 1 Diabetes in Adolescence Affects Adherence to Treatment, Metabolic Control, and Quality of Life

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Introduction: Type 1 diabetes (T1D) is one of the common chronic diseases of childhood. T1D management is affected both by physiological and behavioral factors. Some patients and their parents choose to conceal the disease from others. Concealment of disease status is not unique for T1D, and has been shown to adversely affect clinical outcomes, social support and well-being of patients with other chronic conditions. There is limited data on the effects of concealment of T1D in adolescence, however studies have shown that concealment is prevalent to some extent among children and young adults with T1D. We aimed to evaluate the association between concealment of T1D in adolescence and social support, quality of life, adherence to treatment, and metabolic control.

Methods: We collected cross-sectional data on 69 adolescents with T1D, aged 12-18 years, followed-up at or diabetes clinic. All participants completed questionnaires regarding diabetes management and psychosocial issues. These included: a demographic questionnaire, *The Diabetes Concealment and Fear of Stigma Questionnaire (DCFSQ)*, *Diabetes Quality of Life for Youth (DQOLY)*, the *Perceived Social Support from Friends-PSS-FR*, *The Acceptance of Disability Scale Modified (ADM)*, and a modified version of the *Rosenberg self-esteem scale.* Adherence was assessed via a questionnaire developed at our center. Glycemic control was evaluated by computing a year's average of HbA1c measurements. Multivariate regression models were used to assess the association between degree of concealment, psychosocial variables and clinical outcomes.

Results: Fifty-three participants (77%) concealed their disease to some extent. In a multivariate linear regression analysis with concealment as the dependent variable, we found strong evidence of associations between concealment and negative clinical outcomes including diminished adherence to treatment and elevated HbA1C. In addition, there was an association between degree of concealment and psychosocial parameters including lower self-image, increased diabetes-related worries, and reduced peer support.

Conclusion: Our study shows that T1D concealment in adolescents is common, associated with poor clinical outcome, diminished peer support as well as increased diabetes related worries and general stress. These findings suggest that disease concealment may have a more significant role than previously appreciated affecting both glycemic control and quality of life. Addressing the

aspects of disease concealment by caregivers, advising patients about the consequences, and offering support if they to choose to reveal their disease, may lead to the much-needed improvement in quality of life and metabolic control in adolescents with T1D.

P1-P042

Risky Behaviors of Adolescents with Type 1 Diabetes in Comparison with Their Healthy Peers

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Introduction: Adolescents with type 1 diabetes mellitus (T1D) may differ from their healthy peers with respect to risky behavior.

Purpose: To explore the frequency of risky behaviors of T1D adolescents in comparison with healthy peers and associated factors.

Patients and methods: The study population included 174 adolescents, of whom 58 T1D adolescents (mean±SD age 16.3±2.0 years, disease duration 6.7±3.5 years and HbA1c:8.0±1.3%) and 116 healthy controls (matching 1:2 for school, class and gender). Anonymous, self-reported questionnaires were used to evaluate sexual and risk-taking behaviors.

Results: T1D adolescents had a sexual experience at a significantly lower percentage than healthy peers (74.1% vs 87.4%, p=0.033). The number of sexual partners was similar for both groups. Intoxication by alcohol prior to sexual contact was reported in far fewer cases in T1D adolescents (4.3% vs. 20%, p=0.046). Risky behavior was observed less frequently among T1D adolescents than controls (8.62% vs 23.27% respectively). Less girls than boys in both T1D and control groups had risky behaviors (0% vs 18.5%, p=0.401). T1D adolescents with ≥ 2 risky behaviors were all boys, with an older age than the rest of the T1D group (17.8 vs 16.2 years, p<0.031), a younger age at first sexual intercourse (14.8 vs 16.3 years, p=0.031) and with higher maternal education (p=0.039). No difference in diabetes duration and glycaemic control between the groups with or without risky behavior. When comparing control adolescents according to the presence/absence of risky behaviour, the risky group was also older in age (16.5 vs 15.7 years, p=0.006) and predominantly boys (44% vs 11.1%, p=0.022); however, no significant difference in terms of parental education or age at sexual debut between the two control groups was observed.

Conclusions: Risky behavior was observed less frequently among T1D adolescents than their healthy peers and less frequently among girls of both groups. Risky behavior in T1D group was associated with older age, younger age at sexual debut and higher maternal education, but not with diabetes duration and glycaemic control.

P1-P043

The Effect of Social Burden on Paediatric Diabetes Outcomes

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Introduction: Type 1 diabetes has a major impact on not only the person diagnosed, but also their families/carers. Diabetes control is affected by many factors. Our diabetes patient cohort has a very high level of social burden which we feel impacts significantly on the management of their diabetes.

Methods: We performed a retrospective analysis of all young people supported by the Evelina London Children's Hospital diabetes team in 2017 looking at age, gender, ethnicity and last HbA1C level. We also reviewed all admissions including those in Diabetes Ketoacidosis (DKA) to A&E and the ward between 2014-2017 excluding newly diagnosed patients. We defined social burden as: those known to Social Services and Youth Offending services; housing issues; financial difficulties; complex medical needs; immigration/language issues; those who have poor engagement with our service.

Results: 93 patients, mean age of 11.7 years (1.6-17.8 years), were divided into two groups: Group 1 (n=52, 56%) with one or more identified social issues (26 required Social Services involvement) and Group 2 (n=41, 44%) with no social issues.The mean HbA1c in Group 1 was 10% and for Group 2 8.9%. Mean HbA1c for females was 10.2% in Group 1 and 9.4% in Group 2. In males it was 9.7% and 8.5% respectively. Regarding ethnicity there was an equal distribution of ethnicities in both groups, however in Group 1 the HbA1c was higher for: White, Asian, Black British, Black/ Other and unspecified, than their peers in Group 2. Group 1 had a total of 74 admissions to A&E, 29 of which were due to DKA while Group 2 had 20 admissions with 6 DKA in the same period. The maximum number of admissions per patient was 11 in the first group and 2 in the second. The first group had 56 inpatient admissions compared to 11 in the other group.

Discussion: From our type 1 diabetes patient cohort the group with higher social burden was found to have higher mean HbA1c, more A&E and ward admissions, including more and recurrent DKA episodes.This has a significant impact on their glycaemic control and ultimately their health and long term well-being. We believe that patients with diabetes who have higher levels of social burden often face other more pressing social issues which means that the child's diabetes is not always the main priority. Future research may wish to consider what forms of psycho-social support could help address this.

P1-P044

Parental Anxiety About Hypoglycemia of Children and Adolescents with Type 1 Diabetes Mellitus (T1DM) and the Associated Factors

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Introduction: The anxiety for hypoglycemia is a major stress factor for parents of children with T1DM and has been associated with poor diabetic control, reduced insulin doses and school-age children.

Purpose: To determine the frequency and severity of parental anxiety for hypoglycemia and the associated factors.

Patients and Methods: The study included parents [21 (23.9%) fathers and 67 (76.1%) mothers] of 88 T1DM patients, with a mean±SD age of 12.63±3.58 years and disease duration of 4.56±3.63 years. Questionnaires HFS-P Worry (anxiety scale) and HFS-P Behavior scale were used and analyzed by single-factor analysis.

Results: From the parents of T1DM children, 21.6% frequently experienced and 26.1% almost always experienced anxiety for hypoglycemia. Parental anxiety for hypoglycemia showed a linear correlation with the presence of specific behaviors to avoid it ($p=0.421$, $p<0.001$). Anxiety for hypoglycemia mainly occurred in parents aged between 26-35 years ($p<0.036$) and mothers with the lowest educational level ($p<0.039$). The use of insulin pump ($p<0.034$), younger patients' age ($p<0.001$) and early diabetes diagnosis ($p=0.007$) was associated with a higher rate of specific behaviors to treat hypoglycemia. Parental anxiety for hypoglycemia was marginally non-significantly associated with poor glycemic control (HbA1c>8%) ($p=0.074$).

Conclusions: Parents of T1DM children have anxiety for hypoglycemia in a significant percentage (26.1%). Anxiety for hypoglycemia is mainly experienced by the parents of younger children, with a young age at diagnosis, with low maternal education and the use of insulin pump. Parental anxiety of hypoglycemia does not appear to significantly affect the quality of glycemic control.

P1-P045

Management of Diabetes During Ramadan Fasting in Children and Adolescents: Survey of Physicians' Perceptions and Practices in the Arab Society of Paediatric Endocrinology and Diabetes (ASPED) Countries

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Background: Many Muslim adolescents and children insist on fasting during the holy month of Ramadan. There are limited data on the patterns of diabetes management specifically about children and adolescents.

Aim: To ascertain the knowledge, attitude, and practices to the management of diabetes during Ramadan fasting among physicians who look after children and adolescents living with diabetes in Arab countries.

Methods: An electronic survey was distributed to a large pool of practicing physicians associated with the ASPED countries (no = 464). The questionnaire covered several aspects of management of Ramadan fasting in young patients with diabetes. The survey was provided in English and French.

Results: Of the 166 eligible responders, 142 (85.5%) were pediatricians, and the remaining 20 (12.1%) were adult physicians; all but 10 were specialists or consultants. Most respondents (79.6%) would allow their patients to fast, Ramadan, if they asked for it and 75.2% of them favored structured educational sessions 2-4 weeks before Ramadan, but 23.5% would do it earlier up to 2-3 months. 34.8%, 37.5 %, and 24.1% of respondents allow their patients to fast by the age of 14 and 12 and ten years respectively; while 3.6% allow fasting as young as eight years. 31.0% and 39.3% of the participants stated thought their patients can complete 50% and 80% of the fasting days. 46.9% stated that hypoglycemia unawareness was the most serious complication for a patient to be at "very high-risk" from fasting. 62% of the respondents reported that fasting has to be broken if symptomatic hypoglycemia occurred regardless of the blood glucose level fast and 48.2% of them thought fasting should be discontinued if blood glucose exceeded 300 mg/dl (48.2%). 63.4% of respondents decreased the dose of basal insulin by 25% from original dose, but 23.2% would reduce it by 10% only. 56.4% used rapid-acting analog with meals according to carbohydrate counting. 81.1% recommend a specific dietary regimen for their patients. 52.8% thought that use of insulin pumps decreases the frequency hypoglycemia during fasting compared to multiple daily injections; however, 39.6% were not pump users.

Conclusions: There is a wide variation in the management of children and adolescents with diabetes during Ramadan among ASPED members. This observation calls for targeted educational efforts in the region, highlights the need for ASPED- sponsored guidelines to help clinicians meet the challenges in this area of diabetes care.

P1-P046

Phenotypes of Diabetes and Determinants of Glycemic Control and Diabetes Complications in Haitian Youth Living in Haiti

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Background: In non-Caucasian youth residing in low-income settings, risk of mortality and rates of diabetes complications are substantially higher and clinical phenotypes may be distinct.

Objectives: To assess the clinical presentation, glycemic control, and chronic complications of diabetes in Haitian youth residing in Haiti.

Methods: Retrospective review between 01/2013-03/2018 of youth 0-25 years with diabetes followed at a chronic disease center in Haiti where specialized care, insulin and diabetes supplies are provided free of charge. Symptoms, presence of suspected diabetic ketoacidosis (DKA) and coma at diagnosis, and number of providers consulted before diagnosis were extracted. We documented yearly anthropometric data, total daily insulin dose (TDD), quarterly hemoglobin A1c (A1c), presence of hypertension and chronic complications. We used linear and logistic regression to determine predictors of mean A1c and of presence of chronic complications, respectively.

Results: 91 patients (60% female, mean age at diagnosis 14.1±4.6 years, mean diabetes duration 4.1±3.6 years) were included in the study. DKA and coma at initial presentation were present in 56% and 18%, respectively. 54% consulted at two or more health facilities before being diagnosed. Mean A1c was 10.6±2%. Hypertension was present in 17.8%. In 57 patients with documented evaluation, chronic complications included cataracts (13.9%), retinopathy (15.6%), nephropathy (24.3%), and neuropathy (13.6%). Mean most recent TDD was 0.48±0.29 units/kg/day and remained below 0.5 units/kg/day in a third of patients up to 5 years after diagnosis. Younger age at diagnosis (p=0.004) and longer diabetes duration (p=0.001) predicted a higher mean A1c, while TDD and presence of coma did not. Presence of any complication was predicted by longer diabetes duration (OR 10.3 95%CI 0.001-0.6, p=0.004), lower BMI z-score at presentation (OR 0.1, 95%CI 0.01-0.8, p=0.03), absence of coma at presentation (OR 0.005, 95%CI 0.001-0.6, p=0.03) but not TDD, while a higher mean A1c was marginally predictive (OR 2.5, 95%CI 0.99-6.5, p=0.05).

Conclusions: Haitian youth with diabetes present to care late and frequently experience DKA and coma at diagnosis. Even when a medical home is accessible, glycemic control is suboptimal. Cachexia and absence of coma at presentation in the context of older age at diagnosis and lower insulin requirements compared to Caucasian youth may suggest an attenuated autoimmune process with slower depletion of pancreatic beta cells, resulting in prolonged exposure to hyperglycemia prior to diagnosis and an increased risk of early-onset chronic complications.

P1-P047

Smoke Exposure and Cardio-Metabolic Profile in Youth with Type 1 Diabetes

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Aim: To evaluate the relationship between smoking and metabolic parameters in patients affected by type 1 diabetes (T1D)

Patients and methods: We enrolled 104 children and young adults (50 females and 54 males) with T1D (aged 16.4±8.6 years). The subjects were divided into three groups according to their smoking habits: no smoking (NS), passive smoking (PS), active smoking (AS). The physical examination of the participants included nutritional status assessment by anthropometry and pubertal stage according to Marshall and Tanner as well as blood pressure (BP) measurement. In all patients, metabolic blood assays including fasting blood glucose, insulin, total cholesterol, high-density lipoprotein cholesterol, triglycerides were measured. Insulin resistance was determined by glucose disposal rate (eGDR). Physical activity was also recorded.

Results: Significant differences in biochemical and functional parameters among the three groups were demonstrated, in particular for systolic (p=0.002) and diastolic pressure (p=0.02) and eGDR (p=0.039) (Figure 1). No differences in daily insulin dose (p=0.75) and glycosylated hemoglobin (p=0.39) were observed.

AS group had significantly higher blood pressure ($p<0.05$) and lower eGDR ($p\leq 0.001$) compared to NS and PS. Significant difference was also detected between PS and NS in systolic and diastolic (p=0.02) pressure and eGDR (p=0.01).

In a multivariable model adjusted for age, gender, BMI and physical activity, smoking habits maintained none independent association with metabolic parameters.

Conclusion: Our data support the relationship between smoking and an unfavorable cardio-metabolic profile in adolescents with T1D. On the basis of these findings, smoking tobacco should be considered an important modifiable risk factor for young patients with diabetes mellitus, highlighting the need for intensified smoking prevention and cessation programs.

P1-P048

Menstrual Cycle Disorders in Young Women with Type 1 Diabetes Mellitus

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Background and aim: Epidemiologic observations suggest that women with type 1 diabetes mellitus (T1DM) often suffer from menstrual cycle disorders. There may also be a negative association between the age of onset of T1DM and the age of menarche. Delayed menarche, in turn, may be associated with increased risk for diabetic complications. The aim of this study was to prospectively investigate pathologic manifestations of reproductive function in young women with T1DM and their possible association with stress, glycemic, metabolic, autoimmune or family history parameters.

Patiants and methods: We studied 53 women with T1DM 19.4±4.3 years old with T1DM duration of 8.0±5.6 years. Anthropometric measurements, age and clinical presentation at diagnosis, insulin regimen, glycemic control and hypoglycemic episodes, diabetic complications and other autoimmune diseases were recorded. Information regarding reproductive function included age of menarche, duration of menstrual cycle and manifestations of hyperandrogenism, hirsutism or acne.

Results: Diagnosis of T1DM was made at 11.5±4.7 years, with 17% (9/53) of patients presenting with ketoacidosis. Among patients, 83% (44/53) were on multiple daily insulin injections and the rest on insulin pump therapy (9/53, 17%), with total insulin requirements 0.7±0.22 u/kg. The last HbA1c measurement was 8.4±1.8%, with 7.3±7.9 hypoglycemic episodes per month. Most patients had normal BMI (22.2±2.7 kg/m^2). Only one (1.9%) presented diabetic retinopathy, while three (5.7%) had albuminuria. Autoimmune thyroiditis was present in 22.6% (12/53), whereas two additional patients suffered from other autoimmune diseases (26.4%). Two women (3.8%) had not experienced menarche at the age of 15.5 and 16.6 years, while the mean age of menarche for the rest women was 12.7±1.3 y (slightly higher than the reported average age of menarche of 12.29 y in normal weight Greek girls). The patients who had menarche were studied 7.3±4.7 years after, with 23.5% (12/51) having oligomenorrhea (menstrual cycle duration >35 days). Only 13.2% (7/53) reported positive family history for menstrual disturbances. A high proportion (32.1%, 17/53) had hirsutism, while 45.3% (24/53) had acne, both signs of hyperandrogenism.

Conclusions: Young women with T1DM present increased frequency of menstrual disturbances and signs of hyperandrogenism compared with those reported in non-diabetic Greek females. These findings may be the result of hypercortisolism and hyperandrogenism due to chronic hyperactivation of the hypothalamic-pituitary-adrenal axis, while the effects of glycemic regulation, hyperinsulinemia, complications or autoimmunity should be also further clarified.

P1-P049

Life Changing Decisions Due to Etiological Genetic Diagnosis in Families of Children with Maturity Onset Diabetes of the Young (MODY)

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Background: Maturity Onset Diabetes of the Young (MODY) is a heterogeneous group of disorders characterized by pancreatic beta-cell dysfunction, and usually referred to monogenic forms of diabetes mellitus to distinguish them from the more common type 1 (T1D) or type 2 diabetes (T2D). Fourteen different MODY genetic subtypes have been identified so far. Making a definite diagnosis is very challenging because of overlapping clinical phenotypes between diabetes subtypes. Nevertheless, distinction within childhood diabetes spectrum is crucial as optimal treatments are different, with the possibility of treating some MODY subtypes with oral agents and some can even be managed without medication. Accurate diagnosis is significant to probands as well as to other family members. It is estimated that up to 1-2% of those diagnosed with gestational diabetes, T1D or T2D have MODY.

Patients and Methods: We established a collaboration between the pediatric endocrinology clinic in Safra Children's Hospital and the Integrative Genomics and Modelling of Metabolic Diseases research laboratory at EGID (Lille).

Sixteen probands with suspected MODY based on clinical evaluation were rigorously selected for a comprehensive genetic analysis of all known monogenic diabetes genes using next-generation sequencing and Illumina HiSeq equipment (LIGAN-PM platform at EGID, Lille, France). After human genome alignment, quality controls and variant calling, candidate rare mutations were fully annotated and filtered, and criteria for mutation pathogenicity from the *American College of Medical Genetics* guidelines were used to score the identified mutations as pathogenic or likely pathogenic for MODY.

Results: The genetic diagnosis rate in the clinically suspected MODY patients was 68.7%. In 10 patients, we identified pathogenic/likely pathogenic mutations in *GCK* (7 cases), *HNF1A* (2 cases), *APPL1* (one case with a nonsense mutation) and in *WFS1* (one case with a homozygous mutation). The *WFS1* missense mutation was previously reported in four cases, 2 of them presenting signs of Wolfram syndrome and one with monogenic diabetes.

As a result of the genetic confirmation of MODY mutation, insulin treatment was withheld in two children; in 4 adults insulin treatment was discontinued, (one of them was on insulin pump); and antidiabetic oral medication was discontinued in one adult. Genetic counseling was given to family members.

Conclusion: Our study confirms that a comprehensive NGS analysis guided by a thorough clinical evaluation is an accurate powerful approach to make a precision diagnosis in monogenic diabetes. Distinction between monogenic diabetes and other forms of diabetes enabled us to individualize an adequate treatment.

P1-P050

NBAS Gene Mutation Causes Insulin-Dependent Diabetes Mellitus in a Patient with a Multisystem Disorder Consisting Immunodeficiency and Extremely Short Stature

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We report the case of a 19 years old male patient suffering from a multisystem disease involving of the skeleton, connective tissue, immune system, brain and endocrine system due to compound-heterozygote mutations in the *NBAS* (Neuroblastoma amplified sequence) gene (c.5741G>A [p.(Arg1914His)]; c.6565_6566insT [p.(Glu2189Valfs*7)]), detected using whole-exome-sequencing. He has an immunodeficiency including decreased CD4+ T-cells, B-cells and NK-cells with expanded early CD8+ effector and activated T-cells, and absence of immunoglobulins, which requires regular substitution with immunoglobulins. At the age of 11 years, Insulin-dependent Diabetes mellitus was diagnosed. At the age of 19 years, C-peptide is low, but still measurable. The patient has an extremely short stature (125 cm; height-SDS: -10.7) and is dystrophic (weight 27 kg, BMI 17.3 mg/m^2, BMI-SDS: -2.1). Moreover, he has a cerebellar hypotrophy and skeletal deformities.

The phenotypic variability of patients with NBAS deficiency highlights that mutations in *NBAS* lead to a clinical spectrum ranging from isolated acute liver failure to a multisystem phenotype including short stature, skeletal dysplasia, and immunological abnormalities. Although immunodeficiency and also autoimmune disorders including Celiac disease and Crohn's disease have already been published in patients with *NBAS* deficiency, no patient with Insulin-dependent Diabetes mellitus has been described so far.

In conclusion, we describe the first patient with an Insulin-dependent Diabetes mellitus due to *NBAS* mutations. Probably, the immune dysregulation promoted the development of the Diabetes in our patient.

P1-P051

Identification of Six Novel Mutations in Monogenic Diabetes and Congenital Hyperinsulinism and Detected by Targeted-Exome Sequencing in Korea

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Objectives: Monogenic diabetes and congenital hyperinsulinism (CHI) and are common disorders of glucose-regulated insulin secretion in childhood, with 13 causative genes known for MODY and 10 causative genes identified for CHI. Genetic testing for monogenic diabetes and CHI is important for patient care. We aimed to delineate genetic and clinical manifestations of monogenic diabetes and CHI diagnosed by targeted-exome sequencing (TES).

Methods: Nine probands and their family members (7 monogenic diabetes and 2 CHI) were included. We conducted TES in 7 clinical CHI and monogenic diabetes families to identify genetic variants in Korea. Variants in the dbSNP135 and TIARA databases for Koreans and the variants with minor allele frequencies >0.5% of the 1000 Genomes database were excluded. We selected only the functional variants and conducted a case-control comparison in the family members. The selected variants were scanned for the previously introduced gene set implicated in glucose metabolism

Results: Among the 5 patients with suspected maturity-onset diabetes of the young (MODY), 2 different MODY were identified in the three patients, and the diagnostic yield was 60%. We identified two novel mutations [C.1088C>T (Ala363Val) and c.1127T>C (Met376Thr)] in *HNF4A* gene causing MODY1. All the novel *HNF4A* mutation carriers were successfully transferred from insulin to sulfonylurea. A novel splicing mutation [c.538+8G>C] in *PAX9* gene was identified in a family with MODY9. A novel *PAX9* mutation carrier had a good clinical response when switched from insulin to diet. We also identified a novel variant in potentially candidate gene implicated in susceptibility to diabetes, albeit thus far not in an autosomal dominant mode of inheritance: *NOTCH2*. One of two families with neonatal diabetes showed a compound heterozygous mutation, c.2978C>A (Ala993Asp) and C.356C>T (Ala119Val), the latter of which is a novel mutation, in *INSR* gene who required metformin treatment. The other one showing persistent neonatal diabetes had a missense mutation, c.605G>A (Arg201His), which is a reported mutation, in *KCNJ11* gene, who required sulfonylurea such as glibenclamide. In two families with CHI two novel heterozygous mutations was identified: c.4237C>T (Pro1413Ser) and c.905C>T (Thr302Ile), the former of which is associated with diazoxide responsive CHI, the latter is related to diazoxide non-responsive CHI in terms of clinical courses among the patients.

Conclusions: TES can be useful for screening for monogenic diabetes /CHI mutations. Given the extensive genetic and clinical heterogeneity of monogenic diabetes, TES might provide additional diagnostic potential.

P1-P052

Genetic Susceptibility to Type 1 Diabetes in Children: Analysis of Polymorphisms Rs1990760 - IFIH1, Rs20541 - IL13, Rs231775 - CTLA 4

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Background: Type 1 Diabetes is influenced by genetic and environmental factors. Cytotoxic T-lymphocyte antigen 4 (CTLA-4) gene polymorphism and The interferon induced helicase domain 1 (IFIH1) gene are known to be associated with T1DM, but have not been established in a Caucasian children population yet. The interleukin 13 (IL13) gene polymorphisms impact on the development of Type 1 DM in children has not been reported yet.

Objective and hypotheses: To estimate the association of polymorphisms of IFIH1, IL13, CTLA 4 genes with the predisposition to T1DM in children.

Method: The study was performed in 194 patients with T1DM and 190 healthy volunteers. The three single nucleotide polymorphisms (SNPs): rs1990760 - IFIH1, rs20541- IL13, rs231775-CTLA 4 were genotyped by TaqMan SNP genotyping assay using the real-time PCR.

Results: Rs1990760 T alleles were more frequent in patients with T1DM in comparison to healthy subjects (p=0.001 with OR=5). Rs20541 A alleles were more frequent in T1DM patients in comparison to healthy subjects (p=0.04 with OR=2). Rs231775 G alleles were more frequent in T1DM patients in comparison to healthy subjects (p=0.01, OR=2).

Conclusion: Rs1990760 T/C - IFIH1, rs20541 A/G - IL13, rs231775 G/A – CTLA 4 polymorphisms could contribute to development of T1DM in children. The main risk factor for rs1990760 is T allele, for rs20541 A allele and for rs231775 G allele.

P1-P053

Neonatal Diabetes as a First Symptom of IPEX Syndrom

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Introduction: Immunodysregulation polyendocrinopathy enteropathy x-linked syndrome (IPEX) is characterized by systemic autoimmunity, typically beginning in the first year of life. Most commonly triad of symptoms of diarrhea, dermatitis and endocrinopathy is present.

Case report: Presentatlion of male patient, born with body weight 3840 grams and 10 points in Apgar scale. In 13th day of life vomitting and tachypnoe were noted and in laboratory tests hyperglycemia of 653mg/dl (36.2 mmol/l) and ketoacidosis were reported. Patient was diagnosed with diabetes and treatment with continous insulin infusion by insulin pump was started. Antibodies typical for diabetes type 1 were negative. In 9th month of life boy was hospitalized in the Department of Pediatrics, Diabetology and Endocrinology in Gdansk, Poland and mutation in KCNJ11 gene was excluded, but autoimmune thyroiditis was diagnosed and L-tyroxin treatment was implemented.

In 12th month of life patient was diagnosed with nephrotic syndrome resistant to steroids. Patient had also periodical skin lesions and diarrhea. According to clinical presentation IPEX syndrome was suspected, T regulatory cells levels were normal and sample for genetic test for FOXP3 mutations was sent.

One month later patient was diagnosed with absence seizures. Brain MRI scans were normal, but anti-neuronal antibodies (ABA) were highly possitive. Also anti-tissue transglutaminase antibodies were possitive and gluten free diet was started.

In molecular tests performer in Department of Clicial Genetic in Łódź mutation in FOXP3 was found. Patient had started immunosupresion and had bone marrow transpalantation performed in Medical University in Wroclaw, Poland at the age of 2 years.

Conclusion: Neonatal diabetes in male patient with negative test for most common genetic causes of neonatal diabetes can be first symptom of IPEX syndrome.

P1-P054

CpG Methylation Status Changes Within the Protein Tyrosine Phosphatase Non-Receptor Type 22 Gene Promoters in Children and Adolescents of Greek Origin with Type 1 Diabetes

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Introduction: Protein tyrosine phosphatase non-receptor type 22 (PTPN22) is a well-established genetic locus of type 1 diabetes (T1D). The **aim** of the present study is to compare the methylation level of PTPN22 between children and adolescents of Greek origin with T1D and healthy controls.

Patients and Methods: Twenty T1D participants and 20 age-/gender-matched healthy youngsters were enrolled. DNA was extracted from white blood cells, then treated with sodium bisulphate which converts unmethylated cytosines into uracyls, whereas methylated cytosines remain unchanged under the same conditions. DNA was then amplified by PCR using primers:*(F) primer:5'TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGT TTTGGTTTATGTTGTAGAGT3' and (R) primer:5'GTCTCGTG GGCTCGGAGATGTGTATAAGAGACAGTTACATATAAATA-ATA AAATAAAAT3'.* Amplicons were analysed by electrophoresis (1% agarose gel stained with ethidium bromide), visualized

Table 1. (for Abstract no P1-P054)

4 CpGs in PTPN22 gene	DNA methylation (%)		
	T1D (n=20)	Controls (n=20)	p
Overall mean methylation percentage			
Mean methylation	0.4±0.1	0.46±0.14	0.179
Range	0–1	0–1	
CpG sites			
1-4826	0.35±0.17	0.52±0.28	0.026
2-4950	0.45±0.22	0.51±0.29	0.640
3-5018	0.24±0.09	0.30±0.13	0.065
4-5046	0.56±0.37	0.50±0.34	0.659

Results are expressed as Mean ± Standard Deviation.

by ultraviolet trans-illumination, and then Next Generation Sequencing was applied to identify differences in DNA methylation status. The methylation profile was analyzed at 4 CpG sites of the PTPN22 gene. Comparisons between groups were performed with student's t-test or its non-parametric analogue, Mann Whitney U test, as appropriate.

Results: We found that the methylation level was statistically significant lower at position 1-4826 (p=0.026) in patients (0.35±0.17) compared to controls (0.52±0.28). Furthermore, there was a tendency for statistically significant hypomethylation at position 3-5018 (p=0.065) in patients (0.24±0.09) than in controls (0.30±0.13).

Conclusion: To our knowledge, this is the first time to detect hypomethylation of PTPN22 gene in patients with T1DM.

P1-P055

Wolfram Syndrome Case with Hypergonadotropic Hypogonadism: A Novel Mutation

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Introduction: A rare cause of diabetes mellitus is Wolfram Syndrome, which arises from mutations in wolframin gene found on chromosome 4. Optic nerve atrophy, diabetes insipidus, sensorineural deafness, psychiatric problems can accompany diabetes mellitus, so it can be also named as DIDMOAD syndrome. Hypergonadotrophic hypogonadism can be rarely observed in Wolfram syndrome.

A case of novel homozygous mutation in the wolframin gene has been reported because of concomitant rarely reported hypergonadotropic hypogonadism.

Case: The patient admitted with complaints of drinking too much water and frequent urination at the age of 2,8 years. He was born at term with 3500gr and his parents were second-degree cousin. At the beginning patient's blood sugar was 234 mg/dl and HbA1c was 10% with no metabolic acidosis. Insulin treatment was started immediately with the diagnosis of diabetes mellitus. Older sister of the patient had DIDMOAD syndrome. According to the history and examination, the diagnosis of Wolfram syndrome was considered. There was no optic nerve atrophy in the ophthalmic examination. Diabetes insipidus was not considered due to the normal values of urine density and serum sodium levels. The laboratory examination of the patient for Celiac and Hashimoto diseases was also normal. HbA1c values of the patient being followed for many years with insulin therapy are shown in graph 1.

Optic atrophy was detected for the first time when the patient was 10,4 years old. Neither diabetes insipidus nor deafness has been observed so far. Pubertal development of the patient was compatible with Tanner stage 2 when he was 12,8 years old. In follow-up, it was observed that the testicle volumes increased by 10ml, but did not show any progress. Laboratory examination suggested hypergonadotropic hypogonadism with serum levels of LH (luteinizing hormone): 20.9mIU/ml, FSH (follicle-stimulating hormone):49.9mIU/ml ve Total Testosterone: 347ng/dl. Intramuscular testosterone treatment was initiated after azoospermia was detected in the spermiogram and gradually decreased testosterone levels. Genetic examination revealed a homozygous mutation of c.2069G> A / p(Cys690Tyr) in the wolframine gene, which was not previously reported.

Conclusion: DIDMOAD syndrome should be considered in patients who are diagnosed with antibody-negative diabetes mellitus. It is well known that diabetes insipidus and optic atrophy may develop in the follow-up of these patients, but it should be kept in mind that rarely hypergonadotropic hypogonadism may also accompany Wolfram syndrome as seen in our case.

P1-P056

Different Clinical Findings in Maturity Onset Diabetes of the Young Due to B-Lymphocyte Kinase Gene Mutations

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Background: B-Lymphocyte kinase gene **(***BLK)* gene acts on insulin synthesis and secretion, and mapped locus on chromosome 8p23. Monogenic diabetes due to BLK gene mutation is very rare and it's named as MODY11. We aimed to present differences in clinical, laboratory and treatment of the patients with *BLK* mutations.

Methods: OGTT performed in six patients. A panel of 23 MODY genes was screened. Patients with *BLK* mutations seperated.The Human Gene Mutation Database (HGMD), Clinvar, dbSNP and Exac database used for known or new variants causes MODY. Classification of variants performed according to ACMG 2015 Guidelines.

Results: Case 1 had recurrent hypoglycemic attacts. However her grandmother and maternal uncle have diabetes. Six patients

Table 1. (for Abstract no P1-P056)

No, Sex	Case 1, F	Case 2, M	Case 3, M	Case 4, F	Case 5, F	Case 6, M	Case 7, M
Age at diagnosis, years	15.4	13.08	12.08	11.72	7	4.24	5.88
Birth weight, gr	2850	3400	2900	3200	NA	2730	3730
Affected parents		Father		Mother			
Gestational DM in mother	No	No	Unknown	Yes	No	Yes	Yes
BMI, kg/m^2	20.69	15.52	21.05	15.73	18.06	16.28	21.10
Fasting Glucose mg/dL	77	104	279	141	157	112	130
2 hr-Glucose, mg/dL	68	173	Not performed	166	137	102	102
Fasting insulin, uIU/mL	11.5	8.9	3.6	4.1	5.09	3.8	4.3
Fasting c-peptide, ng/mL	1.6	0.88	0.09	NA	1.57	0.68	1.48
HbA1c,%	5.4	5.7	12.2	6.3	4.5	5.5	5.0
Treatment	Diet	Diet	Insulin	Metformin	Diet	Diet	Diet
Exon	11	4	4	4	9	9	9
c.DNA	c.1075 C>T	c.211G>A	c.211G>A	c.211G>A	c.223C>G	c.900C >A	c.900C >A
A.acid change	p.Arg359Cys	p.Ala71Thr	p.Ala71Thr	p.Ala71Thr	p.Arg75Gly	p.Tyr300Ter	p.Tyr300Ter
ACGM 2015 guideline	Uncertain significance	Likely Benign	Likely Benign	Likely Benign	Uncertain significance	Novel	Novel

had hyperglycemia and diabetes symptoms such as polyuria and polydypsia. Case 6 and 7 were siblings and their parents were first cousin. Seven patients have heterozygous mutation in *BLK* gene. Clinical, laboratory and genetic results of the patients were given in Table. Mutations in siblings were novel. Although basal and bolus insulin therapy for Case 3 and metformin therapy for Case 4 were given, diet was enough to regulate blood glucose.

Conclusion: We found one novel mutation in *BLK* gene. Also two uncertain significances in *BLK* gene were presented. More patient information is needed to identify patients' referral findings and treatment modalities.

P1-P057

Three New Gene Variants (PTPRD, SYT9, and WFS1) Related to Korean MODY Children Decrease Insulin Secretion in Human Pancreatic Beta Cells

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Background & objective: Maturity-onset diabetes of the young (MODY) is a monogenic form of diabetes that is characterized by an early onset, autosomal dominant mode of inheritance and a primary defect in pancreatic β-cell function. MODY has been identified in Asian populations, however, there is a big discrepancy in the genetic locus between Asian and Caucasian patients with MODY. We previously reported that mutations in PTPRD, SYT9 and WFS1 have been identified in Korean families of MODY patients(Horm Res Pediatr, 2015). In this study, we investigated whether mutations (mut) of PTPRD, SYT9 and WFS1 overexpression vectors effected insulin release in human pancreatic beta cell.

Materials & Methods: We used 1.2B4 and 1.4E7 β cell lines for human pancreatic β cells. PTPRD, mut-PTPRD (c.620C>T:p.Thr 207 Ile), SYT9, mut-SYT9 (c.559C>G:p.Gln187Glu), WFS1 and mut-WFS1 (c.1526T>G:p.Val 509 Gly) overexpression vectors were manufactured and transfected into 1.2B4 and 1.4E7 β cells, then confirm insulin release.

Results: Glucose induced insulin release in 1.2B4 and 1.4E7 β cells. There was no change in insulin release by glucose in 1.2B4 and 1.4E7 β cells transfected with PTPRD, SYT9 and WFS1 overexpression vectors. Interestingly, the deficit of increased insulin release was 10-12% for mut-WFS1 and 30-35% for mut-SYT9 and mut-PTPRD, respectively in 1.2B4 and 1.4E7 β cells.

Conclusions: Based on the literatures and our findings, SYT9 and PTPRD are promising candidate genes with the potential of MODY family. In addition, further evaluation of cell signals related to insulin secretion by these genes is needed in the future.

P1-P058

Comprehensive Genetic Testing Shows One in Five Children with Diabetes and Non-Autoimmune Extra-Pancreatic Features Have Monogenic Aetiology

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Background/Aim: Diabetes with extra-pancreatic features in children can have a monogenic aetiology. Single gene testing is undertaken when children present with the characteristic clinical features suggestive of the underlying aetiology. We aim to assess the utility of comprehensive genetic testing for all monogenic diabetes genes in children with diabetes and any non-autoimmune extra-pancreatic features from a population with a high rate of consanguinity.

Method: We recruited 1093 children with young-onset diabetes (median age of diagnosis 8y) from 7 paediatric endocrinology centres in Turkey. All children with one or more non-autoimmune extra-pancreatic features underwent comprehensive genetic testing for 34 known monogenic diabetes genes. We generated a Type 1 Diabetes Genetic Risk Score (T1D-GRS) by genotyping 30 T1D associated single nucleotide polymorphisms. The self-reported consanguinity rate was 29.4%.

Results: 68/1093 (6.2%) children with diabetes had one or more non-autoimmune extra-pancreatic features. Comprehensive genetic testing identified 15/68 (22%) with a monogenic aetiology. In 2/15 (13%) children the identified monogenic aetiology (*GCK*) explained the diabetes only. In 13/15 (87%) children, the genetic aetiology explained both the diabetes and the other features. However, classical clinical features indicative of the underlying genetic aetiology were present in only 2/15(15%) children. The remaining 11/13 (85%) children had an atypical/rare presentation of the genetic syndrome or were diagnosed with diabetes before the typical clinical features presented. Recessive mutations in *WFS1* were the most common aetiology (6/15, 40%). Age of diagnosis (median 5.9y vs. 8.1y, p=0.20), duration of diabetes (4.7y vs. 3.3y, p=0.55), BMI (63rd vs. 58th centile, p=0.42) and proportion clinically reported as non-T1D (40% vs. 30%, p=0.53) was similar in children with and without a monogenic aetiology. T1D-GRS was lower in children with a monogenic aetiology compared to rest of the children (median GRS 0.23 vs. 0.27 p<0.01). Among the children with low T1D-GRS (<0.23), 41% (7/17) had monogenic diabetes compared to only 5% (1/22) with high T1D-GRS (>0.28).

Conclusion: Comprehensive genetic testing enabled early identification of syndromic forms of monogenic diabetes with minimal or an atypical presentation. All children with diabetes and any non-autoimmune extra-pancreatic features from a population with a high rate of consanguinity should be considered for comprehensive genetic testing. T1D-GRS is a novel test that helps to identify children with high probability of a monogenic aetiology.

P1-P059

Impact of Diabetes During Pregnancy in Women Affected with GCK-MODY on Neonatal Health Outcome

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Introduction: Gestational diabetes is one of the most common medical disorders and may cause numerous maternal and fetal complications. It constitutes one of the most frequent pregnancy health problems and may cause wide range of complications such as: preterm births, congenital defects, sacral agenesis, hypertrophic cardiomyopathy, metabolic changes and macrosomia in neonates. Therefore, early detection and implementation of guideline-based screening tests, are crucial. One of the types of diabetes, which may clinically manifest in pregnancy, is GCK-MODY, caused by mutations in glucokinase (GCK) gene, resulting in pancreatic beta cells dysfunction. Clinical course of the disease is mild. Patients usually present slightly elevated fasting glucose concentration.

Aim of the study: The aim of the study was to assess the impact of diabetes during pregnancy in women affected with GCK-MODY on neonatal health outcome. Researchers tried to determine the clinical and biochemical characteristics of newborns delivered by patients with GCK-MODY.

Material and methods: Study was multicenter, involving 50 patients from Diabetology Clinics in Gdansk, Katowice, Bialystok and Lodz. The risk of MODY 2 was evaluated on the basis of medical history of the patient, clinical course of the disease and laboratory tests performed during diagnostic procedures. Data concerning family history, mothers' health status, course of pregnancy and perinatal period was collected.

Results: The study showed that only 32% of women, later diagnosed with GCK-MODY, were tested for blood glucose concentration before pregnancy. In 68% of patients blood glucose measurement was not carried out before conception and women became aware of impaired glycemia during pregnancy. 32% of women, regardless of recognition of diabetes or normal glucose concentration after delivery, were no longer controlled for glucose levels.

Among children with glucokinase mutation, born by mothers affected with GCK-MODY, 62% (n=32) received 10 points in Apgar score in first minute of life, whereas 92% (n=46) obtained 10 points in Apgar score in fifth minute of life. Researchers observed

a statistically significant difference between the absence of macrosomia (birth weight >91 percentile) in children with GCK-MODY diabetes in comparison to general pediatric population (p=0,0229).

Conclusion: According to presented study, possible consequences of GCK-MODY during pregnancy on fetal development are generally less severe and may differ from those characteristic for other types of diabetes. Further investigation of particular phenotypes of GCK-MODY, depending on the type of inherited mutation, in mothers and their children is required.

P1-P060

IPEX as a Result of Mutations in FOXP3 Two Case Reports and Review of the Literature

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Background: Immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations in the Forkhead/winged helix transcription factor (FOXP3) gene and is a rare disorder that increasingly has gained attention as a model of genetic autoimmunity. We report two Chinese families with IPEX and the sequencing of the FOXP3 gene.

Methods: Two unrelated Chinese cases with IPEX were investigated. In case 1, the proband was a 4 month-year-old girl with neonatal type 1 diabetes and severe enteropathy.In case 2, the proband was a 6 day newborn boy who had neonatal type 1 diabetes and ketoacidosis. The venous blood samples of 2 children and their parents were collected and sequenced to detect the mutation of FOXP3 gene coding region.

Results: A novel splice site mutation in intron (c.967+3A>T) was detected in case1. A previously reported, a missense heterozygous mutation in exon 12 (c.1150G>A) was found in case 2.

Conclusions: The thorough investigation of the two cases with IPEX was revealed. A novel splice site mutation in intron (c.967+3A>T) and a missense heterozygous mutation in exon 12 (c.1150G>A) reported in FOXP3 gene were found. FOXP3 gene sequencing helps in IPEX, especially when there is uncertain neonatal diabetes mellitus.

P1-P061

The Prevalence of Autonomic and Peripheral Neuropathy in Children and Adolescents with Type 1 Diabetic Mellitus (T1D) and its Association with the Homozygous Status of Z-2/Z-2 Polymorphism of the Aldose Reductase Gene (AKR1B1) in the Polyol Pathway

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Introduction: Diabetic neuropathy(DN) significantly reduces patients' quality of life and increasescardiovascular death risk. However, it is the least recognized complication of diabetes. Z-2/Z-2 polymorphism of the aldose reductase (*AKP1B1*) gene increases the expression of the relative enzyme and is likely to contribute to DN expression.

Purpose: To study the prevalence of DN in T1D children and adolescents and its associations with the homozygous state of Z-2/Z-2 polymorphism of the *AKR1B1* gene.

Methods: We evaluated 106 T1D children and adolescents (mean±SD age:13.5±3.46 years, T1D duration: 5.3±3.4 years) and 100 healthy controls (age:11.9±2.7 years). Pupillary dilation (PD) in darkness was assessed as an index of autonomic neuropathy. Abnormal cut-off values(<5%) were calculated from control values distribution. Nerve conduction studies (NCS) were performedwith a standard technique using surface electrodes.The polymorphisms of *AKR1B1*gene were evaluated using microsatellite sequence Z.

Results: PD impairment was more frequent in the T1D group (31.6% vs 3.3%,p<0.001). PD was associated with age (r=0.16,p=0.038), HbA1c (r=0.23, p=0.048) and T1D duration (r=0.20, p=0.022). There was a strong correlation between PD and NCS in T1D patients (r=0.34, p=0.008). In T1D patients, NCS was neither associated with age (r=0.01, p=0.91), nor with HbA1c(r=0.14,p=0.27), or disease duration (r=-0.2,p=0.12). Patients homozygous for Z-2 polymorphism of the *AKR1B1* gene had higher prevalence of NCS abnormality (21.74%vs 2.86%,p=0.032) and also PD abnormality(62.5%vs 37.5%,p=0.023) compared to controls.

Conclusions: Impaired indices of peripheral and autonomic DN were present in a significant proportion of young T1D patients, although asymptomatic. Indices of DAN were associated with age, diabetes duration and glycemic control, while NCS were not. PD and NCSabnormalities were related to the homozygosity of Z-2/Z-2 polymorphism of *AKR1B1*gene in the polyol pathway.

P1-P062

Establishment of Iron Overload Insulin Cell Model and the Effect Induced by Iron Overload on Oxidative Stress

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Objective: To establish INS-1 cell iron overload model, and study the effect on proliferation, insulin-secretion and oxidative stress change.

Methods: INS-1 cells were cultured in either normal or high glucose medium. Both groups were treated with different concentrations of (5, 10, 20, 40, 80μmol/L respectively) of ferric ammonium citrate (FAC). Number and state of the cells were detected by trypan blue staining. Labile iron pool (LIP) were calculated by detecting calcein-AM fluorescence. Insulin levels were detected using ELISA kit. After establishment of iron overload model, related oxidative stress (ROS) levels were detected in both normal and high glucose groups.

Results: 1. there were no significant differences of INS-1 cell numbers among different FAC concentration groups and control group after 24h or 48h. LIP level significantly increased with the FAC concentration. 2. In normal glucose medium groups, insulin levels had no correlation with FAC concentration. While in high glucose medium groups, insulin levels were first increased then dropped down with increase of FAC concentration. 3. In iron overload model, ROS level significantly increased in both normal and high glucose groups when compared with control.

Conclusions: To a certain concentration, FAC did not affect INS-1 cell proliferation. Co-cultured in high glucose medium, iron overload may cause glucose metabolic disorder in INS-1 cells, resulting in insulin resistance as well as decrease of insulin secretion. Iron overload can induce significant increase of ROS in INS-1 cells, which is possibly related to the change of cell function and insulin secretion.

P1-P063

Glucose Intolerance in Survivors of Childhood Hematologic Disorders

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Purpose: To investigate overall characteristics of glucose intolerance in childhood survivors of hematologic diseases and suggest risk factors which increase A1c (glycated hemoglobin) level.

Methods: Based on a retrospective review of 394 children who were diagnosed with acute leukemia or aplastic anemia between 2015 and 2016 under the age of 15, glucose intolerance was observed in 14 patients. A definition of glucose intolerance was A1c above 5.7 %. Auxological and biochemical profiles as well as therapeutic factors of the patients were compared.

Results: Among 14 children (3.5 %) with glucose intolerance, 7 (50.0 %) patients were diagnosed with leukemia and 7 with aplastic anemia; median age at diagnosis was 8.3 years (0.66 - 14.8). 8 patients (57.1 %) were diabetic (A1c ≥ 6.5 %, fasting blood glucose ≥ 126.0 mg/dL and clinical presentation of polyuria, polydipsia or weight loss) whereas 6 (42.9 %) were prediabetic (A1c in between 5.7–6.4 %). Median A1c at diagnosis of glucose intolerance was 6.4 % (5.7–9.4) for leukemia group and 6.6 % (5.7–7.8 %) for anemia group. By univariate regression, fasting blood glucose (R^2=0.538, *P=0.003*), glucocorticoid dose (R^2=0.920, *P<0.001*) and volume of transfused red blood cell (R^2=0.789, *P<0.001*) were positively correlated with A1c. Multiple regression analysis suggested accumulated glucocorticoid dose (R^2=0.920, *P=0.019*) as a strong risk factor of glucose intolerance. Using a receiver operating characteristic curve, an optimal cutoff dose of glucocorticoid for the diagnosis of diabetes was 6232.0 mg (area under curve=0.990, p=0.02).

Conclusion: In young survivors after treatment completion of hematologic diseases, several clinical and biochemical factors could influence serum A1c and trigger glucose intolerance. Among them, glucocorticoid dose might be a strong factor which gives rise to newly diagnosed diabetes.

P1-P064

Efficacy of Mecasermin Treatment and Long-Term Survival in a Child with Leprechaunism

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Homozygous mutation of Insulin receptor (INS-R) gene cause an extremely rare disease called Leprechaunism, and induce intrauterine growth restriction with poor postnatal growth, hyperinsulinemia, postprandial hyperglycaemia, pre-prandial hypoglycaemia, typical facies, lack of subcutaneous fat, thick skin, hypertrichosis, macrogenitosomia in males.

The survival is severely compromised in these patients. Treatment with diazoxide could ameliorate glycaemic control, however these patients are signed by a high precocious lethality into the first 1-2 years of life. Anecdotical cases are described with a longer survival.

We describe the clinical case of a child with Leprechaunism, born from consanguineous parents, who had a homozygous mutation of the INS-R gene: c.3289 C>T (CAG->TAG) p.Gln 10975 stop (Q1097X). He was treated with diazoxide (5 mg/kg/day) and captopril (0.04 mg/kg/day), with a reduction of hyperglycaemia and hypertension.

However, the stop in ponderal and linear growth induced to try the off-label treatment with mecasermin (0.04 mg/kg bid). The dose was progressively increased to 0.06 mg/kg/bid. After 2 years of treatment with mecasermin, the child increased the weight to

5.9 kg, length to 65 cm, head circumference to 41 cm. His neuromotor development is significantly improved. He performed an encephalic MRI which showed non-specific alterations of the white matter subcortical and periventricular, possible evolution of neonatal prolonged hypoglycaemic events.

The peculiar outcome of our patient is linked to the long-term survival and the clinical improvement by mecasermin.

P1-P065

Evaluation of Diabetes Related Complications and Endothelial Dysfunction in Adolescents with Type 1 Diabetes

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Introduction: Patients with type 1 diabetes (T1D) are at high risk of developing vascular complications. Endothelial dysfunction is considered the early reversible stage in the development of diabetes related vascular disease. Early detection and management of endothelial dysfunction can delay or even prevent the development of vascular complications.

Aim: Endothelial dysfunction is associated with poor metabolic control in adolescents with T1D. Based on this hypothesis we aimed to determine the relationship between metabolic control and endothelial function in a cohort of adolescents with T1D. We postulated that by Identifying those at increased risk of cardiovascular disease, we could introduce targeted intervention to reduce the occurrence of cardiovascular complications.

Methods: 42 adolescents with T1D attending the Paediatric Diabetes and Endocrinology service at Tallaght Hospital, Dublin were recruited. Candidates attended for assessment following an overnight fast, auxiology and BMI were calculated. Blood pressure was measured in the supine position followed by assessment of the Reactive hyperaemia index (RHI) by Endo-PAT. Blood samples were taken for evaluation of HbA1c, liver, renal function, lipid status and celiac screen. Serum of 20 candidates was reserved for measurement of inflammatory markers (adiponectin, leptin, thrombomodulin, serum intravascular adhesion molecules, E-Selectin and P-Selectin). First morning urine sample was provided for estimation of microalbumin to creatinine ratio. Participants completed a physical activity questionnaire. Baseline data included the date of diagnosis, duration of diabetes, current insulin dose; insulin regimen; daily screen time; and relevant Family history of early cardiovascular disease.

Results: Reactive hyperaemia index correlated with age. Thirteen adolescents (31%) had low RHI, suggesting relatively impaired endothelial function. lower RHI correlated with higher diastolic blood pressure (r=-0.34) and P-Selectin level (r=-0.3) suggesting impairment in vascular health. Poor metabolic control was associated with impaired lipid profile (r= 0.55), higher diastolic blood pressure (r=0.38) and higher level of inflammatory markers P-selectin (r=0.55), thrombomodulin (r=0.31) and adiponectin (r= 0.33). E-Selectin, P-Selectin and thrombomodulin were associated with lower HDL (r= -0.34, -0.38, -0.38). Elevated ACR with E-Selectin (r=0.32) and systolic blood pressure with thrombomodulin (r=0.36). Active life style was associated with improved blood pressure (r=-0.35) and lipid profile (r=-0.39)

Conclusion: Reactive artery tonometry is an easy, non-invasive reliable method of assessing endothelial function. Impaired endothelial function correlated with elevated diastolic blood pressure and elevated P-selectin level. Maintaining a healthy life style improves the general health and in particular vascular health of those with T1D and should be actively encouraged.

P1-P066

Complexities in the Management of New-Onset Diabetes After Transplantation (NODAT) in an Adolescent with Senior-Loken Syndrome

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Background: New-Onset Diabetes after Transplant (NODAT) is a well characterized entity in adult population but less described in paediatric and adolescent population. The development of NODAT is associated with reduced graft function. The consensus for its management is largely available for adult population with a lack of specific guidelines applicable to the paediatric population.

Case: A 16-year-old patient with an established renal failure and visual impairment secondary to Senior-Loken syndrome had a deceased donor renal transplant and was commenced on prednisolone, tacrolimus and azathioprine. Two months later, he developed persistent hyperglycaemia (Blood glucose (BG):10-26 mmol/L) and HbA1C of 86mmol/mol suggestive of diabetes mellitus. He was commenced on insulin glargine, which was subsequently changed to daily insulin degludec (20 units, subcutaneous) that resulted in a more stable BG profile (8-15 mmol/L). The antibodies (GAD, IA2 and ZnT8) were negative and the c-peptide at the time of diagnosis was 554 pmol/L. The tacrolimus and prednisolone were weaned which resulted in an improved fasting BG (5-8 mmol/L) that enabled a gradual weaning of degludec to 12 units/day. There were significant social concerns, anxiety, behaviour and mood issues needing appropriate support. Despite the various levels of support, the compliance with the injection and self-monitoring of blood glucose (SMBG) was extremely challenging. The fasting SMBG on occasional testing and following complete non-compliance with insulin injections was between 7-9 mmol/L. Although insulin is the most commonly used treatment in paediatric diabetes (except Type 2), the NODAT consensus in adults recommends the usage of sulfonylureas/biguanide as the first line treatment options with insulin being initiated or added at a later stage if the control remains poor. Our patient had a reasonable intrinsic endogenous insulin reserve(c-peptide:554pmol/L) but was persistently non-compliant with the insulin injections. He was hence switched to oral gliclazide, 20mg once daily. His occasional fasting SMBG have been reassuring (4-6mmol/L), no reports of hypoglycaemia with the most recent HbA1C of 36mmol/mol.

Conclusion: Although insulin is a safe and reliable anti-hyperglycaemic therapy during the initial stages of diagnosis in paediatric and adolescent patients, the daily injections may add to the already existing disease burden in this group. Oral sulfonylurea or biguanide can be considered as safe alternative; however there is a need for development of robust international guidelines for NODAT, specific to the paediatric and adolescent population.

P1-P067

Insulin Resistance Parameters in Children Who Were Born Very Preterm and Adequate for Gestational Age

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Background: Very preterm neonates are at risk for metabolic syndrome later in life. Our objective was to compare anthropometric measures and insulin resistance variables between children who were born very preterm (VPT, <32 gestational weeks) and term (T, >37 gestational weeks), and adequate for gestational age (AGA).

Methods: In this cross-sectional cohort study we recruited 113 children 5.0 to 8.5 years old from the preterm clinic of our institutions: 72 VPT (gestational age = 29 ± 2 weeks) and 41 T (gestational age 39 ± 1 weeks) with a similar socio-economical background. All children presented a Birth Weight Standard Deviation Score (BW-SDS) higher than 2, as calculated using INTERGROWTH21. We measured height, weight and abdominal circumference, and calculated body mass index (BMI) percentiles using WHO references. After overnight fasting, glycemia, insulin, triglycerides and HDL-Cholesterol were determined. We determined the homeostasis model assessment insulin resistance (HOMA-IR) index, the quantitative insulin-sensitivity check index (QUICKI), and the triglyceride to HDL-C ratio (TG/HDL-C).

Results: VPT and T were comparable in chronological age (6.6 ± 0.9 vs. 6.7 ± 1.0 years; p = 0.535) and anthropometrics variables: height-SDS (-0.19 ± 0.86 vs. 0.10 ± 1.03; p= 0.903), abdominal circumferences (58.5 ± 7.4 vs. 58.50 ± 7.1 cm; p = 0.982), BMI-percentile (59.0 ± 32.0 vs. 64.0 ± 29.0th; p = 0.476), and BW-SDS (0.40 ± 1.03 vs. 0.52 ± 0.72; p = 0.512). Insulin-resistance parameters are presented in the table.

Conclusion: At this age, insulin-resistance parameters in children who were born very preterm and adequate for gestational age were not different compared to children born at term. Nevertheless, TG/HDL-C ratios were higher in VPT which could suggest a potential metabolic risk; therefore, it is essential to follow this group during their lifespan. Fondecyt 1160836

P1-P068

Impact on Final Height of Functional Insulin-Therapy in Type 1 Diabetes Mellitus Pediatric Patients – Experience from a Portuguese Pediatric Endocrinology Unit

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Introduction: Type 1 diabetes mellitus (1DM) has well known long term vascular and neuropathic complications. It has also been described a positive effect of good glycemic control on physical growth and pubertal development, achieved with improvement of insulin-therapy.

Table 1. (for Abstract no P1-P067)

	VPT (n=72)	T (n=41)	TOTAL (n=113)	p value
Glycemia (mg/dL)	84.54±6.52	83.10±7.19	84.02±6.77	0.278
Insulin (uU/mL)	5.79±3.39	5.36±2.56	5.63±3.11	0.485
HOMA-IR	1.23±0.75	1.12±0.56	1.19±0.69	0.425
QUICKI	0.17±0.02	0.17±0.04	0.17±0.03	0.269
TG/HDL-C	1.44 ± 1.03	1.01±0.46	1.28±0.89	0.014

As expected there is a positive correlation BMI and TG/HDL-C ratio (r=0.281; p=0.003).

Aim: To evaluate the effect of functional insulin-therapy on final height in children with type 1 diabetes mellitus.

Methods: Retrospective analysis of a cohort of portuguese 1DM children followed up to final height at a tertiary Hospital clinic from 1981 to 2017. Variables collected: age at diagnosis, sex, 1DM duration, type of treatment (conventional vs functional), height at diagnosis, final height, body mass index, family target height (FTH), age at pubertal start, mean A1c, blood pressure (BP) and lipid profile. Statistical analysis: SPSS®v22 ($p<0.05$). Results: 264 children were distributed according to type of therapy: group A (under conventional therapy), with 108 children, 57 (52,8%) males, with mean age at diagnosis of 8.3± 3.1years, 9.6± 3.5years of disease duration and 164,6± 8,7cm FTH; and group B (under functional therapy), 156 children, 82 (52,6%) males, with mean age at diagnosis of 8.4± 3.9years, 9.7±4.0 years of disease duration and 166,5± 8,9 cm FTH; and group B (under functional therapy). Comparing groups A and B, there were significant statistical differences regarding mean A1c 9% vs 8,1%, r<0,001), systolic BP (123,5 mmHg vs 120 mmHg, r=0,02), diastolic BP (67,5 mmHg vs 65,9 mmHg, r=0,011), HDL cholesterol (1,4 mmol/L vs 1,5 mmol/L, r=0,027) and age at puberty start (11,6 vs 11 years, r<0,001). Final height was higher than FTH in both groups and there was not different between groups (166 vs 168 cm, r=0,079). However, in group B longer duration of functional insulin-therapy was related with higher final height (Pearson 0,17, p=0,03).

Conclusions: Functional insulin-therapy had a positive effect on metabolic control and decreased microvascular complications, but this had no significant impact on final height.

P1-P069

Triglyceride Glucose Index as a Predictor of Impaired Glucose Tolerance in Overweight and Obese Adolescents

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Background: Triglyceride glucose (TyG) index, a product of fasting triglyceride and glucose, was widely used as an alternative tool for identifying insulin resistance in adults but not in children. Recent study in children showed association between the TyG index and HOMA-IR and a usefulness of TyG index as a surrogate marker of insulin resistance among adolescents.

Objective: To evaluated the potential role of the TyG index as a predictor of impaired glucose tolerance among overweight and obese children and adolescents and identified the cutoff values of TyG index for diagnosis of abnormal glucose tolerance test.

Method: Data of overweight and obese patients age 6-20 years who underwent clinical examination, fasting blood testing and oral glucose tolerance test at Phramongkutklao Hospital from January 2002 to December 2016 was reviewed. The TyG index was calculated as ln[fasting triglycerides (mg/dL) x fasting plasma glucose (mg/dL)/2]. Impaired glucose tolerance was defined as two-hour glucose levels of 140 to 199 mg/dL on the 75-gm oral glucose tolerance test.

Results: A total of 203 children and adolescents (122 males and 81 females) were included to our study. Mean age was 12.04 + 2.61 years (range 6.06-18.65) and BMI Z-score was 2.24 + 0.34 (range 1.41-3.01). One hundred and fifty-one children (74.4%) were obese. Of them, two (1%) had type 2 diabetes and 38(18.7%) had pre-diabetes: 1(0.5%) with impaired fasting glucose (IFG), 34(16.7%) with impaired glucose tolerance (IGT) and 3(1.5%) with IFG and IGT. The patient was divided to 2 groups: normal glucose tolerance or NGT (N = 163) and IGT (N = 37) group. Age, fasting blood glucose, HbA1C and TyG index were significantly higher in IGT than the NGT group. The TyG index was 8.27 + 0.43 and 8.54 + 0.58 in NGT and IGT, respectively (p 0.001). The area under the receiver operating characteristics (ROC) curve for TyG index and IGT was 0.648. In subgroup analysis of patients age > 13 years, the optimal cut-offs of the TyG index for diagnosis of impaired glucose tolerance was 8.3. The area under the ROC curve was 0.728 (95% confidence interval: 0.593–0.864) and represent sensitivity of 77.3% and specificity of 50%.

Conclusion: The TyG index is a simple parameter to use as a surrogate marker of impaired glucose tolerance in overweight and obese children age > 13 years compared with oral glucose tolerance test.

P1-P070

Birth Weight in Offsprings of Mothers with Gestational Diabetes Mellitus Due to Mutations in GCK Gene

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Background: The prevalence of MODY2 in the gestational diabetic population has been estimated to be approximately 2%. Risk of macrosomia in GCK/GDM cases depends on maternal glycemic control and fetal mutation status. However, the fetal genotype is unknown before birth. We assessed the effects of insulin therapy on the birth weight of children born to mothers with GCK mutations.

Objective and hypotheses: The study included 38 patients with GDM due to GCK gene mutations and their 38 offsprings (22 affected children and 16 unaffected). All participants were divided into 2 groups depending on offspring's genotype. All women during pregnancy were treated with insulin.

Results: The median birthweight in affected children was 3125 g [2800; 3300], in unaffected, 3550 g [2930; 3890], p=0.036, nevertheless the weight remained in the normal range for gestational age. Among unaffected children diabetic fetopathy was observed in 6 (37.5%) newborns, including one child born at week 31 with weight +2.3 SD. Two affected children had low birth weight. Insulin therapy in these cases was started early (5-7 weeks) with achievement of strict glycemic control and episodes of hypoglycemia.

Conclusions: Since prenatal diagnostics in the mothers with GCK gene mutations is not always justified, we recommend insulin therapy in order to prevent fetal macrosomia, which, however, should be less aggressive than in GDM due to other causes.

P1-P071

Review and Audit of Diabetes Control in Children and Young People with Diabetes Using the FreestyleLibre Flash Glucose Scanning System (FGS)

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Background: The Freestyle Libre Flash Glucose Scanning System (FGS) is a glucose sensing technology device for people with diabetes to monitor plasma glucose levels, reducing the need for routine fingerpricks. The device is worn on the upper arm and produces graphs displaying glucose levels over a period of time. Trials of the Freestyle Libre device have been utilised at Nottingham Children's Hospital (NCH), providing the device is used safely. Potential for most benefit includes patients who have difficulty completing regular fingerprick tests, impaired awareness of hypoglycaemia and patients who undertake glucose monitoring >8 times a day. This audit aims to evaluate the use of the Freestyle Libre device in children and young people attending NCH diabetes clinics to assess its effectiveness in improving diabetes control measured by HbA1c reduction.

Methods: Patients attending the paediatric clinic who had used the FGS device between April 2016 and November 2017 were identified. Data was collected retrospectively from patient records, specifically the Diamond (diabetes record) database and Diasend software, where information from the FGS device is downloaded. We recorded HbA1c levels before using the Freestyle Libre device, whether the patient continued to use the monitor for approximately 3 months and the HbA1c level 3 months after.

Results: 121 patients were identified with T1DM who had used the FGS device. 63 patients stopped using the device in less than 3 months. Patient data was unavailable for 2 patients. The 56 patients who continued to use the device for 3 months included 30 males and 26 females with an average age of 13 years and 6 months when using the device. Duration of diabetes was approximately 8 years and 5 months. Results suggested an average reduction in HbA1c from 63.66mmol/mol(SD±16.3) to 60.41mmol/mol (SD±15.72), a difference of 3.25mmol/mol ($p<0.05$). CI = 0.1 to 6.4. Patients who discontinued using the FGS device had an average increase in HBA1C of 2.48mmol/mol ($p<0.05$), from 57.74mmol/mol(SD±9.73) to 59.95mmol/mol(SD±10.93). CI = -4.02 to -0.43. Reasons for discontinuation of the FGS device included reduced accuracy and financial costs.

Conclusion: The change in HbA1c levels 3 months after using the FGS device suggests it is useful in helping monitor and reduce the average HbA1c level in children and young people. Future work assessing quality of life and level of hypoglycaemia reduction may further inform its use.

P1-P072

Increasing Use of Continuous Glucose Monitoring (CGM) Among Youth with Type 1 Diabetes (T1D): Icomparison of Youth from the T1D Exchange (T1DX) and the DPV Initiative

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Objectives: To assess change in rates of pediatric CGM use over the past 5 years across demographic and clinical characteristics and association with hemoglobin A1c (HbA1c), data from 2 registries were compared: the US-based T1DX and the German/Austrian DPV.

Methods: Registry participants in DPV and T1DX aged <18yrs with T1D duration ≥ 1yr with available data in any of the following years were included in the analysis (N for each year by registry shown in the Table). Demographic data, CGM use, insulin delivery method HbA1c were obtained from medical records.

Results: CGM use increased from 2011 to 2017 in all age groups in both registries, and was most pronounced in the youngest pa-

Table 1. (for Abstract no P1-P072)

	DPV				T1DX			
	2011 N=17632	2013 N=19484	2015 N=20858	2017 N=21707	2011 N=9060	2013 N=8334	2015 N=9089	2017 N=9184
% CGM Use Overall	4%	3%	4%	44%	3%	4%	14%	31%
% CGM Use by Age group								
1-<6 yrs	6%	6%	10%	57%	5%	7%	32%	52%
6-<13 yrs	3%	3%	5%	49%	3%	4%	18%	37%
13-<18 yrs	4%	2%	3%	38%	3%	3%	11%	25%

tients (Table). In the DPV registry, CGM use remained steady from 2011 to 2015 with a dramatic increase from 4% to 44% occurring between years 2015 and 2017, whereas for T1DX, CGM use doubled from 4% in 2013 to 14% in 2015 to 31% in 2017. CGM use in both registries increased from 2011 to 2017 regardless of gender or minority status. Among DPV participants using injections for insulin delivery CGM use increased from 3% to 35% compared with 5% to 50% among pump users. Among T1DX participants CGM use increased from 1% to 13% among injection users and 5% to 40% among pump users. Average age, gender and minority status adjusted HbA1c in 2017 was lower in CGM users than non-users for both registries (T1DX 8.2% / 66mmol/mol vs. 9.2% / 78 mmol/mol; DPV 7.7% / 61mmol/mol vs. 8.0% / 64mmol/mol, P<0.001 for both)

Conclusions: Pediatric CGM use increased in both registries but at different rates from 2011 to 2017. Increase in CGM use over time is likely reflective of changes in insurance coverage and improvements in device technology and availability. Although current CGM users had significantly lower HbA1c than non-users, whether increase in CGM use leads to improvements in glycemic control and reduction in acute complications warrants exploration.

P1-P073

Efficacy of Real-Time Continuous Glucose Monitoring in Type 1 Diabetic Pre-School and School Children Treated with Multiple Daily Injections

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Background: Young children affected by Type 1 Diabetes (T1D) are prone to glucose fluctuations and hardly reach a stable glycometabolic control, especially when treated with a Multiple Daily Insulin Injections (MDI) scheme. The recent Real-Time Continuous Glucose Monitoring (RT-CGM) System, Dexcom G5, the only available device registered for non-adjunctive insulin intervention, potentially facilitates a better management of the disease. Evidence regarding CGM effectiveness among children treated with MDI is limited.

Aim of the study: To evaluate the effect of the RT-CGM on glycometabolic control, glucose variability and hypoglycemia in T1D children under 10 years, treated with MDI, compared to a control group traditionally monitored with Self Monitoring of Blood Glucose (SMBG).

Patients and Methods: 73 T1D children under 10 years were enrolled in this observational study. Patients were subdivided into four groups:

1. 21 children at onset of diabetes monitored with RT-CGM
2. 29 control children at onset of diabetes monitored with SMBG
3. 10 children with Diabetes Duration > 1 year monitored with RT-CGM
4. 13 control children with consolidated T1D monitored with SMBG

Groups were homogeneous for age (respectively 4.3 ± 2.39, 4.0 ± 1.79, 7.0 ± 2.17 and 6.7 ± 2.60 years) and HbA1c (respectively 10.9 ± 2.02, 10.7 ± 1.26, 7.5 ± 0.45 and 7.8 ± 1.14 %). After 12 (T1) and 24 weeks (T2) the following parameters were evaluated: HbA1c, Time in Range (70-180 mg/dl), Time in Hypo (< 70 mg/dl), Time in Hyper (> 180 mg/dl) and Coefficient of Variation (CV). At the end of the study all parents were administered the GMSST1 questionnaire to evaluate the device satisfaction.

Results: Groups 1 and 3 used RT-CGM for 90,19±8,52% of time at T1 and for 91,37±8,33% of time at T2. HbA1c resulted significantly reduced at T2 in the RT-CGM treated groups as compared to control groups (7,2±0,72% vs 7,7±0,94%; p<0.007). TIR resulted significantly (p < 0.03) increased at T2 in the RT-CGM treated groups as compared to control groups. Reduction of Time in Hypo was reported for all patients using CGM, both at onset of diabetes and also during consolidated disease (data statistically non significative). GMSST1 high scores have been reported for all items.

Conclusions: RT-CGM Dexcom G5 was proven to have a clinically significant effect on glucose control in very young children with T1D treated with a MDI scheme, both at onset of diabetes and during disease's follow-up.

P1-P074

Catheter Site Selection and Anthropometric Measurements at Subjects with Type 1 Diabetes and Continuous Subcutaneous Insulin Infusion

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Introduction: The selection of the insulin catheter length for pump T1D users is based mainly on age and though different sites for insertion have been suggested, it is not clear what the ideal site is according to each person's body type and subcutaneous fat.

Aid: Aid of the study is to identify the proper sites for insulin catheter insertion according to subcutaneous fat and anthropometric characteristics.

Methods: Study group was comprised of 43 T1D subjects (median age 7,08, range 1.56-28.0 years, 24 males, median disease duration 2,2 years, range 0.18-20.8 years) who were on CSII and were divided into 3 age categories [≤5 (11 subjects), 5-9 (19), ≥9 years (13)]. Weight, height, BMI, BMI SDS, skin folds, waist and hip circumference and the presence of hypertrophy were recorded. Ultrasound for measuring subcutaneous fat depth was performed at different sites. The size of insulin nebula dose and the distance of its edge to the muscle fascia (DTMF) were evaluated.

Results: There was no difference in gender among age categories. Six subjects used 9mm catheter and 36 6 mm. Seven out of 14 patients who had the catheter on the abdomen at the time of examination were at the lowest quartile of DTMF, while those with the catheter on the gluteal region were at higher quartiles (p=0.003). Subjects who carried the 9 mm catheter had significantly less depth of subcutaneous tissue in the arm compared to those who carried the 6 mm one (p=0.041). However no significant difference

was found in the other catheter sites. A significant difference was found among the various BMI SDS categories and the depth of subcutaneous tissue in the arm (p<0.0005), the front (p=0.019) and side area of the thigh (p=0.013) and the buttock (p=0.013), but not the upper (p=0.092) and lower part of the abdomen(p=0.312). No difference was found among the different age categories and the depth of subcutaneous tissue at the above mentioned catheter sites.

Conclusions: BMI SDS was better indicator than age to evaluate the subcutaneous fat in order to find the ideal area of catheter site. Ultrasound was useful in identifying the proper catheter site especially at thin subjects.

P1-P075

Open Source Artificial Pancreas Systems Used from Bulgarian Children and Young People with Diabetes

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Introduction: The new technologies in diabetology improved not only HbA1c, but also „Time in range", „Glycemic variability Index „/GVI/, and „Patient's Glycemic Status" /PGS/. Parents of children and patients with diabetes demonstrated impatience for artificial pancreas systems /APS/. They initially created „Nightscout" platform for remote monitoring of the glucose sensors and then – Do It Youself Open Source Artificial Pancreas Systems (DIY OpenAPS). Currently 3 OpenAPS are mostly used:

- AndroidAPS (Milos Kozak)(using OpenAPS algorithm running on Android phones);
- OpenAPS (Dana Lewis)(the original, for old Medtronic pumps, running on pocket computer);
- Loop (Pete Schwamb)(different algorithm running on iPhone with old Medtronic pumps)

In Bulgaria there are 75 Type 1 diabetes patients, who use Android APS and 3 use Loop. The systems are applied by the patients or parents step-by- step, controled by the creators and the team of „Culture without borders".

Objectives: To share the results for 17 Bulgarian patients with AndroidAPS and Loop, who gave access to their Nightscout data.

Materials and Methods: Data for 15 patients using AndroidAPS and 2 - using Loop are presented.

Variation analysis was applied for the data obtained from Nightscout platform for 90 and 30 days.

Results: Average age 13.5 (3.8–39.9) years; Duration of diabetes 7,52 (1.8–28.3) years; APS -3 months to 2.3 years. The average levels and ranges of the indices for diabetes control for both periods are shown in the table:

No severe hypoglycemia or DKA were observed. All the patients and parents show satisfaction from the APS.

Discussion: The average values for the glycemic control with DIY OpenAPS show stable results for the examined period. The average time in range above 75% is excellent, while the time in hypoglycemia is comparatively low. GVI and PGS also fall in the desired range for optimal control. The registered ranges in the individual parameters give possibilities for the patients/creators/physicians to puzzle out and upgrade the personal settings.

Conclusion: The presented patients on DIY OpenAPS manifest safety of the systems, excellent results of all the parameters for precise control of diabetes, as well as high satisfaction of this treatment options.

P1-P076

National Survey of Usage of Continuous Glucose Monitoring in Children and Adolescents at Non Reimbursed Setting

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Background: Continuous glucose monitoring (CGM) correlates with optimal control in both children and adults with type 1 diabetes (T1D) regardless of type of treatment. CGM plays a major

Table 1. (for Abstract no P1-P075)

Days	%low <4.4 mmol/L	%Normal >4.4–<10.0	%Hgh >10.0	HbA1c%	HbA1c Mmol/mol	GVI (<1.5)	PGS (35–100)
30	5.9	76.1	17.96	6.43	46.71	1.39	46.1
	0.1–12.6	65–90.5	4.1–26.1	5.1–7.4	33–57	1.1–1.58	13.9–86.0
90	7.0	76.3	16.3	6.44	46.9	1.41	48
	0.1–16.2	63.6–89.9	0.2–28.2	5.1–7.3	33.0–57.0	1.1–1.51	12.8–72.3

Table 1. (for Abstract no P1-P076)

Sensor usage	Continuous	Intermitent	p
MDI	7.43	8.49	0.0004
CSII	7.06	7.49	NS
p	0.004	NS	

role in decreasing the time spent in hypoglycemia and hyperglycemia, and achieving better quality of life.

Aim: To evaluate the usage and benefits of out-patient CGM and assess parents' attitudes to it at a non-reimbursed setting.

Methods: A total of 984 families with child/children with T1D from 8 clinics were invited to participate in the study by filling-in an on-line or paper version short questionnaire.

Results: In total, 354 (36.0%) parents aged 39.4±6.9y, most of whom University (43.8%) and high school graduates (33.3%), responded. Mean age of the children is 11.1±3.9y (<6y. 47; 7-12y 161; 13-18y 143, 3 n.a.), with mean duration of T1D 5.5±13.6y; 180 (50.8%) are boys. According to the therapy, 283 (81.1%) are on insulin analogs, 300 on MDI and 54 on pumps. Participants measure BGL with finger pricks 4.3±2.6 times/day (sensor users vs. non users 3.2 vs. 4.5); 149 (42.1%) measure blood ketones and 44.1% check urine ketones. About one third (39.3%) have never measured ketones. Physicians prescribed glucagon in 83.6% of all.

Almost half of the respondents (159, 44.9%) have used CGM at least once; 108 (30.5%) use it continuously (65 MDI, 43 pumpers). FreeStyle Libre is the most frequent (60%), followed by Dexcom G4 (26%), iPro2 (10%), and EnLite (4%).

Mean HbA1c is 8.35±2.0%, and CGM users show better metabolic control (7.66% vs. 8.9%, p=0.04). HbA1c correlates with consistency of CGM usage (continuous vs. intermittent, 7.32% vs. 8.37%) and with type of therapy (*Tabl. 1*). Most common reasons for CGM usage are: optimizing insulin therapy (82.3%), reducing glucose variability (65.4%), reducing hypoglycemia (56.6%), remote kid's surveillance (56.0%), better HbA1c (52.8%), less Dawn phenomenon (50.3%) and increased independence of the child (41.5%).

Patients and their families acquire information about CGMs mostly from pediatric endocrinologists (81.8%) followed by internet/groups (55.1%) and lectures (12.1%). Most families (82.5%) are discussing innovations and new technologies in T1DM with the pediatric endocrinologist; only 26.8% of them are offered support from a psychologist.

Conclision: CGM usage is increasing in prevalence at a non-reimbursed setting and shows improvement of diabetes control in T1D.

P1-P077

Additional Insulin Is Necessary to Prevent Rise in Blood Glucose After Fat-Protein-Rich Meals in Type 1 Diabetes

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Background: High amounts of protein in meals increase blood glucose in patients with type 1 diabetes. Fat delays the increase of blood glucose. Till now we do not know the amount of insulin necessary to prevent the increase of blood glucose after a fat and protein rich meal (FPRM).

Aim: To find the Insulin dosage to normalize glucose level after a FPRM.

Patients: Sixteen patients with type 1 diabetes (mean±SD; Age 19.7±2.7 years; diabetes duration 12.0±5.7 years; HbA1c 7.4±0.75%).

Methods: Application of a FPRM as evening meal (carbohydrates 57.2 g; protein 92.4 g; fat 38.8 g; fibers 7.2 g; calories 974.2 kcal) with additional 20% or 40% more Insulin compared to a standard meal (SM; carbohydrates 70 g; protein 28 g; fat 19 g; fibers 10 g; calories 560 kcal) or carbohydrates only. Insulin was administered as regular insulin for patients with ICT or as a 4 hours delayed bolus in patients on pump therapy. Recording of glucose levels during 12 hours after the meal was carried out with CGM (Enlite-Sensors, Medtronic Corporation). Comparison of Glucose levels between FPRM and SM and calculation of additional insulin amount based on 100 g of proteins as a multiple of the carbohydrate unit.

Results: Glucose levels (median, mg/dl) 12 hours after the meal with 20% vs. 40% vs. dose for SM was 103.5 vs. 103.0 vs. 82.0. Glucose-AUC during 12 hours after the meal with 20% vs. 40% vs. dose for SM was 1489 vs. 1488 vs. 1415 mg/dl/12 h (no significant differences). Glucose levels in the target range with 20% vs. 40% more Insulin were 60% vs. 69% (Chi-Square-Test, p<0.01). Glucose levels <60 mg/dl did not increase by use of 40% more Insulin. This corresponds to the 2.15 fold carbohydrate unit for 100 g Protein.

Conclusion: To normalize glucose levels after a FPRM we recommend the extra administration of double the dose used per one carbohydrate unit for 100 g protein. We therefore suggest giving additional Insulin corresponding to that amount after a FPRM.

P1-P078

Efficacy of Autologous Hematopoietic Stem Cell Transplantation in the Treatment of Childhood Type 1 Diabetes Efficacy of Autologous Hematopoietic Stem Cell Transplantation in the Treatment of Childhood Type 1 Diabetes

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Objective: To observe and analyze the efficacy and safety of autologous stem cell transplantation (AHSCT) in children with type 1 diabetes.

Methods: Twelve children were enrolled in our study who were newly diagnosed as type 1 diabetes in Children's Hospital of Fudan University from Sep 2009 to Dec 2011. Changes in the exogenous insulin requirement were observed and HbA1C and C peptide level were measured before and after AHSCT.

Results: After transplantation, insulin dependence was observed in 2/12 patients. Complete remission rates were 2/3, 1/2 and 1/4 after transplantation for 6, 24 and 48 months respectively. One child had a complete remission for almost 63 months. The level of HbA1C decreased significantly after transplantation (p=0.000). Meanwhile, the C peptide level enhanced a lot (p=0.004). However, no relationship was found between complete remission duration and other parameters, such as height, weight, BMI, DKA or not, HbA1C level, C peptide level before transplantation. No serious complication was observed during the whole phase.

Conclusions: Our data indicated that AHSCT has slight complication and could significantly improve β-cell function. Although AHSCT failed to cure type 1 diabetes, but it can prolong the remission period for new onset patients.

Key words: hematopoietic stem cell, transplantation, type 1 diabetes, HbA1C, C-peptide

P1-P079

A Novel *SLCA16A1* Mutation in an Infant with Hypoglycemia and Severe Metabolic Ketoacidosis

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Background: Recurrent episodes of ketoacidosis with or without hypoglycemia have been reported with homozygous or heterozygous mutations in the solute carrier family 16 member 1 (SLC16A1) gene. This gene encodes for the monocarboxylate transporter 1 (MCT-1) which plays a key role in lactate, pyruvate and ketone body transport.

Objective(s): To describe the youngest patient with a novel SLC16A1 gene who presented with recurrent episodes of ketoacidosis and hypoglycemia.

Case presentation: The patient was born following a NVD. At 3 days of age she presented with hypothermia and acidosis. At 6 months, she presented again with vomiting and was biochemically noticed to have hypoglycemia and metabolic acidosis. Family history was significant for consanguinity (first degree cousin parents). Our patient is developmentally normal at the age of 2.

Methods: Whole Exome Sequencing (WES) analysis was performed in the patient at 6 months of age and her parents using NetGen sequencing on an Illumina system. Sequence and copy number alterations were reported according to the Human Genome Variation Society (HGVS) and International System for human Cytogenetic Nomenclature (ISCN) guideline.

Results: WES showed that the patient was homozygous for the c.218delG pathogenic mutation in the *SLC16A1* Gene (P.Gly73ValfsX8 in exon 3 in the SLC16A1 gene). The patient's mother and father were heterozygous for the mutation. The c.218delG mutation has not been reported previously as a pathogenic or benign. The c.218delG mutation causes a frameshift starting with codon Glycine 73, changing this amino acid to Valine residue and creating a premature Stop codon at position 8 of the new reading frame. This identified mutation is anticipated to cause loss of normal protein function either through protein truncation or nonsense-mediated mRNA decay. The c.218delG mutation is not observed in large population cohorts.

Conclusions: We report a novel mutation in the *SLC16A1* gene leading to recurrent metabolic ketoacidosis and hypoglycemia. Our patient is one of the youngest presenting and diagnosed with this disorder. Further research is required to understand the role of the MCT-1 in key tissues such as the liver, muscle and ketone body metabolism. Disruption of MCT1 in the central nervous system produces axon damage and neuronal loss in mice, yet it remains unclear at this stage whether this is a direct effect of the absence of MCT1 in the brain or caused by episodes of profound ketoacidosis. Nevertheless, neurodevelopmental follow up should be considered in this patient.

P1-P080

Successful Transition to Sulfonylurea Therapy in Infant with Neonatal Diabetes, Developmental Delay, Epilepsy (DEND Syndrome) Due to F132L *ABCC8* Mutation

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Introduction: The heterozygous activating mutations in the *KCNJ11* and *ABCC8* are the commonest causes of permanent neonatal diabetes mellitus (PNDM). The most severe clinical form of NDM is DEND syndrome.

Besides diabetes mellitus such patients show severe developmental delay, hypotonia and therapy-resistant epilepsy. To our knowledge only some cases of DEND syndrome due to ABCC8 mutations are sulfonylurea-responsive.

Here we report case of DEND syndrome due to F132L *ABCC8* mutation who was completely switched from insulin to sulfonylurea monotherapy.

Clinical case: A boy was born as a first child of non-consanguineous parents following an uneventful pregnancy and spontaneous term delivery. His birthweight was 2830 g (-1,77 SDS). At 3 month of age he presented with failure to thrive, hyperglycemia (18 mmol/l), ketosis, severe hypotonia and frequent generalized clonic-tonic seizures unresponsive to increasing doses of the antiepileptic drugs (phenobarbital, valproic acid, levetiracetam, vigabatrin).

NDM was diagnosed and continuous subcutaneous insulin pump therapy was started. At 5 month of age he was referred to our hospital because of ongoing seizures and poor glycemic control (HbA1c was 10,5%). Also he had hypotonia and severe developmental delay.

Most of the time he spent lying on his back, did not hold his head and did not roll over. He couldn't babble and was not interested in toys.

De novo heterozygous mutation F132L in *ABBC8* gene was identified. After genetic testing the patient was successfully transferred to glibenclamide at a daily dose of 0,4 mg/kg.

Now he is 1 year and 6 months old. His HbA1c decreased to 5,7%. The glibenclamide dose remained unchanged (0,4 mg/kg/day). During period of observation we have not seen any side effects, including severe hypoglycemia.

Also we have noticed an improvement in his neurological status. He doesn't have seizures and sings of hypsarrhythmia according to EEG. His tone is also improved so he is able to hold his head, roll over and sit with support

Conclusion: Any patient with NDM should be genetically tested and then referred to a tertiary center with experience of NDM management. The F132L/*ABCC8* mutation seems to have a chance of positive response to glibenclamide monotherapy in doses around 0,4 mg/kg/day with improvement of neurological symptoms.

P1-P081

ZFP57-Associated Transient Neonatal Diabetes Is Responsive to Oral Sulfonylurea Treatment

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Background: Transient neonatal diabetes (TNDM) is commonly caused by a methylation loss in the 6q24 region, either in isolation or as multiple-loci demethylation due to *ZFP57* gene mutation. TNDM is biphasic; usually resolves after 2-3 months but often recurs between age 4 and late adolescence.

Case: The boy was born at 38 weeks of gestation (birth weight 3340 g, healthy consanguineous Turkish parents, unremarkable pregnancy). He presented at 4 weeks of age with left-sided seizures, and hyperglycaemia of 669mg/dl (37.1mmol/l) without ketoacidosis. C-peptide level (0.3nmol/l) was low, pancreatic autoantibodies negative. Echocardiography, cranial and abdominal ultrasound results were normal. Due to ongoing seizures, phenobarbital therapy was initiated, while the patient exhibited abnormal muscle tone and opisthotonus. DEND (developmental encephalopathy and neonatal diabetes) syndrome was suspected, usually caused by potassium channel mutations. Cerebral MRI showed agenesis of corpus callosum and unspecific periventricular white matter hyperintensities. No other laboratory abnormalities or syndromic features were evident.

Intravenous insulin was started (0.25IU/kg/d), stabilizing blood glucose (BG) at around 160-180mg/dl (9-10mmol/l). Because of decreasing insulin requirements, insulin was stopped after 7 days, but hyperglycaemia resumed with BG above 300mg/dl (16.7mmol/l). After detailed counselling with the parents, oral sulfonylurea (glibenclamide) treatment was started on his 38th day of life, while genetic results were pending. Dosing was gradually increased from 0.1mg/kg/d to 1.0mg/kg/d, resulting in good BG response (BG 70-160mg/dl [3.9-9mmol/l] without additional insulin applications or signs of ketosis).

Pathogenic mutation in *INS, ABCC* and *KCNJ11* were ruled out; however, a homozygous mutation in *ZFP57* (c.1372C>G, p.[His458Asp], NM_001109809.2; alternative nomenclature: c.1312C>G, p.[His438Asp]) was found in next-generation-sequencing of all NDM genes, resulting in a loss of methylation in 6q24 as shown by methylation-specific PCR. *ZFP57* regulates methylation at several sites in the genome. Thus, multiple-locus demethylation explains the extrapancreatic features with striking clinical overlap to DEND syndrome. This same mutation was described previously in TNDM. A trend toward hypoglycaemia was observed after 10 days of treatment, leading to a dose reduction. Treatment was discontinued after 14 days (52th day of life) due to diabetes remission.

Conclusion: While TNDM cases due to K-ATPase channel mutations (*ABCC* and *KCNJ11*) are routinely treated with oral sulfonylurea, this is the first description of successful glibenclamide treatment in *ZFP57*-associated TNDM. Furthermore, it underlines the benefits of early broad genetic differential diagnosis in neonatal diabetes.

P1-P082

The Comparison of the Occurrence of Beta Cells Autoantibody and Regulatory T Cells (CD4+CD25+FoxP3+) in Patients with Type 1 Diabetes Mellitus, Their Siblings and Healthy Children

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Background: Regulatory T cells (Treg) of phenotype CD4+CD25+FoxP3+ involves active suppression of excessive immune response. The population of Treg cells from patients with type 1 diabetes (DM1) have numeric and functional abnormalities.

Although there are many reports of investigations on human and animal populations, the role of regulatory T cells in the development of type 1 diabetes is still unclear.

Objective and hypotheses: The aim of the study is to compare the population of regulatory T cells and the correlation between Treg cells and beta cells autoantibody in healthy siblings of children with DM1 to healthy children from non-diabetic families and to children with DM1.

Method: Peripheral blood mononuclear blood cells were obtained from 76 children with DM1, their siblings - 101, and 30 healthy children. Treg cells were characterized by flow cytometry FACSCalibur (Becton Dickinson, USA). The auto-antibodies were determined by ELISA. The results were analyzed with STATISTICA 10 PL.

Results: The number of regulatory T cells from diabetic patients was higher (average percentage 0,23±0,20) than that in the siblings (0,15±0,14) (p=0,004). There was no significant difference in the number of Treg cells between children with DM1 and the control group (0,19±0,15; p=0,11) and between siblings and the control group (p=0,09).

The levels of anti IA2 and anti ZnT8 antibodies were statistically significant higher in siblings in comparison to the control group (anti IA2 Ab p=0,0000001; anti ZnT8 Ab p=0,00001). The level of anti-GAD in siblings was similar to that in the control group. There was no correlation between the number of Treg cells and the co-occurrence of beta cells auto-antibody.

Conclusion: The results suggest that regulatory T cells probably provide protection from development of disease and the dysfunction of Treg cells contributes to the autoimmune pathogenesis of type 1 diabetes.

P1-P083

HERV-W-Env Protein Expression in Pediatric Type 1 Diabetes Patients

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Introduction: The envelope protein of Human Endogenous Retrovirus type W (HERV-W-Env) has been shown to be associated with type 1 diabetes (T1D) pathogenesis in adults patients. This protein is expressed in pancreas of T1D patients and it seems to correlate with macrophage infiltrations. In vitro and in vivo studies have demonstrated that HERV-W-Env inhibits insulin secretion and promotes hyperglycemia. Furthermore, HERV could be implicated in other auto-immune disorders. The purpose of this study was to investigate the prevalence of HERV-W-Env protein and its corresponding RNA in pediatric T1D patients.

Methods: We performed a preliminary study in a monocentric pediatric cohort (n=19). Inclusion criteria were T1D, absence of any acute inflammatory or infectious disease or anti-inflammatory medication. The results were compared to a previously studied cohort of 30 healthy adults. HERV-W-Env expression was assessed by Elisa in sera and by quantitative reverse transcription PCR (RT-qPCR) in peripheral blood mononuclear cells (PBMC). Other clinical data evaluated in the pediatric group were: age, age at onset of diabetes, length of diabetes, BMI, daily insulin dose, fasting glycemia, HbA1C, C-peptide, ACTH, TSH, total Cholesterol, HDL, LDL, Ratio HDL/total cholesterol, HLA typing, specific auto-antibodies (anti GAD, anti-insulin, ant-IA2).

Results: HERV-W-Env protein was significantly detected in T1D pediatric patients compared to control individuals ($P < 0.01$). We detected *HERV-W-env* RNA expression in PBMC of 7/19 (37%) T1D patients (not statistically significant compared with control individuals). 7/17 (41%) sera of T1D patients were positive for HERV-W-Env, whereas 4/30 (13%) control individuals had low positivity of unknown origin. HERV-W-Env expression was not related to age, age at onset, HbA1c or diabetes duration. Daily insulin dose was positively correlated with HERV-W-Env expression ($P < 0.05$). Additionally, none of the T1D pediatric patients positive for HERV-W-Env had detectable C-peptide. Interestingly we found a positive correlation HERV-W-Env expression and TSH levels ($p < 0.05$).

Conclusions: HERV-W-Env protein was significantly detected in about 40% of T1D pediatric patients. Levels of HERV-W-Env were positively correlated with daily insulin dose, suggesting that HERV-W-Env may be associated with complete insulin deficiency. As HERV could be implicated in other auto-immune disorders and could affect endothelial cells and Schwann cells, a close monitoring of T1D comorbidities in these patients seems essential. Overall, our results suggest that a pediatric subgroup of T1D might benefit from an anti-HERV-W-Env therapy.

P1-P084

The Comparison of the Occurrence of Beta Cells Autoantibody and Natural Killer Cells in Patients with Type 1 Diabetes Mellitus, Their Siblings and Healthy Children

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Background: Natural killer cells are a type of cytotoxic lymphocyte critical to the innate immune system. NK cells from patients with type 1 diabetes (DM1) have numeric and functional abnormalities. However, little is known about the number of NK cells in healthy siblings of children with DM1.

Objective and hypotheses: The aim of the study is to compare the population of NK cells and the correlation between NK cells and beta cells autoantibody in healthy siblings of children with DM1 to healthy children from non-diabetic families and to children with DM1.

Method: Peripheral blood mononuclear blood cells were obtained from 76 children with DM1, their siblings - 101, and 30 healthy children. NK cells were characterized by flow cytometry FACSCalibur (Becton Dickinson, USA). The auto-antibodies were determined by ELISA. The results were analyzed with STATISTICA 10 PL.

Results: The lowest percentage of NK cells was observed in diabetic patients (average percentage 10,59±5,37) and was lower than that in the control group (14,89±7,78) (p=0,002). The number of NK from the siblings was similar to patients with diabetes mellitus type 1, there was no significant difference in the number of NK cells between children with DM1 and their siblings (p=0,11). NK cells from siblings was lower (average percentage 11,93±5,62) than that in the control group (p=0,02).

The levels of anti IA2 and anti ZnT8 antibodies were statistically significant higher in siblings in comparison to the control group (anti IA2 Ab p=0,0000001; anti ZnT8 Ab p=0,00001). The level of anti-GAD in siblings was similar to that in the control group. There was a positive correlation between the reduced number of NK cells and the co-occurrence of anti-GAD and anti ZnT8 Ab (the May-Whitney test Z=-2,02; p=0,04) in the diabetic patients.

Conclusion: The results suggest that the dysfunction of NK cells may contributes to the autoimmune pathogenesis of type 1 diabetes and is connected with genetic predisposition to DM1.

P1-P085

T – and B-Lymphocytes Levels in Children with Type 1 Diabetes in Association with *Candida* Infection

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Although type 1 diabetes (T1D) is most common autoimmune chronic metabolic disease in childhood, data about the role of T-Lymphocytes (T-Ly) and B-Lymphocytes (B-Ly) in children after the diabetes onset are still controversial.

The **aim** of the study was to evaluate the serum levels of T– and B-Ly in children with T1D as a predisposing factor for genital candidiasis (GC)

Material: We studied 71 children with T1D at the age of 6 to 18 years, divided into two groups – with and without GC and 30 age-matched healthy controls.

Methods: A flow-cytometry immunophenotyping of T-Ly (CD3+), Ts (CD8+), Th (CD4+) and B-Ly (CD19+) was performed. Microbiological culture of genital discharge by the patients with T1D for diagnostic of GC was made. Glycated hemoglobin (HbA1c) for assessment of metabolic control of T1D was measured. Statistical analysis with Statgraph and SPSS software was performed and as statistical significant a P-value < 0.05 was defined.

Results: Positive cultures for candidal infection of genitalia had 24 (33,8%) of 71 studied diabetic patients. The mean level of HbA1c showed a poor long term metabolic control in all researched T1D-patients - 10,09±2,28%, significantly higher in the group with GC - 11,09±2,26% than those without infection - 9,39±2,18% (p=0,0002).

Serum levels of CD3+, CD4+ and CD8+ in all patients with T1D were found within the lower part of the normal reference range. No statistical significance with the control group was established (p>0,05).

Serum levels of B-Ly 11,02% (P_{25} 8,83; P_{75} 13,85) in all diabetic children were significantly lower than those in heathy controls 14,52% (P_{25} 12,23; P_{75} 17,76) (p=0,001)

We found no significant differences between the researched T- and B-Ly levels in diabetic children with and without *Candida*.

Although the increased mean level of HbA1c in the studied patients, no significant correlation between the immunological parameters and metabolic control was found.

Conclusion: In the researched children with T1D was found poor long term metabolic control. Their T-Ly levels were distributed at the lower reference range and B-Ly were decreased, with no significant differences in association with *Candida* infection.

P1-P086

Coincidence of Newly Diagnosed Type 1 Diabetes Mellitus with Enteroviruses and Respiratory Tract Viruses

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Background: Viruses, which trigger and promote islet cell destruction, cause type 1 diabetes mellitus (T1DM). However, the existence of a cause-and-effect relationship is under debate. The aim of this study was to investigate sero-epidemiological and molecular evidence of enteroviruses and respiratory viruses in patients with newly diagnosed T1DM during cold season.

Methods: This study included 40 children with newly diagnosed T1DM and 30 healthy children during a year. Children were studied for coxsackievirus B4 (CVB4) RNA and screened in serum for IgM antibodies to a number of viruses including enteroviruses and respiratory viruses. The seasons of diagnosis were classified into autumn-winter and spring-summer. The months of diagnosis were separated in terms of cold, moderate, or warm temperature.
Results: The following percentages of IgM antibodies against the most common viruses were detected in the patients: Influenza B (IVB) (70%), echovirus 7 (ECHO7) (45%), parainfluenza virus 4 (PIV4) (40%), coxsackievirus A7 (CAV7) (27.5%), H3N2 (22.5%). Compared with the control group, these viruses had a significant association with T1DM (p=0.000, p=0.000, p=0.035, p=0.003, p=0.023, respectively). coxsackievirus B4 RNA was not detected in any serum. A total of 75% and 95% patients were diagnosed with T1DM in autumn-winter and cold or moderate months, respectively.

Conclusion: Our study demonstrates significant association of T1DM with seropositivity for IgM antibodies against IVB, ECHO7, PIV4, CAV7, and H3N2, and the majority of newly diagnosed T1DM appeared in autumn-winter, suggesting that enteroviruses and respiratory viruses, in addition to seasonal variation could play a role in the etiopathogenesis and clinical onset of T1DM.

P1-P087

Investigation Into B-Cell Adaptation During Puberty

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Background: Puberty is a time of hormonal changes that are associated with insulin resistance. Although insulin sensitivity is restored at the end of puberty in healthy youth, it does not resolve in obese adolescents leading to an increase of cardio metabolic disease such as type 2 diabetes.

In response to an increase in insulin demand, as during pregnancy or obesity-induced insulin resistance, β-cells increase their functional mass to maintain glucose homeostasis. However, the mechanism of pancreatic β-cell compensation in the face of pubertal insulin resistance has not been established. Hormonal changes during puberty could be linked to this β-cell adaptation.

Objective: To characterize pancreatic β-cell adaptation to pubertal insulin-resistance.

Methods: Metabolic (body weight, fasted plasma insulin, glucose tolerance) and hormonal (vaginal opening, estradiol, testosterone, IGF1 levels) parameters were measured in Wistar rats from weaning to adulthood. β-cell proliferation was assessed by immunostaining of pancreatic cryosections for Ki67 and insulin to mark β-cells and β-cell mass by morphometric analysis of insulin staining.

Results: As expected we observed glucose intolerance and an increase in insulin levels during puberty in female and male rats, suggesting increased insulin resistance. An increase in β-cell proliferation at puberty was found, interestingly correlated with the rise in IGF1 levels rather than sex steroids.

Conclusion: Insulin resistance and β-cell proliferation increase during puberty in rats. The parallel increase in IGF1 levels and β-cell proliferation point to a possible role of growth hormone in compensatory β-cell expansion.

In future studies we will assess whether β-cell adaptation is compromised in a pathological model of metabolic stress during puberty.

P1-P088

The Shape of the Glucose Curve and Time to Glucose Peak During an Oral Glucose Tolerance Test as Indicators of Beta Cell Function in Obese Adolescents

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Introduction: Morphological characteristics of the glucose concentration curve during an oral glucose tolerance test (OGTT) may reflect differences in insulin secretion and sensitivity. Whether the shape of the glucose curve and time to peak glucose concentration can be used as indicators of beta cell function and markers of type 2 diabetes risk in obese adolecents is still uncertain.

Aims/hypothesis: The purpose of this cross-sectional study was to assess whether the shape of the glucose response curve (monophasic vs biphasic) and timing of the post challenge peak blood glucose (30 vs ≥60 min) during OGTT can be indicators of beta cell function in obese adolescents with normal glucose tolerance (NGT). We hypothesised that monophasic glucose curve and delayed timing of peak glucose (≥60 min) are independently associated with impaired beta cell function estimated through oral disposition index (oDI).

Research design and methods: A total of 159 obese adolescents who completed a 2-h OGTT and were classified as NGT, were further categorised by the glucose curve shape as either a monophasic or a biphasic group, or by the time to maximal glucose concentration as either a group with early (30 minutes) or late glucose peak (≥60 minutes). Groups were compared with respect to insulin sensitivity (whole body insulin sensitivity index, WBISI), early-phase insulin secretion (insulinogenic index, IGI) and beta cell function (oral disposition index, oDI).

Results: 84 (52.8%) adolescents had a monophasic and 75 (47.2%) a biphasic curve shape. Participants with monophasic curve had lower IGI (p=0.001) and poorer beta cell function relative to insulin sensitivity as reflected by lower oDI (p<0.001) compared with the biphasic curve group. No differences were found in the degree of obesity (BMI z-score) between groups, but participants in the biphasic group were younger (p=0.001), with higher proportion of prepubertal and early pubertal subjects and male predominance. With respect to glucose peak, 92 (57.9%) participants had an early and 67 (42.1%) a late peak. The latter group had lower IGI (p=0.038) and lower oDI (<0.001). There were no significant differences between early and late glucose peak groups in the degree of obesity, puberty stage and gender, but subjects with late glucose peak were younger (p=0.03).

Conclusion: Among obese adolescents with NGT, those with monophasic curve shape as well as those with glucose peak ≥60 minutes during an OGTT, are at increased risk of beta cell dysphunction.

P1-P089

Features of T2DM in Adolescents with Low Titer of ICA and IAA

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Purpose: To assess the prevalence of pancreatic autoantibodies (Ab) and their impact on the course of type 2 diabetes mellitus (DM2) in adolescents.

Materials and methods: ICA, GADA, IA-2 and IAA were measured in 66 patients with DM2. Depending on the presence of autoantibodies (Ab) patients were divided into 2 groups: Ab^- and Ab^+. HLA-typing was carried out in 45 patients. The secretion of C-peptide in the standard carbohydrate breakfast test (50 g carbohydrates) in the debut of the disease and after 1 year was studied.

Results: Specific Ab were detected in 15.2% (ICA - 9.1% and IAA – 6.1% in low titer (up to 20 IU/ml); GADA and IA-2 were not detected). Patients of 2 groups (Ab^-, n=56, and Ab^+, n=10) did not differ significantly in age of diagnosis, sex ratio, obesity degree, frequency of „acanthosis nigricans". The frequency of HLA-haplotypes of high risk DM1 in Ab^+ was higher (77.8% against 36.1%, p<0.05), but the frequency of HLA-genotypes of high risk DM1 in the two groups did not differ significantly. The level of HbA1c in the debut of DM was higher in Ab^+ (7.4% (7.0; 10.6) against 6.75% (6.1; 7.9), p<0.05), after 1 year HbA1c did not differ (6.4% (5.9; 7.8) and 6.1% (5.7; 6.8)). Basal level of C-peptide in the disease debut did not differ significantly (2,3 ng/ml (1,8; 4,0) in Ab^+ and 3.4 ng/ml (1.9; 4.4) in Ab^-), the stimulated C-peptide level was higher by 120 min in Ab^- (3.2 ng/ml (3.0; 8.4) versus 15.6 ng/ml (5.1; 17.2), p<0.05). After 1 year the secretion did not differ. Insulin therapy in the debut of the disease received 40% of Ab^+ and 25% - of Ab^-, p=0.3. Insulin therapy was not needed in any patient minimum 1 year from the diagnosis.

Conclusions: The incidence of pancreatic Ab in adolescents diagnosed with DM2 was 15.2%. In Ab^+ patients in the debut of the disease, there is a lower secretion of C-peptide at a higher level of HbA1c, but after 1 year, the secretion of C-peptide increases, and HbA1c decreases to the level in patients Ab^-. The presence of low titre ICA and IAA is not associated with the emergence of the need for insulin for 1 year minimum.

Keywords: Type 1 diabetes mellitus; type 2 diabetes mellitus; adolescents; autoantibody.

P1-P090

Increasing Trend of Fasting Plasma Glucose Levels and Impaired Fasting Glucose in Non-Diabetic Korean Youth and Young Adults: A Nationally Representative Population-Based Study

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Objectives: Diabetes in children and young adults is increasing worldwide. However, the study of change in fasting glucose among general pediatric and young adult population was lacking. The aim of this study was to investigate the secular trend of fasting plasma glucose (FPG) levels in non-diabetic Korean youth and young adults and to evaluate the change in the proportion of impaired fasting glucose (IFG).

Methods: Study subjects were Korean youth aged 10-19 years and young adults aged 20-29 years who participated in the Korea National Health and Nutrition Examination Survey (KNHANES). KNAHNES was a nationally representative cross-sectional survey. KNHANES wave 3 (K3) was performed in 2005, KNHANES 4 (K4) in 2007-09, KNHANES 5 (K5) in 2010-12 and KNHANES 6 (K6) in 2013-15. Subjects were classified according to FPG: normal plasma glucose (<100 mg/dL); IFG (100-125 mg/dL).

Results: A total of 14,128 eligible participants (youth 6,872) with available FPG were enrolled. Mean FPG (mg/dL) in youth was 87.6 ± 0.3 in K3, 88.6 ± 0.2 in K4, 88.5 ± 0.2 in K5, and 91.3 ± 0.2 in K6, respectively (P<0.001). In young adults, mean FPG was 85.1 ± 0.4 in K3, 87.3 ± 0.2 in K4, 87.4 ± 0.2 in K5, and 89.0 ± 0.3 in K6, respectively (P<0.001). The absolute change in FPG between K3 and K6 was 3.7 ± 0.4 mg/dL in youth and 3.9 ± 0.5 mg/dL in young adults. The proportion of IFG in youth was 3.2% in K3, 5.2% in K4, 4.6% in K5, and 9.9% in K6 (P<0.001). In young adults, the proportion of IFG was 2.1% in K3, 5.5% in K4, 5.0% in K5, and 6.8% in K6, respectively(P=0.005). In overweight and obese population, the proportion of IFG was 3.9% in K3, 11.3% in K4, 11.3% in K5 and 12.0% in K6, respectively (P = 0.02). In normal weight population, the proportion of IFG was 3.1% in K3, 4.5% in K4, 3.5% in K5, and 8.4% in K6, respectively (P<0.001). In multiple regression analyses, mean FPG showed significant linear correlation with KNAHNES wave after adjusting sex, age, and body mass index (adjusted R^2 = 0.073, P<0.001).

Conclusions: In Korean youth and young adults, mean FPG showed increasing tendency over the last 10 years. The proportion of IFG was also increasing, especially in male and obese population. Further research is needed to investigate associated factors with this trend.

P1-P091

Screening For T2d In High Risk Egyptian Children and Adolescents Using Strip Hba1c and Ogtt

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Background: The prevalence of type 2 diabetes (T2D) is significantly increased in pediatric population, which is affected by obesity worldwide. The progression of insulin resistance to T2D in obese children has been shown to be faster than in adults. Therefore, screening for T2D seems meaningful especially in high risk groups such as children and adolescents with obesity, family history of T2D, and those with clinical features of insulin resistance (hypertension, dyslipidemia, polycystic ovarian syndrome, or acanthosis nigricans).

Aim of work: To estimate the prevalence of prediabetes and T2D and their associated risk factors among obese and overweight high risk Egyptian children and adolescents using strip HbA1c as a screening test.

Patients and methods: A cross- sectional study conducted on 339 children and adolescents (between 5 and 18 years) at risk for T2D recruited from Cairo University Children's Hospital outpatient clinics over a period of 10 months. Patients with hemoglobinopathies, known T1D and children on steroid therapy were excluded. Study population was subjected to full history taking, clinical evaluation, anthropometric measurements, and screened for prediabetes and T2D using strip HbA1c and OGTT. Subjects with abnormal HbA1c (defined as HbA1c >5.7%) were subjected to serum HbA1c for confirmation.

Results: Prevalence of prediabetes and T2D using OGTT were 15% and 0.3% respectively, while strip HbA1c showed higher prevalence for prediabetes and T2D (31%). Strip HbA1c showed 81.63% sensitivity & 76.84% specificity at cut off point ≥5.6 for prediabetes and diabetes. Moderate direct significant correlation was detected between strip HbA1c and each of FBS (r= 0.39, p=0.001) and OGTT (r=0.26, p=0.0001). There was a strong correlation between venous and capillary HbA1c in diagnosing diabetes. Significant association between age and prediabetes/T2D was found using both OGTT and strip HbA1c (p value of 0.03 & 0.001 respectively). Physical inactivity, puberty, abdominal obesity, and presence of hirsutism were significantly associated with prediabetes and T2D.

Conclusion: T2D and prediabetes are common conditions in obese and overweight Egyptian children and adolescents based on OGTT. Higher prevalence was detected based on strip HbA1c. Strip HbA1c had high sensitivity and specificity compared to OGTT and can be used for screening for prediabetes and T2D in high risk group.

P1-P092

Association of the Sizes and Composition of HDL with Hepatic Steatosis in Adolescents with Type 2 Diabetes (T2D)

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Background: Type 2 diabetes (T2D) is an emerging disease in the pediatric population. The association between T2D and non-alcoholic fatty liver disease (NAFLD) has been described; this increases the risk of coronary heart disease (CHD). Recent evidence suggests that sizes and composition of HDL may be more important that HDL-C levels in predicting CHD. There is not data regarding the HDL subclasses distribution and composition in T2D youths with hepatic steatosis (HE).

Objective: To evaluate the association between the sizes and composition of HDL with HE in T2D youths.

Material and method: The protocol was approved by the local Ethics and Research Committees. This Cross-sectional study included a total of 70 adolescents, 47 adolescents with T2D and 23 healthy adolescents. The characteristics of the study were explained to all the participants; a complete clinical history, anthropometry and physical examination were performed. The presence of HE was determined by magnetic resonance by spectroscopy (MRS). In a venous blood sample (12 hours fasting); glucose, HbA1c and lipid profile were determined. The size and composition of the HDL subpopulations were analyzed by polyacrylamide gel electrophoresis (PAGE).

Results: 31 adolescents with T2D and HE (PDFF≥5%), 16 with T2D without HE (PDFF<5%) and 23 healthy adolescents formed the study. The values of HDL-C were compared between the 3 groups, characteristically they were higher in the group of healthy adolescents compared with the two groups of patients with T2D (p<0.001). Regarding the distribution of HDL particles; we observed an association between the percentage of liver fat (PDFF) and the HDL2b concentration (p=0.011), HDL2a (p=0.014) and average particle size (p=0.011), and a negative correlation with HDL3c (p=0.021). Likewise, a positive correlation was found with the PDFF and the proportion of TG in the particles (p=0.007), as a negative correlation with the free cholesterol (p<0.001) and cholesterol esters of the particles (p=0.010).

To better assess the effect of hepatic steatosis on the HDL subclasses distribution and composition, we performed a multiple linear regression analyses; we found that percentage of liver fat was associated with a lower proportion of HDL2b subclass (p=0.004), TG enriched (p=0.013) and CE depleted (p=0.030) in HDL particles. These associations were independent of age, sex, Tanner stage, BMI, levels of HbA1c and diabetes duration.

Conclusions: In adolescents with T2D, the presence of HE is associated with abnormalities in the distribution of HDL subpopulations, as well as in the lipid composition of the particles.

Diabetes & Insulin P2

P2-P060

Incidence of Childhood Type 1 and Type 2 Diabetes Mellitus in Qatar Between 2012–2016

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Introduction: The overall age-adjusted incidence of type 1 diabetes (T1DM) varied from 0.1/100,000 per year in China and Venezuela to 36.8/100,000 per year in Sardinia and 36.5/100,000 per year in Finland. This represents a 350-fold variation in the incidence among the 100 populations Worldwide. In the early 1990s, T2DM it was representing about 3 percent only of pediatric diabetes in the United States, but by 2003, T2DM reached about 20 percent of pediatric diabetes.

Objective: The aim of this study was to determine the incidence of T1DM, T2DM and the percentage of familial diabetes among these children aged 0–14 years in Qatar over 5 years period from2012 - 2016.

Design and methods: This was a retrospective cohort study of the incidence of childhood T1DM, T2DM and the percentage of familial diabetes in children aged 0–14 years that were diagnosed with diabetes from 2012 to 2016 in Qatar. Identified case subjects during this time period were ascertained from several sources and verified using the capture-recapture technique. Data were obtained from the only Pediatric Diabetes center, Hamad Medical Center (HMC) in Qatar.

Results: Over the study period, 473 children aged 0–14 years in Qatar were diagnosed diabetes, 431of them were T1DM and 42 were T2DM.

The incidence of diabetes in this population over the period 2012–2016 inclusive was 29.88 (table 1) with a 95% CI of 30.5. This incidence is significantly higher compared to the pervious incidence reported over the period 2006–2011 (inclusive of 24.88/100,000). No gender difference found in T1DM. The incidence of T2DM was higher in female (1.5:1). Familial diabetes formed 14.69 % of cases of DM (Both T1DM and T2DM). T1DM had the highest incidence during autumn and winter seasons.

Discussion: Several studies reported large variations in T1DM in the MENA region. The incidence among Arab countries ranges from a low of 2.54/100,000 in Oman to a high of 29/100,000 in Saudi Arabia. These variations can be attributed to the vast diversity of socioeconomic status among Arabs, wide geographical range, and differences in marriage culture practices.

Conclusion: Qatar has a relatively high incidence of T1DM and T2DM compared to many Arab countries. The incidence increased over the period 2012-2016 compared to previous years. Familial cases formed 14.69 % of these children with DM.

P2-P061

The Prevalence of Double Diabetes in Children and Adolescents in Qatar

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The incidence of both type 1 (T1DM) and type 2 diabetes (T2DM) has shown a rise in Qatar in parallel with a notable increase in the incidence of a new expression of the disease in children and adolescents, with the characteristics of a mixture of the two types of diabetes and referred to as ‚double diabetes' (DD). Insulin resistance and obesity, together with the presence of markers of pancreatic autoimmunity - namely, autoantibodies to islet cell antigens - typically define this condition. The prevalence of obesity in children and adolescents in Qatar is one of the highest in the world.

The aim of this study was to determine the incidence of DD among children aged 6 months: 14 years in a large cohort of children with Diabetes attending the Diabetes Centre, Hamad General Hospital, Doha, Qatar.

Patients and Methods: This was a cross sectional descriptive study to determine the prevalence of double diabetes in obese diabetic children with acanthosis nigricans (AN) and family history of metabolic syndrome with normal C peptide level (> 2 ng/ml) with the presence of beta cell autoimmunity (Anti GAD, anti-islet cell and anti-insulin antibodies) in a large cohort of children and adolescent (aged 2-16 years) with DM (n = 450) investigated at their first presentation at Hamad General Hospital Diabetes Center, Doha, Qatar (2012: 2016)

Results: Out of 450 diabetic children, 59 had T2DM. Out of those 14 had obesity with AN, family history of metabolic syndrome and normal C peptide level the characteristics of DD with autoantibodies against beta cells. All the 14 had anti GAD antibodies, 5 had anti islet cell antibodies and 7 had anti-insulin antibodies. This gives a prevalence of 3.1% in our diabetic patients and 23.7% of patients of patients with T2DM.

Discussion: The high prevalence of obesity in children and adolescents in Qatar appears to result in this new expression of diabetes mellitus designated as DD. The entity encompasses the autoimmune load of T1D and the metabolic load of T2D. There is no consensus on the best therapeutic modality for this new expression.

Conclusion: Double diabetes has a frequency of 23.7% in our children and adolescents with T2DM. Optimum therapeutic options must address the coexistence of both metabolic and autoimmune components of diabetes mellitus in these patients

P2-P062

Prevalence of Diabetes Type 1 and Type 2 in Children and Adults in Kazakhstan in 2016

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Introduction: The prevalence of diabetes for all age-groups worldwide was estimated to be 28/1000 in 2000 and 44/1000 in 2030 [1]. In the SEARCH study in a population of 3,458,974 US youth less than 20 yrs the prevalence of T1D was 1.93/1,000 and type 2 diabetes 0.24/1,000 [2].

Methods: We reviewed data on already diagnosed patients with type 1 and type 2 diabetes from official statistical collection of Ministry of Health of Kazakhstan in 2016 [3].

Results: see Table 1.

Conclusion: In Kazakhstan prevalence of diabetes type 1 in children less than 15 yrs is 0.6 in 1000 children. There is significant geographic differences in prevalence of diabetes type 1 in children less than 15 yrs. in countries around Kazakhstan: Russia 16/1000, China 7.7/1000, Ukraine 3.3/1000, Pakistan 1.6/1000, Uzbekistan 0.6/1000, Armenia 0.3/1000, Tajikistan 0.2/1000, Turkmenistan and Kyrgyzstan 0.1/1000 [4].

Such low prevalence in this area of Kazakhstan, Uzbekistan, Armenia, Tajikistan, Turkmenistan and Kyrgyzstan is poorly understood. It can be because of genetic background, different HLA types, diet preference. Furher study of genetic background, HLA pheotype and diet in Kazakhstan can help to explain ethiology of diabetes type 1 in Kazakhstan and understand such low prevalence.

References

1. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Wild S, Roglic G, Green A, Sicree R, King H Diabetes Care 2004, 27: 1047–1053.
2. Prevalence of Diabetes in U.S. Youth in 2009: The SEARCH for Diabetes in Youth Study Group. Diabetes Care 2014 Feb; 37(2): 402-408.
3. Health of the population of the Republic of Kazakhstan and the activities of health organizations in 2016. Birtanov EA, Tsoy AV, Aktaeva LM, Tulegalieva A. Statistical collection, Astana 2017.
4. Diabetes in the young - a global view and worldwide estimates of numbers of children with type 1 diabetes. Patterson C, et al. Diabetes Res Clin Prac, 2014 Feb;103(2):161-75.

Table 1. (for Abstract no P2-P062)

Region	Children 0–15 y		Adolescents 15–18y		Adults		Population End of 2016
	DM1	DM2	DM1	DM2	DM1	DM2	
Kazakhstan	2,942	485	969	214	27,453	342,325	Total 17,918,200 Adults 12,294,900 Children 4,962,400 Adolescents 660,900
Prevalence in Kazakhstan	0.6 in 1,000	0.09 in 1,000	1.4 in 1,000	0.32 in 1,000	2.2 in 1,000	27 in 1,000	
Almaty City	450	36	142	35	3,551	46,892	Total 1,751,300 Adults 1,326,200 Children 376,400 Adolescents 48,700
Prevalence in Almaty City	1.2 in 1,000	0.09 in 1,000	2.9 in 1,000	0.7 in 1,000	2.6 in 1,000	35 in 1,000	

P2-P063

Detection of the Pathogenic Genes in the Diagnosis and Treatment of Hyperglycemia Infants and Children

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Objectives: To explore the clinical value of common pathogenic gene detection in the diagnosis and treatment in hyperglycemia infants and children.

Subjects and Methods: Subjects were in-patients with hyperglycemia, age of onset before 1 year-old, or insulin antibody negative and with family history of diabetes. Gene sequencing for *ABCC8*, *KCNJ11*, *INS* and *GCK* were performed and potential mutations were analyzed. The patients with *ABCC8* and *KCNJ11* gene mutations were treated with sulfonylurea, patients with *GCK* mutations were given the lifestyle intervention and others with insulin.

Results: Total 21 patients were enrolled, 15 patients were found with pathogenic gene mutations, 52.4% in *ABCC8* gene and *KCNJ11* gene (11/21). The patients with *KCNJ11* or *ABCC8* gene mutation are with average age 2.01±1.62 months or 2.52±2.60 months, respectively. *GCK* gene mutations were detected in children with age of onset more than or equal to 12 months, at 58.33±43.02 months of age. There existed significant statistical difference among the onset ages of the three genetic variants, $P = 0.001$. The onset random blood glucose levels were significantly higher in the patients with *INS* gene mutation (66.70 mmol/L) than those of *GCK* gene mutation patients (9.73 + 1.97mmol/L, P=0.003). 11 patients with *ABCC8* or *KCNJ11* gene mutation were treated with sulfonylurea and 9 patients reached euglycemia.

Conclusions: Mutations in potassium channel related genes (*KCNJ11* and *ABCC8*) were the most common cause of neonatal diabetes in Chinese. Sulfonylurea therapy was effective and euglycemia were reached in most of the patients with the mutations in *KCNJ11* and *ABCC8*. Patients who were diagnosed hyperglycemia before 1 year-old, or with negative antibody testing and family history of diabetes were referred for gene testing, even by targeted next-generation sequencing of all known related genes. The target therapy based on gene diagnosis is more effective and improvement of life quality.

P2-P064

Early Diagnosis of Diabetes Type 2 in Children with Progeria Syndromes

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Progeria syndromes are rare in children and include several diseases which lead to premature ageing already in children. Therefore, the pediatrician may be confronted with diseases which are normally seen only in persons with advanced age. We report about two children with progeria, in whom diabetes type 2 become manifest early and with a fulminant course in one patient.

The first boy was known with Cockayne syndrome, which belongs to the progeria syndromes. He suffered from leucodystrophy, microcephaly, convulsions, severe psychomotor retardation and hepatopathy. He manifested at the age of 7 years with hyperglycemic-hyperosmolar coma (glucose 925 mg/dl, HbA1c 7.3%, c-peptide 9 ng/ml, serum osmolarity 345 mosm/kg, pH 7.4). Blood glucose was lowered slowly with small amounts of insulin and rehydration during several days. The final therapy consisted of regular insulin administered to the feeding by tube.

The second girl was also known with progeria syndrome, severe coronary arterial disease and hyporegenerative anemia with regular transfusions. During routine controls the diagnosis of diabetes type 2 was made with glucose 324 mg/dl, HbA1c 8.6%, c-peptide 20 ng/ml and insulin 500 mU/l. Due to the severe course of the disease and after discussion with the parents, no specific therapy was started as the patient was in a palliative state. Both children are deceased in the meantime.

Regular screening for diabetes type 2 should be installed early in life in children with progeria syndroms including blood glucose and HbA1c measurements and oral glucose tolerance testing to avoid severe and life threatening manifestation. Early therapy with metformin might have a positive effect on metabolic control and the clinical course in children with progeria syndromes.

P2-P065

Transient Neonatal Diabetes Mellitus Due to Not Described Mutation in ABCC8 Gene with Different Behaviour in Affected Family Members

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Neonatal diabetes (ND), classified as either permanent(PND) or transient(TND), occurs in 1/200,000 live births.In 50% cases of TND, remission presents within the first year of life, only to relapse later before puberty in 50% of cases.The most frequent cause is mutation of the 6q24 gene accompanied by mutations in heterozygosis of ABCC8 gene.80% of mutations in this gene are in novo, due to autosomal recessive inheritance.Such cases respond to treatment with sulfonylurea (SU).We present a case of TND that motivated the change of diagnosis in both (mother and baby)

Material and method: A term male infant was born at 38 weeks'gestation, weighing 2660gr(10-25th centile), length: 48cm (40th centile). Presented isolated hyperglycemia in the first 48 hours, with true hyperglycemia on the 4th day, requiring treatment with Actrapid0.2 UI/KG/D. One month later the insulin requirements were0.2-0.3UI / kg/d.

FH: Non-Consanguinean parents. Type 1 DM mother at 9 years old,onset with hyperglycemia, requiring insulin treatment. Maternal grandmother at 38 years old, was diagnosed with Type I Diabetes requiring insulin treatment.

Laboratory tests:Glucose:300mg/dl,HBA1c 4.7%, no ketonuria, C-Peptide; 0.58ng/dl, Fasting insulin: 0.6mUI/ml. Negative diabetes antibodies (Anti-GAD, Islet, insulin autoantibodies) in mother and neonate.Genetic study of both: mutation in heterozygosis of exon 21 of the ABBC8 gene(p.C24982G>C, Gly.833G>Ala), associated with PND.A glycaemic control and study of pancreatic reserve (prior to the transition from insulin treatment to Sulfonylureas), were assessed 2 months after the change and 6 months after and the medication was removed 15 days before.

Results:

Evolution HBA1c:4.7-5%.
Previous glucagon test:C-Peptide: 0': 0.22, 6: 0.82ng/dl.
At 2 months: 0.42.6'; 0.91 ng/ ml.
Six months: 0': 0.27. 6':0.37 ng/ml
Previous GOTT:
Insulin 0': 4, 120': 5.4 mU/ml.
Glucose: 0': 230, 120': 298 m/dl.
Two months:Glucose: 0': 80, 120': 238 mg/dl.
Six months;Glucose: 0': 66, 120': 127 mg/dl.
Insulin: 0':3 and 120': 2.8 mUI /ml

His mother had HBA1c:6.5% wich decreased to 6% following commencement on sulfonyilureas. His grandmother had HBA1c:10% wich similarly reduced to 6% following sulfonylureas treatment.

Conclusion: Clinical onset of diabetes in patients with mutations in ABCC8 gene in the first month of life are well documented. However, clinical picture can be different depending on the severity in the mutation as the case we present in the 3 family generations.Treatment with sulfonylureas improves the pancreatic reserve and metabolic control.Clinical follow-up of these patients is important,due to the risk of recurrence in 50% cases of DNT.

P2-P066

Prothrombin Gene *20210A* Mutation Heterozygosity and MTHFR Gene *C677T* Mutation Homozygosity Detected in a Male Toddler Experiencing Femoral Venous Thrombosis During Diabetic Ketoacidosis

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Introduction: Diabetic ketoacidosis (DKA) as an inflammatory state combined with the disruption of the normal coagulation cascade can lead patients to an increased risk of thrombosis. Especially, patients that are genetically susceptible to thrombosis could develop deep venous thrombosis (DVT) due to inflammation, dehydration, and hyperviscosity secondarily to DKA. It is noteworthy that children with DKA who underwent central venous catheter placement could develop DVT, especially those that are less than 3years old. This can be explained due to smaller vessel diameter and worse presentation of the illness at the beginning. Purpose: To describe femoral venous thrombosis during the course of severe ketoacidosis in a male toddler diagnosed with T1D. Case report: A $2^{6/12}$ years old boy was admitted to our hospital with severe DKA (pH 6.95, HCO3 4mmol/L) and hyperglycaemia (485mg/dl) as well as extremely dehydrated. Despite the applying of current guidelines for the management of DKA, the patient was deteriorated and transferred to PICU. In the PICU he was intubated and a central venous

catheter was inserted in the right femoral vein. On the 4th day of hospitalization a swelling on his right thigh developed accompanied by fever. A femoral venous thrombosis was confirmed by a Doppler ultrasound and a medication with low molecular weight heparin (LMWH) administrated. Despite the heparin administration the anticoagulant response (anti-factor Xa activity) was poor. A further investigation concerning thrombophilia screening was performed, which revealed a prothrombin Gene *20210A* mutation heterozygosity and MTHFR Gene *C677T* mutation homozygosity. Subsequently the dose of LMWH was increased and 10 days later the levels of anti-Xa activity were normalized. One month later the child has a good glycemic control and a normal anti-factor Xa activity. All family members are recommended to be screened for thrombophilia. Conclusion: Femoral venous thrombosis is a rare complication of DKA in children, associated with the use of central venous catheter; however, in our case an undiagnosed thrombophilia further predisposed to coagulopathy. Although the above findings are rare, a high index of clinical suspicion for thrombotic episodes is required in severe forms of DKA. Thrombophilia screening should be considered in selected cases.

P2-P067

Frequency of Occurrence of MODY in the Population of Diabetic Patients in St. Petersburg

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The purpose of this study is to determine the frequency of occurrence and molecular-genetic characteristics of MODY in patients with diabetes mellitus aged 1 to 18 years, residents of St. Petersburg.

Materials and methods: In St. Petersburg in 2017, there were 1620 patients with diabetes mellitus under the age of 18 years. 54 of them had evidence of hereditary variants of diabetes with chronic hyperglycemia at normal c-peptide indices for 2 years after the diagnosis of the disease, lack of immunological criteria for type 1 diabetes mellitus.

In a study of DNA, 54 patients with suspicion of MODY used the full-sequence sequencing method. NGS-diagnostic panels were used to study the coding regions of genes, including the following genes: *HNF1A, GCK, HNF4A, HNF1B, PDX1, NEUROD1, KLF11, CEL, PAX4, INS, BLK, EIF2AK3, RFX6, WFS1, ZFP57, FOXP3, KCNJ11, ABCC8, GLUD1, HADH (SCHAD), SLC16A1, UCP2, INSR, AKT2, GCG, GCGR, PPARG, PTF1A*.

Results: DNA samples of patients with suspicion of MODY were examined. Mutations in the studied genes were found in 32 children from 54, which was 59% of all examined. The most common mutations in the *GCK* gene were 81.25%(n = 26), *HNF1A* 12.5%(n = 4), *WFS1* 3.12%(n = 1), *PAX4* = 3.12%(n = 1). The incidence of hereditary variants of diabetes among all cases of children(1620 patients), respectively, was 2%.

Conclusions: molecular-genetic confirmation of MODY diagnosis among patients with non-immune forms is high enough and is 59%. However, the frequency of monogenic forms of the disease among all children with diabetes in St. Petersburg does not exceed 2%.

P2-P068

Acute Painful Diabetic Neuropathy (APDN) in a Boy with Type 1 Diabetes

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A 15y10m boy was presented to our hospital (in March 2017) with the complaints of acute, severe, continuous, burning pain affecting soles and both legs, insomnia, loss of body weight and appetite. He described his pain as stabbing and burning. He also perceived contact with bed clothing, socks, shoes or floor as causing extreme discomfort. He could barely move out of bed. He had no symptoms in hands or any other neurological complaints.

An. Morbi: type 1 diabetes was diagnosed 7 years ago in 2011, was initiated on Actrapid and Protaphane insulin. First came to our hospital in January 2017. His glycosylated haemoglobin A1c (HbA1c) was 10.77 %, fructosamine was 472.88 μmol/l. His compliance and glycaemic control were poor. We changed his insulin to glargine and glulisine to achieve normoglycaemia. He had "lessons" in the diabetes school. Repeat HbA1c three month after (March 2017) was 8.34%, fructosamine was 322.02 μmol/l.

On examination: his height is 145 cm, weight – 33.5 kg, BMI – 15.9 kg/m^2

H-SDS= -3.4 SD, Tanner stage 2.

His vitals and general physical examination were unremarkable. On neurological examination, cranial nerves were normal. On electromyography (EMG):

sensory motor axonal polyneuropathy of the lower extremities.

He was discharged on carbamazepine (8 mg/k/d) and benfotiamine 150 mg twice daily, NSAID analgesics (for intermittent use) and pregabalin 75 mg/d (in case of severe pain).

Gradually over the next six months his pain decreased, but still the patient continued to feel pain.

His glycaemic control has remained between optimal and suboptimal. His HbA1c (October 2017) was 8.21 %, fructosamine was 290.34 μmol/l. He continuous to take benfotiamine (Benfogamma, Woerwag Pharma) 150 mg twice daily.

Conclusion: in the face of current recommendations for achieving glycaemic targets quickly, a paradoxical occurrence of APDN should be kept in mind. It is important for the paediatric endocrinologists and neurologists to recognize this rare entity for the need to provide adequate analgesia for relief from severe pain.

Is this pain completely reversible?

P2-P069

Features of Japanese Patients with Early-Onset, MODY-Like Diabetes without Mutations in the Major MODY Genes

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We perfomed mutational analyses of the major MODY genes (*HNF1A*, *HNF4A*, *HNF1B*, *GCK*) on 263 Japanese patients with early-onset, nonobese, MODY-like diabetes mellitus referred to Osaka City General Hospital for diagnosis. Mutations were identified in 103 (35.9%) patients; 57 mutations in *GCK*; 29, *HNF1A*; 7, *HNF4A*; and 10, *HNF1B.* Compared with these mutation-positive patients, 160 mutation-negative patients were significantly older ($p = 0.003$), and had higher BMI percentile at diagnosis ($p = 0.0006$). Biparental diabetes was found only in mutation-negative patients, and interestingly, when patients with single affected parents were compared, maternal inheritance of diabetes was significantly more common in mutation-negative patients ($p = 0.0332$). These results suggest that mutation-negative patients have clinical characteristics in common with early-onset type 2 diabetes, and non-Mendelian inheritance should be considered at least for part of these patients.

P2-P070

Frequency and Etiologic Spectrum of Monogenic Diabetes in Pediatric Diabetes in a Single Academic Center

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Purpose: Type 1 diabetes mellitus (DM) is the most common cause of diabetes in children and adolescents. Prevalence of monogenic DM is estimated for about 1%–5% of all patients with DM. Overlapping clinical features of various forms of diabetes make differential diagnosis challenging. This study was performed to investigate frequency and genetic etiologies of monogenic diabetes in a single academic center.

Methods: This study included 466 consecutive patients with DM diagnosed before 18 years of age from January 1996 to July 2017. Clinical features, biochemical findings, β-cell autoantibodies, and molecular characteristics were reviewed retrospectively.

Results: Three hundred and thirty two patients (71.2%) had type 1 DM, while 108 patients (23.2%) were type 2 DM. Genetic etiologies were identified in the remaining 26 patients (5.6%). Three patients diagnosed with maturity onset diabetes of the young with mutations in *HNF1A* (p.G292Rfs*26) and *HNF1B* (p.S148L, p.A166P). Two siblings manifested bilateral optic atrophy and urinary incontinence at adolescent period and were diagnosed with Wolfram syndrome caused by *WFS1* mutation. A male with acanthosis nigricans, hirsutism, high insulin level, and intrauterine growth retardation was compound heterozygote for *INSR* (p.R1066*/p.Q1232*). IPEX syndrome was found in a male who presented membranous glomerulopathy, pure red cell aplasia, and posterior reversible encephalopathy syndrome. Eight patients were diagnosed with neonatal DM: two with transient form caused by paternal uniparental disomy of 6q24 and the other six with permanent form with mutations in K_{ATP} channel genes, including a male DEND syndrome. A 3-month-old Arab girl presented with diabetes and liver failure, and were diagnosed with Wolcott-Rallison syndrome caused by *EIF2AK3* p.W431* mutation. Two patients *CFTR* mutations displayed diabetes with associated features such as pancreatitis and recurrent infections. Eight patients with MELAS syndrome were classified as mitochondrial DM at age 27.3 ± 11.3 years with the HbA1c level of 6.6 ± 1.8%.

Conclusions: It should be considered that diabetic patients who had family history or extra-pancreatic features without β-cell autoantibodies might have monogenic diabetes. Identification of the genetic cause of DM is critical to provide appropriate therapeutic options and genetic counselling.

P2-P071

Clinical Details, Molecular Genetic Analysisand Clinical Pheonotype Correlation of 14 Patients with Neonatal Diabetes from the South India – A Single Centre Experience

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Background: Neonatal diabetes mellitus (NDM) is a relatively rare form of monogenic diabetes and usually presents in the first 6 -9 months of life. In this study, our objective was to report the clinical details, perform a detailed genetic analysis and acquire a clinical –phenotype correlation of our cohort.

Materials and methods: NDM patients referred to SN Endocrine centre between period of Nov 2014 to April 2017 and patients under follow-up with presumed type 1 diabetes mellitus, with onset before 9 months of age were recruited. Molecular genetic analysis was performed at Royal Devon and Exeter Hospital, Exeter.

Results: Fifteen patients (54% males) were diagnosed with NDM (TNDM-1; PNDM-14). Molecular genetic analysis identified a mutation in 12 (78%) patients who had undergone a mutation analysis among which 10 mutations (65%) were definitely pathogenic. The one TNDM case had a KCNJ11 mutation, while in the rest GCK, INS, ABCC8, STAT3, IL2RA, GATA6 mutations were identified. Two PNDM patients had partial response to Sulphonylurea transition, manifest by reduced insulin doses in both

and improved DQ in one, while the TNDM case responded to low doses of SU and is now off all therapy for diabetes.

Conclusions: Mutations in GCK, INS and KCNJ11 were the commonest causes of NDM in our cohort. The high rate of detection of a mutation likely reflects the increased consanguinity within our cohort, as also the combined use of Sanger and targeted Next Gen Sequencing.

P2-P072

Syndromic Patients with Negative Islet Autoantibodies Should Be Tested for Mongenic Diabetes: Lessons from Patient with *TRMT10A* Mutation

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Aim: Glucose metabolism can affect by several genes, and some of them represent distictive clinical and laboratory features. tRNA methyltransferase 10 homologue A (*TRMT10A)* gene is a tRNA methyl transferase, and localised to the nucleolus, where tRNA modifications occur. Very recently, a novel syndrome of abnormal glucose homeostasis or nonautoimmune diabetes associated with microcephaly, epilepsy, intellectual disability, failure to thrive, delayed puberty caused by mutations in the *TRMA10A* were reported in four family.

Case report: The patient was the second child born to nonconsanguineous parents. The child's birth weight was 2100 g and she had microcephaly. She was found to have difficulty in feeding at the first two years of age, not getting enough weight, fasting hypoglcaemia and retarded of neuromotor development with mild intellectual disability (24 months walking, 36 months speech). Dysmorphic features were apparent from early age, including a small face and deeply located eyes. She was diagnosed with epilepsy at 2.5 years old and treated with phenobarbital. On the cranial imaging, a pituitary normal structure, but an anterior arachnoid cyst of the left temporal lobe 3.5x2 cm was detected.

At 3.65 years of age, her height was SDS: -3.26, weight was SDS:-2.22, and bone age was 2 years and 6 months. Growth hormone stimulation tests appropppriate with partial growth hormone deficiency. Growth velocity was low during follow-up, then at 5.47 years of age rhGH therapy was initiated.

She had incidental diagnosis of diabetes at age 11.41 years. She no antibodies, had normal c-petpide level (1.29 ng/ml) and treated with Metformin. Pubertal delay and low basal and stimulated gonadotropins were detected at the age of 13 years, and the patient underwent estrogen replacement.

Mutation of the *TRMT10A* NM_001134665.2:c.379C>T (p.Arg127*) was detected in the molecular study.

At last examination, she is 14,25 years of age, and height: 142 cm (HSDS:-2,95), Weight: 29,4 kg, RBMI: 72%. With metformine therapy, blood glucose level were normal and HbA1c level was 6.8%.

Conclusion: *TRMT10A* mutation appears to cause a syndrome of intellectual disability, microcephaly and delayed puberty. These features are associated with an unusual form of impaired glucose metabolism presenting in early childhood with hypoglycemia and nonautoimmune insulinopenic diabetes becomes evident as in our patient. Arachnoid cyst, although not reported before, and hypophyseal dysfunction can be additional findings of this syndrome. Slow onset diabetes with antibody negative with extras pancreatic features should be tested for monogenic diabetes.

P2-P073

A Novel Mutation in *PHKA2*: Idiopathic Ketotic Hypoglycaemia May Represent Mild GSDIXa

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Background: Idiopathic ketotic hypoglycaemia (IKH) is an exclusion diagnosis and the most common cause of hypoglycaemia in childhood. Glycogen Storage disease (GSD) type IX comprises one quarter of all GSD's. GSDIXa, encoded by *PHKA2*, is the most frequent subtype.

Objective: To investigate whether IKH may be undiagnosed GSDIXa.

Methods: Hospital file review and next generation sequence 29 gene GSD-panel.

Results: From 8 month's age, a 6 year-old Caucasian boy diagnosed with IKH had recurrent fasting hypoglycaemia down to 1.8mmol/L; B-ketones 1.7mmol/L. He had no dysmorphic features, height +0.4SD. Normal investigations included liver enzymes, hepatic ultrasound, synachten test, i.m. glucagon test, p-insulin suppression during hypoglycaemia, urine metabolic screening and p-carnitine profile. A subnormal peak GH at stimulation tests prompted GH treatment age 2.5-3 years with no effect on hypoglycaemia. Brain MRI showed white matter lesions in the right hemisphere possibly due to hypoglycaemia.

Hypoglycaemia symptoms in childhood were reported in the mother, maternal grandmother and the mother's two sisters and one of their daughters. The grandmother's monozygotic twin died 3-month-old for unknown reason. The patient's 4-year-old brother had hypoglycaemia down to 2.8 mmol/L.

Family history prompted reevaluation of the IKH diagnosis on suspicion of X-linked hypoglycaemia. GSD panel identified a novel, maternal *PHKA2* mutation, c.4C>G, p.(Arg2Gly), classified as a variance of unknown significance.

Conclusion: IKH and GSDIXa may clinically overlap, why GSDIXa may be under/un-diagnosed. We hypothesize that IKH may represent milder variants of GSD. GSD gene panel and family testing is encouraged in IKH to improve precision of treatment and prognosis, and to diagnose affected family members.

P2-P074

The Application of Next Generation Sequencing MODY Gene Panel in Greek Patients

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Background: Maturity Onset Diabetes of the Young (MODY) constitutes a genetically and clinically heterogeneous type of Monogenic Diabetes (MD). It is characterized by early onset, autosomal dominant inheritance and a defect in β cell insulin secretion. To date 14 different MODY subtypes have been reported each one with a distinct genetic aetiology. However four are the most common subtypes, namely MODY 1 (*HNF4A*), MODY2 (*GCK*), MODY3 (*HNF1A*), MODY 5 (*HNF1B*).

Objective: To identify the molecular defect of 48 MODY patients employing the methodology of Next Generation Sequencing (NGS) Targeted Gene Panel (TGP).

Patients and Methods: We studied 48 patients who met MODY criteria; young age of onset, autosomal dominant inheritance and b cell defect.

Forty of them had been previously tested by Sanger sequencing of the genes *GCK, HNF1A, HNF4A* and *HNF1B* according to their phenotype, but a mutation had not been identified.

A panel of 7 MODY genes (*GCK, HNF1A, HNF4A, HNF1B, INS, ABCC8, KCNJ11*) was designed by the Thermo Fisher Scientific Ion AmpliSeq Designer platform (version 5.6). NGS was performed on the Ion Torrent Personal Genome Machine (PGM) platform (Thermo Fisher Scientific, Waltham, MA, USA). Bioinformatic tools were used to test the pathogenicity of the new variants detected.

Results: Pathogenic variants were identified in 11 of the 48 MODY patients tested (23%). All variants were point mutations; 2 nonsense, 8 missense and 1 splice site. Three novel pathogenic variants were detected in: *GCK* (p.Cys371X), *HNF1A* (p.Asn402Tyr) and *ABCC8* (p.Met1513Thr). Three patients were found to be heterozygotes for *GCK,* two patients for *HNF1A*, one for *HNF1B* and four for *ABCC8* variants. One patient was found to carry two different gene variants, one of the *GCK* gene (p.Tyr61X) and one of the A*BCC8* gene (p.Leu135Val). All mutations were confirmed by Sanger sequencing in the patients and the parents with the MODY phenotype (when available).

Conclusions: The application of NGS TGP offered genetic diagnosis in 11/48 MODY patients, and allowed the identification of three novel gene mutations. Although the diagnosis rate is approximately 25% and a large number of MODY patients remain without the exact MODY type identification, the application of NGS methodology in MD diagnosis provide rapid results, is cost effective compared to Sanger sequencing and increases diagnostic accuracy. Accurate genetic diagnosis and determination of the MODY subtype is very important for the choice of the right treatment, disease prognosis and family counselling.

P2-P075

Type 5 Monogenic Diabetes. Report of 7 Cases

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Introduction: Type 5 monogenic diabetes is an autosomal dominant disease due to a mutation in *HNF1beta* gene. This gene is expressed predominantly in kidney and pancreas, thus clinical manifestations are characterised by renal abnormalities and diabetes.

Objectives: To review the clinical characteristics of patients who were diagnosed with type 5 monogenic diabetes in the Pediatric Endocrinology Unit of a tertiary referral hospital.

Patients And Methods: The medical history of 7 children who were diagnosed with type 5 monogenic diabetes with genetic confirmation were reviewed.

Results: A mutation in HNF1beta gene was detected in all the patients (4 male and 2 female) between 14 and 18 years old. The genetic study in their first-degree relatives was normal in all the cases.

Related to prenatal history, fetal growth restriction was presented in 6 of 7 patients, and 2 had sonographic renal abnormalities. However, the initial clinical manifestations were very different: 3 presented renal alterations, 2 transaminitis and the other 2 hyperglycemia; although while 1 patient only presented hyperglycemia, the other one had a non-ketosic debut diabetes.

6 patients had renal morphological abnormalitites at the beginning of the clinical manifestations, except one. However, renal cortical cysts were found in this last patient during disease progression. 3 patients developed chronic kidney disease, leading to a renal transplant in one of them. Neither woman presented mullerian abnormalities.

During disease progression some other complications appeared: exocrine pancreatic insufficiency (1 patient), hyperuricemia (1 patient), hypomagnesemia (2 patients), hypertrygliceridemia (1 patient) o transaminitis (2 patients).

4 patients met diagnostic criteria for diabetes, thus they were treated with insulin. None of them presented positive antibodies for diabetes (see attached table).

Conclusion: Phenotypic variability at the onset of Type 5 monogenic diabetes implies a diagnostic challenge.

The study of *HNF1beta* gene should be considered in any patient with hyperglucemia, negative antibodies for diabetes, family history of type 2 diabetes and renal abnormalities.

While progressive disfunction of beta cells is observed, not all the patients require insulin treatment at the beginning of the disease.

P2-P076

Novel GATA6-Mutation in a Boy with Neonatal Diabetes and Diaphragmatic Hernia

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Background: Onset of diabetes in the neonatal period with additional malformations e.g. congenital heart defects should always be suspicious for an underlying genetic disorder. For example, GATA6-mutations were identified in children with congenital heart defects and neonatal diabetes. The latter may be due to pancreas agenesis. Herein we present a novel GATA6-mutation in a boy with transient neonatal diabetes, diaphragmatic hernia, congenital heart defect and early onset scoliosis.

Case study: A term-born boy developed severe hyperglycemia with blood glucose levels up to 100 mmol/l within the first day of life. He was treated with intravenous insulin normalizing blood glucose levels. Diabetes resolved after 5 days and insulin supplementation could be stopped. In addition to diabetes, the boy presented with congenital heart defects (high grad stenosis of the left pulmonary artery, ventricular septal defect, persistent ductus arteriosus, atrial septum secundum defect), a diaphragmatic hernia and an early onset scoliosis. At the age of three years, a random evaluation revealed an HbA_{1c}-level of 7.8% without any diabetes-related symptoms. Autoantibodies to insulin, glutamic acid decarboxylase, beta islet cells and zinc transporter-8 were negative. He was started on single insulin injection with degludec 2.5 IE and a loosened food diet without strict counting of carbohydrates. Under such regimen, HbA_{1c}-value decreased to 6.7%. His mother presented with an autoantibody-negative diabetes at the age of 25 years and had a history of a congenital heart defect. The clinical features of our patient mirroring his mother´s medical history ultimately strengthened the suspicion of an underlying genetic disorder. Accordingly, identical heterozygous GATA6-gene mutation (c.1291C>T p.(Gln431*)) was identified in both, patient and mother. Such mutation results in an early stop-codon, presumably leading to an incomplete function of the allele's product. To the best of our knowledge, this mutation has not been described so far in the literature. However, GATA6 mutations were previously described in patients with diabetes and congenital heart defects.

Finally, aggravation of the boy´s symptoms in comparison to his mother (i.e. earlier diabetes onset, absence of diaphragmatic hernia in the mother) anticipation may be postulated.

Conclusions: A GATA6 mutation must be considered in children with neonatal diabetes and associated congenital heart defects and potentially other malformations. Anticipation and aggravation to the next generation may occur.

P2-P077

Clinical and Genetic Characterizations of Maturity Onset Diabetes of the Young: Single Center Results

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Background: Maturity onset diabetes of the young (MODY) is a group of monogenic disorders classically presenting in adolescence or young adults before the age of 25 years. MODY is a rare cause of diabetes.

Methods: In this study, a panel of 23 MODY genes was screened. The Human Gene Mutation Database (HGMD), Clinvar, dbSNP and Exac database used for known or new variants causes MODY. Classification of variants performed according to ACMG 2015 Guidelines. We clinically evaluated 49 patients and 39 their relatives.

Results: Clinical, laboratory and genetic findings were given in table. At the diagnosis, pubertal status, BMI, BMI-SD, birth weight and fasting c-peptide were significantly different in MODY groups. Mutations were detected in 27 out of 49 patients. 13 patients had GCK mutations. Four new variants were found in five patients: c.1265 G>C, p.Arg422 Pro in exon 10; c.128G>T, p.Arg431 Leu in exon 2; c.532 delG and c.C129Y. Two patients had de novo GCK mutations. Seven patients had BLK gene mutations. Two of them was siblings and they have new mutation in exon 9 (c.900C >A,

Table 1. (for Abstract no P2-P077)

At the diagnosis	Glucokinase	BLK	HNF4A	HNF1A	p
Age, years	7.52±4	9.91±4.1	13.9±2.8	14.2±1.4	0.06
Gestational-Diabetes, n	7	3	4	–	0.026
Birth-weight, g	2,816±633	3,135±381	4,166±650	4,500±707	0.029
BMI, kg/m^2	16.1±1.8	18.3±2.5	16.1±1.8	31.4±2.3	0.004
Fasting-Glucose, mg/dL	175±137	142.8±65	138.2±88	134.5±12	
Fasting c-peptide, ng/mL	0.71±0.4	1.05±0.6	2.04 (12)*	4.1±0	0.009
HbA1c,%	7.2±2.5	6.5±2.5	5.97±1	7.95±1.0	
G-120 at OGTT,mg/dL (n:25)	164.3±55	124.6±41	220±141	213±49	
I-0 at OGTT, uIU/mL	2.1 (4.81)*	4.3 (5.1)*	11.4±4	20.6±14	
I-120 at OGTT, uIU/mL	26.3±29	28.2±19	36.7±19	20.7±18	

p.Tyr300Ter). Four patients had known HNF4A mutations in exon 8. Two patients were siblings. Same HNF1A mutation was found in unrelated two patients, and INS gene mutation was identified in one.

Conclusion: Our study present four novel mutations in GCK, and one novel mutation in BLK gene. Although clinical findings were differing in each MODY group, laboratory results were similar.

P2-P078

Protein and Fat Effects on Post - Prandial Glucose Responses Among Egyptian Children and Adolescents with Type 1 Diabetes Mellitus

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Background: In the light of emerging recent researches and the use of continuous glucose monitoring it was shown that other nutritional properties of food, including fat, protein, and glycemic index (GI), can significantly affect postprandial glucose excursions. These findings highlight the need for alternative mealtime insulin dosing algorithms and have important implications for nutrition education and counseling in patients with diabetes.

Objective and hypothesis: The current study was conducted to determine the effect of high protein and fat content on postprandial glycemic response in Egyptian children and adolescents with type 1 diabetes

Patients and method: Each patient was served each of three breakfast meals on three separate days; the standard meal, high protein meal 31.25 gm (with extra 125 kcal protein) and high fat meal (with extra 125 kcal fat). Blood glucose was measured preprandial and every half an hour for 5 hours after each kind of meals using caliberated glucometer. The preprandial blood glucose values before the three test meals were comparable which allowed the testing of the effect.

Results: The current study included 51 children and adolescents with type 1 diabetes following up at Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU), at Children's hospital, Cairo University. The age of the patients ranged from 6 to 18 years (11.24 ±2.413) with a mean diabetes duration of 4.76. After the standard meal, the blood glucose started to rise gradually till reached its peak at 3 hours postprandial then decreased gradually till the end of 5 hours but didn't reach the preprandial level. After high protein meal (31.25 gm protein) ; plasma glucose levels gradually rose post prandial till reached peak glucose excursion at 4.5hrs, then started to decline at 5 hours but didn't reach the preprandial level. However after high fat meal, the blood glucose levels rose to reach a peak level at 2 hours then started to decline gradually to reach the preprandial level at 5 hours.

Conclusion: Protein and fat contents of meals affect the timing and values of the peak excursion of blood glucose as well as the duration of postprandial hyperglycemia. Therefore fat protein unit should be taken in consideration in calculating the bolus insulin dose and the anticipation of postprandial glucose response.

Key words: Type 1 diabetes, high fat meal, high protein meal, post prandial glycemia

P2-P079

Amino Acids Plasma Profile in Children with Type 1 Diabetes

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Background: Insulin deficiency inhibits protein synthesis and stimulates protein degradation, and then amino acids metabolism could be altered in diabetes mellitus.

Objective: The aim of this study is to analyze amino acid plasma profile in a group of children with type 1 diabetes, and to evaluate its potential application as markers of metabolic control of the disease.

Subjects/Methods: A clinical assessment and metabolic study (amino acid plasma concentrations) was accomplished in a group of 49 children diagnosed with type 1 diabetes, aged 8.6 to 14.3 years, and a group of 48 healthy children (control group), aged 7.4 to 14.8 years.

Results: Plasma concentrations of ARG, GLN, ILE, PHE, THR, TYR, VAL and TAU were significantly higher ($p<0.05$) within the diabetic group with respect to the control group. Likewise, plasma concentrations of branched-chain (347.65±58.76 vs. 285.20±45.20 nmol/ml), glucogenic (1252.74±236.82 vs. 1053.69±211.19 nmol/ml) and ketogenic amino acids (441.62±57.09 vs. 354.13±53.45 nmol/ml) were significantly higher ($p< 0.05$) in the diabetic group with respect to the control group. There was no correlation between the single amino acid (or amino acids groups) plasma levels and the evolution of the disease (years) or Hb1Ac.

Conclusions: The study of changes in amino acid plasma profile in the young diabetic, probably as a consequence of insulinopenia, could have interest as a marker of metabolic control for the disease.

P2-P080

Betatrophin as a New Biomarker of Type 1 Diabetes Mellitus in Paediatrics

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Introduction: Type 1 Diabetes Mellitus (DM1) is an autoimmune disease resulting from the destruction of pancreatic β cells. After the diagnosis, up to 80% of patients spontaneously experi-

ence partial remission (PR) for months. New biomarkers are being studied, such as the betatrophin protein (ANGPTL8) of unknown function, but which could be involved in the evolution of DM1, in this phase of RP and even used as a therapeutic target.

Methods: Observational follow-up study. Plasma was collected from 22 patients with DM1, age at the beginning of the study 9 ± 4.5 (years ± SD), 50% women, without obesity or other autoimmune disease. Plasma levels of beta-trophin (ELISA) were analyzed at debut and after 6, 12 and 18 months of follow-up. They were compared with the levels of 14 healthy non-obese controls of similar ages and with one patient with DM1 (initial HbA1c of 13.5%, normal weight) who persisted in RP 6 years after diagnosis. This requires low doses of insulin (<0.5UI / kg / day), has stimulated C-peptide levels of 1.3ng / ml and a HbA1c adjusted for insulin dose (IDDAA1c) <9, which indicates RP. The antibodies (GAD / IA2 / Zn) are repeatedly negative, as well as the MODY study. Typing HLA DR4 / DQ8.

Results: Plasma levels of betatrophin were significantly higher in patients with DM1 in all phases studied compared to control subjects (258.4 ± 77.2pg / ml, mean ± SD). A biological tendency was observed, although not significant, to decrease plasma betatrophin levels at 6 and 12 months (724.1 ± 633.9pg / ml, 683.7 ± 832.7pg / ml) with respect to diagnosis (746.9 ± 784.1pg / ml). The patient in RP presented significantly higher levels of beta-trophin (1535 pg / ml).

Conclusions: Betatrophin levels are increased in patients with DM1 during the first 18 months after diagnosis compared to the control group, demonstrating that betatrophin is a biomarker of pediatric DM1. The high values of this hormone in a patient with persistent RP may be related to the chronification of remission. It would be important to consider the study of betatrophin levels in more advanced phases and correlate it with the degree of autoimmunity and pancreatic reserve to determine its potential as a biomarker.

P2-P081

Vitamin D Status Among Children and Adolescent with T1DM

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Background: Vitamin D deficiency is currently a topic of intense interest, and is widely prevalent. Low vitamin D levels have been reported in many immune disorders as type 1 diabetes Mellitus (T1DM).AIM of this study is to assess the vitamin D status in T1DM children and adolescent in Karbala.

Patients and methods: A case control study, a total of 171 subject, consisted of two groups; diabetic patients 121 cases (48 male and 73 female), aged 5-16 years and a control group 50 (26 female and 24 male) non diabetic children with matched age. Serum 25-hydroxyvitamin D was measured for all subjects, glycosylated hemoglobin was measured for diabetic cases. Vitamin D status classified according to American academy of pediatrics recommendations.

Results: level of vitamin D was significantly lower for diabetic cases (Mdn = 11.4) than for controls (Mdn = 13.8), U = 2161.5, Z=-2.93(p =. 003). Further analysis of vitamin D level using 10ng/ml as cutoff level to assess the severity of vitamin D deficiency between diabetic cases and controls shows that percent of severe vitamin D deficiency within diabetic cases (42%) was more than control (12%) which was highly significant.

Conclusion: diabetic children are more vulnerable to vitamin D deficiency than non-diabetic with more incidence of severe vitamin D deficiency among them. Routine screening of vitamin D level for all children and adolescent with T1DM should be considered. Further studies are recommended to evaluate the effect of vitamin D supplementation for T1DM patients with vitamin D deficiency on glycemic control. Vitamin D supplementation of T1DM children and adolescent with low vitamin D levels should be warranted.

P2-P082

IGF-1 Relationship with Growth Velocity in Precocious Puberty with GnRHa Treatment

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Background: Although it is reported that central precocious puberty (CPP) GnRH analogue (GnRHa) treatment decreases the growth velocity, its relation with IGF-1 is controversial. We aimed to investigate the effects of GnRHa treatment on IGF-1 level and the relationship between IGF-1 level and growth velocity (GV) in our study.

Method: Forty-four girls with CPP, who started breast development before the age of 8 years, were enrolled in the study. IGF-1 level was measured at the onset of treatment and at sixth month of treatment. The first year growth velocities of the patients were evaluated.

Results: The mean IGF-1 level was 317.7±127.4 at pretreatment. IGF-1 SDS according to chronologic age (CA-IGF-1) was 1.41±1.56; while IGF-1 SDS according to BA (BA-IGF-1) was 0.41±1.05. The GV SDS in the first year of treatment was 1.24±2.23. The mean level of IGF-I in the 6th month was 319.1±129.6. The 6th month CA-IGF-1 SDS was 1.12±1.30. Level of IGF-1 at diagnosis and 6th month were positively correlated with CA, BA, BA-CA, height, weight, breast stage, pubic stage, FSH, LH, estradiol, uterine length, over volume ($p<0.05$). CA-IGF-1 SDS at diagnosis was positively correlated with height SDS, weight SDS at diagnosis and BA-CA ($p<0.05$). Δ-IGF-1 SDS according to CA was positively correlated with height SDS, weight SDS at the diagnosis, height SDS, weight SDS at the first year of treatment ($p<0.05$). There was no correlation between IGF-1 and GV SDS but ΔIGF-1 level in patients with decreased IGF-1 level at 6th; was positively correlated with GV and GV SDS ($p<0.05$). We found that the patients whose IGF-1 level was decreased by treatment, have lower height SDS, CA-IGF-1 SDS and BA-IGF-1 SDS ($p<0.05$).

Conclusion: In our study, there was a positive correlation between IGF-1 level and GV in patients whose IGF-1 level was decreased by treatment. It suggests that starting the treatment at the

beginning of puberty increases risk of the IGF-1 and growth velocity's decrease because the patients whose IGF-1 level was decreased by treatment have lower height SDS and IGF-1 SDS. However, it should be considered that the decreased GV in patients with no IGF-1 decrease may be due to excessive suppression of sex steroids.

P2-P083

Relation Between Hypomagnesemia and Increased Level of HbA1c in Patients with Diabetes Mellitus

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Background: Hypomagnesemia is a frequent condition in patients with diabetes mellitus (DM). It could influence metabolic control in patients with DM. Relevant studies concern mainly adults and there are few data from the pediatric population. The aim of the present study was to evaluate magnesium levels and examine their possible association with glycemic control in pediatric patients with diabetes mellitus

Methods: In all, 36 patients with DM (type 1, 31; type 2, 5) aged between 2 and 25 were included in the study. Using a cross-sectional design, we measured anthropometric parameters, HbA1c, serum magnesium, serum calcium, urinary magnesium, urinary calcium, lipid profile and parathyroid hormone. Hypomagnesemia was defined as magnesium levels < 1.9 mg/dL.

Results: The mean age of the subject was 16.3 years. The mean duration of diabetes was 8 years. Hypomanesemia was found in 20 (55.6%) patients. Patients with hypomagnesemia showed significant higher HbA1c than patients without hypomagenemia (10.7 ± 2.8 vs 8.6 ± 2.2, $P = 0.017$). Serum magnesium levels were negatively correlated with HbA1c (r = -0.405; P = 0.014) as well as the duration of diabetes (r = -0.35+; $P = 0.033$). Urinary calcium-creatinine ratio and urinary magnesium-creatinine ration were not different between the two groups. In lipid profiles, triglyceride was significantly increased in the group of hypomagnesemia (168.2 ± 99.3 vs 97.4 ± 47, $P = 0.021$). Prevalence of polyneuropathy was not different between the groups.

Conclusions: Patients with DM are at risk of hypomagnesemia. Low serum magnesium levels in pediatric patients with DM could be involved in the development of poor glycemic control and chronic complications. We will compare the clinical and laboratory parameter after giving oral magnesium to hypomanesemia group.

P2-P084

PID1 Alters Antilipolytic Action of Insulin and Increases Lipolysis via Inhibited the Activation of AKT/PKA Pathway

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Objective: The aim was to investigate the mechanism for impaired control of lipolysis in obesity by investigating the effect of PID1 on insulin-induced activation of AKT/PKA/HSL pathway and lipolysis.

Methods: First, CIDEC expression was detected in adipose tissue and blood insulin and glycerol levels were measured in high-fat diet-induced obese rats. Next, we examined the effect of different concentrations of insulin on lipolysis and AKT/PKA/HSL pathway in 3T3-L1cells.We also investigated the role of PID1 in regulating AKT/PKA/HSL cascade and lipolysis after insulin treatment and lipofectamine overexpression.

Results: PID1 expression is increased in adipose tissue from HFD rat and positive correlation with insulin levels and lipolysis. In 3T3-L1 adipocytes, we found that antilipolytic effect of insulin is mediated by AKT and AKT activated by insulin can results in phosphorylation of PKA and HSL and suppresses glycerol release. However, over-expression of PID1 counteracts insulin action as indicated by glycerol release and reduced level of Akt phosphorylation in accordance with a decrease in the activity of insulin-dependent PKA/HSL signaling cascade.

Conclusions: All together, these data showed that activation of PID1 in adipose tissue increases lipolysis by altering the antilipolytic action of insulin. This suggests that PID1 may constitute a new strategy to ameliorate adipocyte lipolysis and hence to improve insulin sensitivity.

P2-P085

The Efficacy of Tri-Ponderal Mass Index and Body Mass Index in Estimating Insulin Resistance, Hyperlipidemia and Impaired Liver Enzymes During Childhood and Adolescents

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Body mass index (BMI) is used to diagnose obesity in children and adolescents. Recently, the tri-ponderal mass index (TMI) has been reported to be nearly stable throughout adolescence and estimate body fat levels more accurately than BMI especially in adolescents

Aim: To compare the efficacy of TMI and BMI in forecasting of insulin resistance, hyperlipidemia and impaired liver enzymes

Method: One hundred and forty-two overweight or obese children which were classified with BMI z-scores, were involved in the study. Children with BMI z-scores between +1.0 and +2.0 were overweight when children with BMD z-scores more than or equal to +2.0 were obese. BMI and TMI were calculated as weight(kg)/height(m2) and weight(kg)/height(m3), respectively. All anthropometric variables and laboratory results were collected retrospectively. The TMI thresholds to diagnose overweight status were 16.0 kg/m3 for boys, 16.8 kg/m3 for girls and were 18.8 kg/m3 for boys, 19.7 kg/m3 for girls to diagnose obese status. Fasting blood glucose, insulin, homeostasis model assessment insulin resistance (HOMA-IR), high (HDL) and low density (LDL) lipoprotein cholesterol, triglycerides, total cholesterol and liver function enzymes were evaluated. The HOMA-IR thresholds of Turkish children were used to diagnose insulin resistance (2.22 for prepubertal girls, 2.67 for prepubertal boys, 3.82 pubertal girls, 5.22 for pubertal boys).

Results: Twenty-two overweight and 8 obese children were classified as normal when we used the TMI. Twenty-two overweight children with normal TMI had 22.7% insulin resistance, 9.1% high total cholesterol level, 4.5% low HDL and high triglyceride level and 50% higher LDL levels than 100 mg/dL. Two of 8 obese children with normal TMI had insulin resistance and low HDL levels. There was no incerase in liver enzyme levels in any child with normal TMI. Forty-four obese children were classified as overweight according to the TMI. In this group, insulin resistance were detected in of 40.9%, low HDL in 34.1% and at least one of elevated liver enzyme in 11.4%. Fifty-four patients were obese according to the both BMI z score and TMI.

In conclusion, when we use TMI, we may have a risk of skip over the insulin resistance. However, if we assume that liver enzymes are elevated as a finding of visceral adiposity, TMI can be used as an auxiliary parameter to show visceral effects of adiposity. Normal TMI may indicate that visceral organ functions have not deteriorated yet.

P2-P086

Local Experience of Diabetes and Deafness

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Aim: There is a well described association between diabetes and deafness in many syndromes Collect baseline data about syndromes of diabetes and deafness in Sudan and the underline etiology

Methods: All records of patients with diabetes registered from (Jan.2006 to Dece.2015) were reviewed. Those confirmed to have deafness where further reviewed to find the etiology and management.

Result: Ten cases of Wolfram syndrome were identified 9 female and one male median age at onset of diabetes was (4.6 years). Eight cases were diagnosed with sensorineural deafness based on hearing assessment. Neurogenic bladder was the most common associated condition. Genetic analysis to identify the causative gen was done in EXTER molecular genetics laboratory UK). WFS1 was identified in all cases. Five cases of Thiamine –responsive megaloblastic anemia (Rogers syndromes) five female and one male with the median age of diabetes onset 9.7 months and 12 months for deafness. Ophthalmic complication nystagmus and cataract were diagnosed in 2 patients one patient diagnosed with Stroke at the age of 2 years this patient also was diagnosed with SVT. SLC19A2 gene mutation identified in 3 cases. One case of H- Syndrome A 19-year-old male was born of a consanguineous marriage developed deafness at the age of 8 months diabetes at the age of 15 and noticed to be short recurrent bouts of oily stool. Homozygous mutation in SLC29A3 was identified

Conclusions: Syndromes of congenital deafness and diabetes are rare. Identification of this syndromes needs high index of suspicion. Earlier recognition of these syndrome could improve quality of life by allowing earlier intervention.

P2-P087

Translating the A1C Assay Into Estimated Average Glucose Values in Children with Type 1 Diabetes Mellitus

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Objective: The A1C assay, expressed as the percent of hemoglobin that is glycated, measures chronic glycemia and is widely used to judge the adequacy of diabetes treatment and adjust therapy. Day-to-day management is guided by self-monitoring of capillary glucose concentrations (milligrams per deciliter or millimoles per liter) as well as by using continuous glucose monitoring systems (CGMS). We found a mathematical relationship between A1C and average glucose (AG) levels measured by CGMS over 5 days and determined the correlation between the variable CGMS parameters and HbA1c in 50 children with type 1 diabetes mellitus (DM-1) on MDI therapy.

Research design and methods: A total of 50 diabetic children randomly selected from a cohort of children with DM-1 were in-

Table 1. (for Abstract no P2-P087)

AG, mg/dl	HbA1C %
80	4
90	4.45
100	4.94
120	5.93
140	6.92
160	7.9
180	8.8
200	9.8
240	11.8
280	13.8
300	14.8

cluded in the analyses. A1C levels obtained at the end of 3 months and measured in a central laboratory were compared with the AG levels during the previous 5 days recorded by CGMS. AG was calculated by combining weighted results from 5 days of continuous glucose monitoring performed before measuring HbA1C, with 3-5 point daily self-monitoring of capillary (fingerstick) glucose.

Results: Linear regression analysis between the A1C and AG values provided the tightest correlations HbA1c = 0.0494 MG- 2E-14, $R^2 = 0.90$, $P < 0.0001$), allowing calculation of an estimated average glucose (eAG) for A1C values.

Conclusion: Our study showed a linear relationship between A1C and AG values measured by CGMS for 5 days before HbA1c measurement. The AG can be easily calculated using a formula derived from linear regression analysis of HbA1c data obtained in our diabetic children. The proper use of CGMS enables monitoring glucose variability and can help controlling glucose fluctuations.

P2-P088

Relationship Between Residual Endogenous Insulin Secretion and Glycemic Control in Japanese Children and Adolescents with Type 1 Diabetes

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Background: Difficulty of glycemic control varies among subjects with type 1diabetes (T1D). Influence of residual endogenous insulin detected by serum C-peptide (CPR) levels has noted to be on glycemic control. Flush glucose monitoring (FGM) detects glucose concentration in intercellular fluid (sensor glucose) every 15 minutes to reveal daily glucose profiles.

Aims: We tried to clarify the relationship between serum CPR and the excursion of blood glucose using FGM in Japanese children and adolescents with T1D.

Subjects and Methods: Eighteen (male 6: female 12) childhood onset T1D were enrolled at Saitama Medical University Hospital (6–24 years old, median: 12.5 years old). HbA1c, glycated albumin (GA) and CPR of non-fasting blood sample were measured. Sensor glucose values were measured using FreeStyle Libre Pro® (Abbott Diabetes Care Inc.). Mean (SGM), standard deviation (SGSD) and coefficient of variation (SGCV = SGSD/SGM) of sensor glucose values were calculated. The subjects were divided into 2 groups of depletion and non-depletion defined at the level CPR ≤ 0.01 ng/mL. We analyzed the relationship between serum CPR as the objective variable and glycemic control markers (HbA1c, GA, SGM, SGSD and SGCV) using Spearman's rank correlation coefficient, and compared glycemic control markers between 2 groups using Wilcoxon signed-rank test.

Results: CPR, HbA1c and GA were 0.01–1.51 ng/mL (median 0.01 ng/mL), 7.1–10.4% (54–90 mmol/mol) (median 8.1% (65 mmol/mol)) and 17.9–33.9% (median 24.7%), respectively. SGM, SGSD and SGCV were 174–276 mg/dL (median 224 mg/dL), 78–154 mg/dL (median 96 mg/dL) and SGCV 29–57% (median 45%), respectively. There was a significant inverse correlation between SGCV and casual CPR ($\rho = -0.515$, $p < 0.05$). However, any other parameter did not show the correlation with serum CPR. SGCV showed significant difference between depletion group (n = 12) and non-depletion group (n = 6), 42.1% and 48.6% (p = 0.02), respectively.

Conclusions: The glycemic excursion in childhood onset T1D was associated with residual endogenous insulin. Non-fasting serum CPR which is simple blood collect test can be a useful marker to estimate the excess excursion of glycemic control in T1D.

P2-P089

A Curious Case of Persistent Lactic Acidosis in a Child with Diabetic Ketoacidosis

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Summary: An 11 year old girl with poorly controlled type 1 diabetes mellitus (T1DM) presented with persistent lactic acidosis and transaminitis despite resolution of diabetic ketoacidosis (DKA), subsequently confirmed histologically to have glycogen hepatopathy (GH). This case describes a rare but known complication of poorly controlled DM and offers some novel insights in the management of GH.

Clinical Case: The patient had a history of poor compliance to insulin therapy with a history of recurrent DKA. She presented with severe DKA with serum pH 7.02, bicarbonate 3.6 mmol/L and beta-hydroxybutyrate (BOHB) 8.1 mmol/L. She was managed with intravenous fluid hydration, intravenous insulin therapy titrated closely against her arterial blood gas, serum glucose and BOHB levels.

Within 24 hours of therapy, despite complete resolution of the ketosis with unmeasurable BOHB levels, there was worsening high anion gap metabolic acidosis, secondary to lactic acidosis, hyperlactataemia at 10.1 mmol/L. In addition, she also developed acute tender hepatomegaly of 11cm 48 hours after admission. Biochemically, there was severe transaminitis (AST 6681 U/L, ALT 1493 U/L, normal bilirubin), a stark contrast to the pristine LFT on admission. Liver synthetic function was preserved.

Evaluation for this sudden onset hepatomegaly associated with hyperlactaemia and transaminitis included work up for viral, autoimmune and metabolic causes, which returned negative. The patient subsequently underwent an ultrasound-guided percutaneous liver biopsy which demonstrated the presence of glycogen-laden hepatocytes, confirming the diagnosis of GH.

Discussion: GH is a known complication of poorly controlled DM resulting from the glucose-glycogen metabolism in response to the action of insulin in hepatocytes. The occurrence of frequent episodes of hyperglycaemia and supraphysiological doses of insulin administered for DKA leads to glycogen accumulation in the liver, resulting in hepatomegaly and hepatocellular damage.

The lactic acidosis in GH could be related to the reduction of hepatic gluconeogenesis during insulin administration, resulting in the conversion of pyruvate to lactate. We postulate that glycogenic hepatopathy could also result in a secondary inhibition of the respiratory chain resulting in lactic acidosis.

New Insights: Patients with T1DM have also been shown to have thiamine deficiency which may be worsened by treatment.

Thiamine is used as a cofactor in the pyruvate dehydrogenase complex in the generation of acetyl-CoA from pyruvate for the Krebs cycle. In thiamine deficiency, pyruvate is converted to lactate by lactate dehydrogenase. As treatment with thiamine is safe and inexpensive, we initiated this for our patient.

P2-P090

An Unusual Case of an Exclusively Vegan Child with Diabetic Acidosis

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Case presentation: A 17month old female child was transferred to our hospital from another hospital where she was admitted to the intensive care unit (ICU) due to cerebral edema, diabetic acidosis and severe dehydration. The patient had fever, polyuria, polydipsia and vomiting presented four days before admission. At her admission she was unconscious with dilated pupils, no reaction to painful stimuli (GCS 4/15) and Kussmaul breathing. Her initial blood glucose level was 391 mg/dl, pH 6.85, HC03=5 mmo/L, lactic Acid=1.8 and urine test ketones +. Her personal history was unremarkable with no vaccinations and exclusively vegan diet. She remained at the ICU 18 days, where she developed renal failure (urea 104 mg/dl, creatinine 2,86 mg/dl, creatinine clearance 2,6ml/min/1.73m^2, urine albumin 93mg/24h), hypoalbuminemia (albumin=2,7mg/dl), hypokalemia, thrombosis of right femoral artery, anemia (Hb 8.7-13.7 g/dl, required 7 blood transfusions), thrombocytopenia, hypertransaminasemia- hyperamylasemia (SGOT 480 mg/dl, 171mg/dl, amylase 629 U/L), febrile infection and extended skin edema with epidermal necrosis. Plasma lipids levels were: total cholesterol=67mg/dl, triglycerides=329mg/dl. Her initial HbA1c= 9,4%. When she was admitted to our hospital she was afebrile, without metabolic acidosis with extended exfoliation of the skin. Laboratory tests were: Glucose 53mg/dl, urea=20 mg/dl, creatinine= 0.4 mg/dl, K=4.5 mmol/l, Na=139 mmol/l, amylase 32U/L, lipase 56 U/l, total cholesterol= 108mg/dl, HDL= 47mg/dl, LDL=41mg/dl, TGL= 135mg/dl, TSH 23.49 mIU/ml, HbA1C=5.8% (last blood transfusion 6 days before admission to our hospital), C-peptide<0.1ng/ml, ICA and ZnT8 antibodies (-). She was treated with multiple dose insulin injections and her general condition improved.

Discussion: We present an unusual case of severe diabetic acidosis with mild ketosis and normal lactic acid in an exclusively vegan diet child. This could be possible due to the effects of vegetarian diets on low blood lipid concentrations. Differential diagnosis includes the case of fulminant diabetes due to acute-onset of diabetes clinical symptoms, low c-peptide, negative auto-antibodies and increased pancreatic enzyme levels, according to the international diagnostic criteria.

Conclusion: Diabetes is considered a rather heterogeneous disease. This case does not fit into the existing concepts of either fulminant or idiopathic type 1a diabetes, thereby further highlighting the heterogeneity of diabetes. The vegan diet may possible affect the presentation of the disease, therefore the influence on vegan diet in the disease presentation needs further investigation.

P2-P091

"HLA-DQ Genotyping in Patients with Type 1 Diabetes Mellitus and Celiac Disease"

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Objective and context: Celiac disease (CD) is a common autoimmune disorder in type 1 diabetes (T1D), ranging from 5–10% in Caucasian population. There is limited data on the prevalence of CD in T1D and its association with HLA-DQ in India. We studied the HLA genotyping in patients of T1DM with CD in India.

Design: The study was done in case control design.

Patients and measurements: In a cross-sectional study, 146 T1D patients and 61 age sex matched healthy controls were screened for CD by clinical and immunological criteria [anti-tissue transglutaminase antibody (tTG) antibody], and confirmed by endoscopic duodenal biopsy. HLA typing was performed by SSP-PCR method in patients with CD.

Results: The mean age of T1D patients was 18.3±8.1 years. Male to female ratio was 1.5:1, anti-tTG was positive in 20.5% patients, while the biopsy confirmed CD in 20 (13.6%) cases only. The most common clinical feature was failure to thrive followed by short stature and anemia. There was a significant correlation between the high-risk allele DQ2.5 (DQA1*05:01-DQB1*02:01) in CD with T1D (9 cases, 45%) while none of controls had it.

Conclusion: There was high prevalence of CD in T1D in our study. HLA DQ2.5 as a high-risk genotype was seen in 45% patients with type 1 diabetes and celiac disease and none of the controls. DQ typing can help detect CD risk.

P2-P092

Hypertriglyceridemia in Type 1 Diabetes Children During Diabetic Ketoacidosis; Relation to DKA Severity and Glycemic Control

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Background: Diabetic ketoacidosis (DKA) is a common, life-threatening complication of type 1 diabetes (T1D). Insulin deficiency impairs lipoprotein lipase (LPL) resulting in elevated serum triglycerides (TG) that usually normalize after establishing IV insulin.

Objectives: To study the prevalence of hypertriglyceridemia during DKA in T1D patients and assess its relation to DKA severity and glycemic control after 3 months.

Methodology: This cohort study included 84 children with T1D presenting with DKA at the Diabetes, Endocrine and Metabolism Pediatric Unit (DEMPU), Cairo University. Patients were evaluated for serum TG on admission and 48 h after initiating insulin therapy. HbA1c was assessed 3 months later.

Results: In our cohort, 74 patients (88.1%) had hypertriglyceridemia at onset of DKA that resolved in 41 of them after 48 h, while 33 patients still had hypertriglyceridemia. There was significant improvement in TG after 48 h of DKA management ($p<0.001$). When basal serum TG was correlated with other study parameters, a significant positive correlation was found with BG ($p=0.005$) and duration of ICU stay ($p< 0.001$), while a significant negative correlation was found with serum bicarbonate and GCS (i.e.conscious level) with a p value of 0.012 & 0.022 respectively. No significant correlation was found between TG (basal & after 48 h) and glycemic control or insulin requirements after 3 months.

Conclusion: Hypertriglyceridemia was detected in most patients of T1D during DKA that significantly improved with insulin therapy. TG correlated with the DKA severity and BG levels. However, it did not affect glycemic control or insulin dose later.

P2-P093

Acute Mononeuropathy in an 8-Year-Old-Girl with Newly Diagnosed Type 1 Diabetes

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Introduction: Neuropathy, as a complication of type 1 diabetes (T1D), is a heterogeneous group with chronic polyneuropathy being the most frequent form. Acute mononeuropathy is rare and its pathophysiology has not been elucidated.

Purpose: To describe acute mononeuropathy during the course of severe ketoacidosis in an 8-year-old girl diagnosed with T1D.

Case Report: An 8-year old girl was admitted to the Emergency Department because of respiratory distress. She also complained for fatigue and drowsiness over the last two days. Physical examination revealed severe dehydration, Kussmaul respiration and ketotic breath. She was diagnosed with T1D based on hyperglycemia (Dextrostix 462 mg/dl) and severe ketoacidosis (pH 7.09, $HCO3^-$ 1.7 mmol/l). Furthermore, low insulin and C-peptide levels and positive glutamic acid decarboxylase (GAD) autoantibodies confirmed the diagnosis. The patient was treated with aggressive intravenous infusion of fluids and insulin according to international guidelines. Due to clinical and biochemical deterioration, she was tranferred to the Pediatric Intensive Care Unit (PICU). Diabetic ketoacidosis (DKA) was managed successfully and she was discharged to our department after four days. Subsequently, the patient started multiple daily injection of insulin and diabetes education. On the seventh day of her hospitilization, foot drop of right foot with loss of sensation in the dorsal surface, mild edema and redness were observed. After excluding osteomyelitis and thrombophlebitis, cellulitis was treated successfully with intravenous antibiotics. Further evaluation of foot drop with electrophysiological study revealed reduced conduction velocities indicative of severe axonal damage of right sciatic nerve and mild axonal damage of right femoral nerve. Otherwise, cyanocobalamin, folic acid, thyroid stimulating hormone (TSH) and free T4 levels were within normal ranges. Patient was advised physiotherapy and B6 and B12 vitamins and magnesium were prescribed. Four months later, she has no signs of clinical improvement.

Conclusion: Acute mononeuropathy as a complication of DKA is extremely rare in pediatric population and only a few cases have been described. The pathogenesis of this complication is still unknown.

P2-P094

HLA- G Gene Promoter Methylation Status in Children and Adolescents with Type 1 Diabetes

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Introduction: HLA-G gene is involved in the control of immune response. It plays a primary role on immune tolerance and may participate in controlling autoimmune responses serving as a potential independent susceptibility marker. HLA-G has been isolated in some secretory granules and on the cell surface of primary islet cells induced to secrete insulin. Subsequently, it could be hypothesized that HLA-G methylation at pancreatic islet could sustain T cell activation and onset of diabetes. To the best of our knowledge the methylation of HLA-G gene promoter has not been studied yet in T1D. We **aimed** to investigate the methylation patterns of HLA-G CpG loci in T1D paediatric population.

Patients and Methods: Twenty T1D participants and 20 age-/gender-matched healthy youngsters were enrolled. DNA was extracted from white blood cells, then treated with sodium bisulphate which converts unmethylated cytosines into uracyls, whereas methylated cytosines remain unchanged under the same conditions. DNA was then amplified by PCR using primers:*(F)primer:5'TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGTAGGGAGTTTAGTTTAGGGAT3' and (R)primer:5'GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGCCATAACCACCATCCTTAA3'.*Amplicons were analyzed by electrophoresis (1% agarose gel stained with ethidium bromide), visualized by ultraviolet transillumination, and then Next Generation Sequencing was applied to identify differences in DNA methylation status. The methylation

Table 1. Overall mean methylation percentage (P2-P094)

19 CpGs in HLA-G gene	T1D (n=20)	Controls (n=20)	p
Mean methylation	42.99 ± 5.23	43.94 ± 4.31	0.602
Range	36–51	37–52	

Results are expressed as Mean ± Standard Deviation.

profile was analyzed at 19 CpG sites of the HLA-G gene (*1-5446,2-5484,3-5550,4-5568,5-5579, 6-5599, 7-5629, 8-5652, 9-5654, 10-5690, 11-5715, 12-5719, 13-5772, 14-5775, 15-5778, 16-5780, 17-5801, 18-5813,19-5832).* Comparisons between groups were performed with student's t-test or its non-parametric analogue, Mann Whitney U test, as appropriate.

Results: The results are described in table. HLA-G gene did not exhibit significant differences regarding the methylation status within its promoter sites compared to healthy individuals.

Conclusions: Despite the described close association of HLA-G with autoimmunity, we failed to find any methylation differences in HLA-G promoter sites between T1D patients and controls.

P2-P095

Impaired Adrenal Function in Pediatric Patients with Diabetes Mellitus Type 1 Evaluated with Low-Dose Synacthen Test

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Backround: Primary adrenocortical insufficiency (Addison's disease) is reported to be five more times frequent in adult patients with type 1 diabetes mellitus (T1DM) than in the general population with a multifactorial aetiology involving autoimmune, inflammatory and metabolic mediators. Recent data indicate that more than half of children with T1DM show subnormal cortisol response. Subnormal cortisol response may impair the metabolic control of patients with T1DM as they are more susceptible to recurrent hypoglycemia.

Objective: To evaluate adrenal function in pediatric patients with T1DM and correlate these results with demographic and anthropometric data as well as metabolic control, presence of severe or recurrent hypoglycemia, other autoimmune diseases and the presence of autoantibodies against adrenal cells.

Methods: Patients with T1DM, aged > 6 years, with no history of use of corticosteroids or immunosuppressive drugs were assessed with a low-dose Synacthen test (500ng per 1.73m^2 of body surface). The test was performed three hours after the insertion of a vein catheter and blood samples for serum cortisol measurements were collected at time intervals 0, 5, 10, 15, 20, 25, 30, 35, 40 and 45 minutes after Synacthen administration. A cortisol response below 18.125 mcg/dl or an elevation below 7.25 mcg/dl from baseline value was considered abnormal.

Results: Thirty-five patients (19 boys and 16 girls) with T1DM and a mean age of 13.26 ± 4.10 years (range: 6-19 years) were finally analyzed. In 30 of them a history of recurrent hypoglycemia was recorded. Mean glycosylated hemoglobin (HbA1C) was 7.60 ± 1.19 and duration of diabetes was 5.46 ± 3.58 years widely ranging from 1 to 15 years. In 10 patients (28.57%) a subnormal cortisol response was recorded with predominance in male patients (9 out of 10, p=0.01). No statistical significant difference was observed between patients with normal and sub-normal cortisol response regarding HbA1c levels, age, z-scores of anthropometric parameters (weight, height, BMI), or the presence of other autoimmune disease. Years since diagnosis were lower in patients with normal compared to those with subnormal response to Synacthen test with a difference that was approaching significance (4.76 ± 3.31 versus 7.20 ± 3.82, p=0.07). No patient in our study showed positivity to adrenal autoantibodies.

Conclusions: Approximately one-third of pediatric patients with T1DM showed subnormal response in low-dose Synacthen test despite the absence of autoantibodies against adrenals and this should be taken into consideration especially when evaluating T1DM patients with recurrent hypoglycemia.

P2-P096

The Incorporation of Available Technologies for Diabetes Care Among Different Worldwide Centers: The ESPE/ISPAD Working Group on Diabetes Technology Survey

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Objective: International Societies for diabetes care are aiming to facilitate and improve the uptake of diabetes technologies. This survey investigated healthcare professional (HCP) evaluation of the role of technology in diabetes care within their centres.

Methods: Between April to November 2017, 215 HCPs from six continents (132 Europe, 36 Asia, 23 North and 7 South America, 9 Africa and 8 Australasia) replied to an online survey and provided data for analysis.

Results: Of those participants responding to the survey, the mean number of patients with diabetes within each service was 702, ranging from 10 to 10,000. Eighty percent of respondents re-

ported provision of 24/7 support for patients and 35.3% had an organized national diabetes registry. The mean number of visits to clinic by patients was 4.4/year.

Insulin pumps were used by 35.3% of patients and glucose sensors by 23.0%. One fifth of centres had over 50%, and 10 centres had over 80% of insulin pump users within their service. The proportion of technology users varied greatly between continents; highest usage of technology was reported in Australia (51.5% insulin pumps and 58.1% glucose sensors), followed by North America (45.8% and 28.3%) and Europe (42.0% and 24.5%). The availability of diabetes technology was relatively low in Asia (13.3% and 13.8%), Africa (4.4% and 4.2%), and South America (4.0% and 1.3%).

Reimbursement for insulin analogues was provided by 89.3% centers, for insulin pumps by 75.3%, and for glucose sensors by 59.5% of responding centers. In 73% of centers, insulin pump initiation was performed in an outpatient setting. Eight centers (3.7%) reported a lower age limit for insulin pump initiation and seven (3.3%) for glucose sensor use. The majority reported an individualized approach for technology induction.

Each centres' multidisciplinary diabetes team consisted of on average, per 100 patients, 1.1 consultant physicians, 0.9 nurses, 0.9 dietitians and 0.5 psychologists/social workers with a mean of 3.2 HCPs/100 patients. The lowest number of HCPs/100 patient ratio was reported in North America (1.5) and Africa (1.6), followed by Asia (2.4), Australia (2.6), South America (3.6), and Europe (3.8).

Conclusions: Despite increased availability, the incorporation of technology within diabetes care remains a challenge, especially in lower income regions. Ensuring that individuals with diabetes have access to both technology and sufficient trained personnel to educate and support appropriate usage is paramount to broaden uptake to allow safe achievement of optimal glycaemic control.

P2-P097

Higher Percentage of Insulin Pump Users at Isle of Man (IOM) – Two Years Observational Data

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Introduction: Insulin pump service has changed the outlook of diabetes management in children with diabetes. Studies have shown that better metabolic control is achievable even in patients with poor adherence to medical management. NICE in UK recommends the use of insulin pump for children with poor metabolic control, disabling hypoglycaemia and also when facing challenges with MDI insulin use.

National Paediatric Diabetes Audit (NPDA) reports helps to measure our clinical performances against wider national data. Though IOM not part of NPDA cohort aims to deliver highest standards of care by comparing unit performance against NPDA outcomes.

Aims: The aim is to compare the prevalence of insulin pump users, other performance outcomes such as HbA1c and compare it against published NPDA report. Also to identify factors that helps to promote wider use of insulin pump in T1D.

Table 1. (for Abstract no P2-P097)

Outcomes	NPDA 2015–16	IOM 2015–16	IOM 2016–17
Total [M]	27089 [14191]	48 [25]	45 [22]
Age range	0–19	6.2–19	2.5–17
Pump users in %	28	90 (43/48)	87 (39/45)
Mean HbA1c (mmol/mol)	68.3	63.3	63.8
<58 mmol/mol in %	26.6	31.2	39.5
>80 mmol/mol in %	17.9	6.2	7.2

Methodology: A retrospective observational study was carried out on all diabetic children managed by our Paediatric unit between April 2015- March 2017. Data on key outcomes like age, HbA1c, associated conditions and acute admissions were analysed. All the results were compared to published NPDA reports for the identical period.

Results: *[Combined England & Wales data]* A total of 48 [M-25] children with T1D and median age was 13.2 years [range 9.2-19] during the year 2015-16. The mean HbA1c was 63.3mmol/mol ***[68.3]*** with 90% (43/48, 27-Animas, 15-Omnipod and 1-Medtronic who moved from UK) were on insulin pump compared to ***28%*** in England & Wales combined for the same period.

The results for year 2016-17 summarised in table-1 with no published NPDA data available for comparison.

Acute admissions and associated conditions in our unit over this 2 years period were same though few more coeliac diseases diagnosed in 2016-17. Table-1 summarises all the results.

Conclusions: 1. Higher rate of insulin pump usage is achievable without compromising various measured outcomes 2. Provision of only 2 different insulin pumps helped in better utilisation of expertise and at the same time providing crucial choice for the end users (tube vs. patch pump). 3. Liberal funding by health care provider is crucial for pump services.

P2-P098

Use of Continuous Glucose Monitoring Systems in the Early Detection and Management of Cystic Fibrosis Related Diabetes in Children

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Background: Development of cystic fibrosis–related diabetes (CFRD) is associated with worse pulmonary function, poorer nutritional status, more chest infections and increased mortality. In cystic fibrosis (CF) patients, abnormality of the 1 hour glucose during Glucose Tolerance test (GTT) is reported to be a better predictor of early CFRD and is associated with decline in pulmonary function compared to the 2-hour glucose level during GTT. We report a case series of 4 patients and their early detection and management of CFRD using Continuous Glucose Monitoring (CGM).

Methods: Our local practice since 2017 was to commence 2-weeks of CGM in children with CF who show a 1-hour glucose abnormality on the annual GTT screen. Depending on the CGM data, we initiate bolus prandial insulin initially as postprandial hyperglycaemia is usually the primary abnormality. We would then add basal insulin when fasting glucose becomes abnormal or insulin bolus requirements become significantly high. CGM is continued every month until blood glucose and insulin dosing is stable.

Results: 4 patients with CF ages 6-15 years had impaired glucose at 1 hour GTT > 11.1mmol. CGM was commenced in all 4 patients with targeted multidisciplinary approach. In 3 patients, sustained postprandial glucose abnormalities were detected. One patient also showed frequent elevated overnight, fasting and postprandial glucose levels. CGM data guided the decision to start insulin, the choice of insulin regimen and insulin dosing. 1 patient commenced on multiple basal bolus insulin, 2 patients were commenced on prandial bolus insulin while one patient had regular intensive dietary advice with regular cappillary blood glucose monitoring. Nutritional status and FEV1 lung function improved in all 4 patients six months following targeted interventions. HbA1c improved in 3 patients who were commenced on insulin therapy. No side effects of hypoglycaemia was reported in the 3 patients who were commenced on insulin.

Conclusions: Abnormalities of glucose metabolism have a negative impact on morbidity and mortality in CF patients. Our study shows that early detection of glucose abnormalities using CGM and early MDT targeted intervention improves lung function and nutritional status. We recommend a pragmatic approach with insulin use to target initially postprandial glucose excursions and regular use of CGM to guide insulin dosing. Further studies are warranted on optimum timing of insulin initiation and the use of CGM in early detection and management of CFRD.

P2-P099

Metabolic Improvement Offered by Medtronic Minimed 640 G Associated to Transient Insulin Perfusion Suspension Before Hypoglycemia in Young Patients with Type 1 Diabetes

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Objective: Fear of hypoglycemia interferes frequently with metabolic control of type 1 diabetes especially in patients under 5 years of age who are at high risk of hypoglycemia and low metabolic control. Medtronic Minimed 640 G insulin pump with Smart Guard technology (suspension of insulin perfusion in predictive hypoglycemia situations) appears to be an adequate system for these patients by reducing the risk of hypoglycemia.

Research design and methods: Retrospective study, patients with type 1 diabetes using Medtronic Minimed 640 G with Smart Guard technology. Carelink-Pro software used to follow continuous glucose monitoring (CGM) as well as HbA1c.

Results: 11 patients with type 1 diabetes, median age 4.5 years old (22 months - 8 years old), 27 % girls, 73 % boys. Median age at diagnosis 22 months old (11 - 40 months old). Insulin pump (Medtronic Minimed 640 G) used on average 12.5 months after diagnosis. CGM + Smart Guard technology added on average 7.1 months after starting insulin pump. Study duration : 6–24 months.

Significant reduction of time spent in hypoglycemia : 6 - 90 episodes of hypoglycemia per month before intervention, 0 - 10 minutes of hypoglycemia during the last month of the study and an average duration of 145 minutes of stopped insulin administration (113 - 204 minutes). No major hypoglycemia noted neither hyperglycemia or Ketosis secondary to transient treatment suspension.

Significant improvement of metabolic control, average HbA1c 8,26% before intervention and, 7.7 % at the end of the follow-up : 0.56% of average reduction (p=0.03).

Conclusion: The Medtronic Minimed 640 G with the option of transient insulin administration suspension before hypoglycemia shows a positive impact in the treatment of type 1 diabetes allowing physicians to attempt metabolic control, with limited episodes of hypoglycemia and better quality of life of patients and their families.

P2-P100

The Glycemic Variability in Children with Diabetes Mellitus

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The glycemic variability (GV) - is the scope of changes in blood glucose levels for a certain period of time. In patients with diabetes mellitus type 1 (DM1), GV are more pronounced, especially in children.

The aim: analyze the glycemic variability in children with diabetes mellitus.

Materials and methods: 126 children aged from 6 to 17 years with duration from DM 16 years were examined. Investigated: glycated hemoglobin (HbA1c), insulin demand, insulin therapy method. Computed by GV: CV, SD, MAGE and the amplitude of the oscillations according to the scatter profiles of blood glucose. The basis was taken CV, as an indicator reflecting not only the fluctuations themselves, but also the level of glycemia in which they occur.

Results: The analysis of HbA1c and CV values resulted in a negative correlation (r=-0.216, p<0,05).Correlation analysis showed a strong relationship between the studied indicators of blood glucose. The largest relationship in this case are the amplitude and SD (r=of 0.965,p<0,01). Having estimated influence of duration of disease on GV it was received that interrelation of indicators of GV with duration of disease had no statistical significance. Correlation analysis demonstrated a decrease in CV as they grow older patients. Analysis of change in CV for years has shown that the reduction in CV below 30% is only 13 years. At the same time, the maximum «peak» of CV is 7-8 years (36% and 42%, p<0,01). It was noted a slight rise in CV at the age of 14 years (30,7%, p<0,05), followed by stabilization of the values of CV of about 28%. With regard to gender differences in CV, the highest CV values were found in girls aged 6 years compared to boys (26 and 31,6 %, p<0,05), as well as in the age of 11 years (26 % for girls,

36 % for boys, p<0,01). Analysis of the method of insulin therapy and daily insulin requirements did not reveal any statistically significant correlation with CV, p>0,05.

Summary: The glycated hemoglobin does not reflect the glycemic variability. The considered methods of evaluation of glycemic variability can be used both in isolation and in complex in assessing the degree of compensation of diabetes mellitus. The glycemic variability does not depend on the duration of the disease, insulin dose and insulin therapy. However, there is an inverse dependence of glycemic variability on the age of patients with "peaks" in 7-8 years and 13 years.

P2-P101

The Levels of Blood Glucose and Counting of Carbohydrate-Fat-Protein in Diabetic Children Using Pump with Aspart and Glulisine

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Introduction: In children with Type 1 diabetes, the insulin dose administered to, fasting blood sugar, the amount of food,contents and glycemic index can affect the postprandial blood sugar. Despite the intensive insulin therapy and carbohydrate (CHO) counting the expected improvements in glycemic control is not observed. Compared to other fast affecting analogues, Insulin glulisine has a faster onset of effect and a shorter duration. It has previously been reported that, in children who have undergone insulin pump therapy, glulisine is more effective and does not lead to hypoglycemia.

Aim: A comparison of insulin glulisine and aspart effect on blood sugar levels and CHO/CHO- fat- protein count in children with Type 1 diabetes using insulin pump.

Method: It was planned to work with 15 children and adolescents between the ages of 6-18 years with T1DM using insulin infusion pump. Preliminary results were given to 5 patients who completed the study. The first week cases used Aspart İnsülin for 6 days and blood glucose levels were monitored while Medtronic Ipro2 was continuously attached to the glucose measurement device. And then insulin glulisine was taken after 2 weeks for 6 days. On the 2nd and 5th days, a pizza of 84 g CHO (38.4%), 36g fat(39.9%) and 46g protein(21.7%) was consumed at lunch. On the 2nd day there was normal bolus according to the amount of CHO and on the 5th day according to the amount of CHO, there was normal bolus and an additional insulin spreading bolus for fat-protein content were applied (calculated according to the algorithm of Pankowsa et al)

Results: A significant increase in the frequency of hypoglycemia with a lower mean blood glucose levels were seen with glulisine insulin (Table 1). This was associated to the low number of cases and the frequent occurrence of hypoglycemia in one case. Blood glucose regulation was better in the CHO-fat-protein count with both aspart and glulisine insulin compared to the CHO count alone (p>0.05). There was no difference between the insulin levels in terms of CHO and CHO-fat-protein counts.

Table 1. Effects of Aspart and glulisine on blood sugar (for Abstract no P2-P101)

	Aspart	Glulisine	P
Mean Glucose (mg/dl)	159.8±24.1	133.2±21.8	0.043
>140 mg/dl (%)	59±17.8	30.8±17.7	0.043
140–70 mg/dl (%)	38.8±17	62.6±13.5	0.043
<70 mg/dl (%)	2.2±2.3	6.6±8.4	0.192

Conclusion: In children Glulisine insulin is an effective and safe in the treatment of insulin pump. The CHO-fat-protein count at high fat content provides better regulation for blood sugar.

P2-P102

A Novel Missense Variant, p.(Thr405Arg), in the *SLC19A2* Gene in an Infant with Thiamine Responsive Megaloblastic Anemia Syndrome Presenting with Anemia and Diabetes But with Normal Hearing

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Objectives: Thiamine responsive megaloblastic anemia syndrome (TRMA) is characterized by the clinical triad of megaloblastic anemia, non-immune diabetes mellitus and sensorineural deafness. It is a very rare autosomal recessive disease with an increased frequency in consanguineous marriages and isolated communities. The syndrome is due to intracellular thiamine deficiency which is the result of a defective high affinity low performance thiamine transporter protein (THTR1) encoded by the *SLC19A2* gene. Treatment with pharmacological doses of thiamine leads to an increase in intracellular thiamine concentrations and resolution of anemia and better glycemic control, but apparently does not affect hearing loss. To date approximately 50 different mutations in 80 patients have been described.

Patients and Methods: We present a 4 months old boy born to non-consanguineous parents who presented with failure to thrive, profound anemia (Hgb 58, Hct 0.170, MCV 92.4 fL), diabetes mellitus (blood glucose 24.4 mmol/L, HbA1c 7.1%) and preserved hearing. After initial red blood cell transfusion and insulin treatment (0.66 IU/kg/day) a diagnosis of TRMA syndrome was suspected and the patient was started empirically on oral thiamine (100 mg/day). Insulin treatment could be stopped on the second day of thiamine treatment and his hemoglobin level improved.

Results: Analysis of all coding regions and exon/intron boundaries of the *SLC19A2* gene (NM_006996.2) by Sanger sequencing

was performed and revealed that our patient is a compound heterozygote for a nonsense, c.373C>T; p.(Gln125Ter), and a novel missense variant, c.1214C>G; p.(Thr405Arg), in the *SLC19A2* gene. Both variants are predicted to be pathogenic and this result confirms the TRMA diagnosis

Conclusion: Of about 80 patients with TRMA that have been reported to date, only a few presented with neonatal diabetes mellitus, and even fewer with preserved hearing. Only a couple of patients started thiamine treatment at age 4 month or earlier, and this could be crucial for the preservation of hearing, or at least for postponing hearing loss. Also it is possible that compound heterozygotes may have less severe phenotype regarding hearing loss but further data is needed. Follow- up is needed to evaluate effect of novel gene variant and therapy on hearing in our patient.

Key words: Thiamine responsive megaloblastic anemia; neonatal diabetes mellitus; hearing loss; novel *SLC19A2* gene variant.

P2-P103

Donohue syndrome with Hypertrophic Cardiomyopathy

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Donohue Syndrome is a rare and lethal autosomal recessive disease caused by mutations in the insulin receptor gene. It presents severe insulin resistance, fasting hypoglycemia, post-prandial hyperglycemia, intrauterine and postnatal growth retardation, dysmorphic features, hypertrichosis.The diagnosis of Donohue syndrome was based on the clinical characteristics, laboratory evaluation and determination of the INSR mutation.We report a Turkish female patient with genetically proven Donohue syndrome who had hypertrophic cardiomyopathy.

Case: Our patient is the second child of healthy first degree consanguineous parents of Turkısh family. She was born at 36 weeks of gestation via caesarean section due to severe intrauterine growth retardation.

She had hyperglycemia (328 mg/dl) with hyperinsulinemia (insulin:5253 µIU/ml, C peptide: 76.16 ng/ml) in eighth day of hospitalization. Because of severe hyperglycemia iv insulin infusion was started at 0.01U/kg/h and progressively increased to 0.5 U/kg/h. In followed-up clinical time 2U/kg/day insulin glargine added treatment and potentiated 15 U/kg/day.

At the age of twenty five days she presented with cholestasis. Serum total bilirubin level was8,93 gr/dl, direct bilirubin level was 6,8 gr/dl, serum aspartate transaminase was 265U/L and serum alanine aminotransferase was 240 U/L.

Molecular study found that the patient was homozygous deletion at exon3-22of the INSR gene

At the age of three months she admitted our hospital because of fasting hypoglycemia.. During this admission, echocardiographic examination showed an increase of both inverventriculer septum and left ventricle posterior wall diameter. Septal thickness increased to 5.4 mm with left ventricular outflow tract obstruction and systolic anterior movement of the mitral valve. Treatment with propranolol was started. Recombinant ınsulin-like growth factor-I was not given because of risk for further cardiac hypertrophy.

She was died at the age of 7 months because of respiratory insufficiency caused by a fulminant pulmanory infection.

Discussion: Our patient had a mild cardiac hypertrophy in later control echocardiograms.The data about the mechanism of myocardial hypertrophy in these patients is still conflicting. However, the most commonly accepted hypothesis is that myocardial hypertrophy is the result of the IGF-1activation which is also found in the heart caused by elevated insulin concentrations.

Hypertrophic cardiomyopathy is frequently observed in Donohue syndrome and has high mortality. Therefore hypertrophic cardiomyopathy demands extra attention in Donohue syndrome. Treatment is generally hard and unsuccessful. Generally patients die in infantile period of life. So prenatal diagnosis and genetic counseling are quite important.

P2-P104

Age and Exocrine Pancreatic Enzyme Requirements Are Major Determinants for Carbohydrate Metabolism Impairment in Children Affected with Cystic Fibrosis

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Introduction: Cystic fibrosis related diabetes (CFRD) is associated with a poorer nutritional status, respiratory function and an increase in mortality rate. Screening is recommended from age 10; however, prediabetic conditions are diagnosed earlier.

Objectives:

1) To characterize the degree of carbohydrate metabolism impairment (CMI) in 50 CF patients.
2) To explore the association with clinical parameters as eventual predictors of these conditions.

Patients and methods: HbA1c measurement and an oral glucose tolerance test (OGTT) for glucose and insulin were performed in 50 CF patients (27 males/23 females; mean age 12.3±3.7 years). Twenty-eight patients (56%) were normoglycemic (NG). Those with impaired glycemia at fasting [≥100 mg/dl (n=1)]; glucose tolerance [≥144 mg/dl at 120´(n=13)]; IAG: ≥200 mg/dl at 30´or 60´, (n=5)]; T2DM [≥200 mg/dl at 120´in the OGTT or ≥126 mg/dl fasting (n=3)]) were offered continuous subcutaneous glucose monitoring (CSGM, accepted by n=16).

Mutations in *CFTR*, age, pubertal status, clinical and anthropometric evolution, microbiologic colonisation in the previous year and exocrine pancreatic enzyme requirement at the time of

study were recorded and compared between groups. HOMA index and area under the curve (AUC) for glucose and insulin in the OGTT and time (%) with glycemia above 144 mg/dl (*T>144mg/dl*) in CSGM were calculated, compared between groups and their relationship with the rest of clinical parameters explored.

Results: Significant differences between groups ($p<0.05$ for all) were found in HbA1c, age and standardized height (the more severe the CMI, the older the patient, higher HbA1c and lower height-SDS).CFTR mutations, lung function, nutritional status and the number of exacerbations/hospital admissions in the previous year showed no differences between groups. Patients colonised by methicilin-resistant Staphiloccocus aureus (n=3) had CMI. HbA1c was positively correlated with $AUC_{glucose}$ ($r=+0.49$; $p<0.001$), glycemia at 120′ ($r= 0.54$;$p<0.001$) and *T>144mg/dl* ($r=+0.57$; $p<0.05$). Enzime requirements (U/kg) were inversely correlated with $AUC_{insulin}$ ($r = -0.36$; $p<0.05$) and directly with HbA1c ($r=+0.28$; $p<0.05$), $AUC_{glucose}$ ($r=+0.29$;$p<0.05$) and *T>144mg/dl* ($r=+0.57$;$p<0.05$).

Conclusions: 1) Older age and higher enzyme requirements are associated with a higher rate of CMI in CF. 2) Insulin/glucose AUC study and CSGM analysis do not afford substantial additional information to warrant the studies. 3) HbA1c is a reliable marker of the time in hyperglycaemia also in CF patients.

P2-P105

Post-Prandial Hyperinsulinaemic Hypoglycaemia After Oesophageal Surgery in Children

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Introduction: Post-prandial hyperinsulinaemic hypoglycaemia (PPHH) is a recognised complication of various gastric surgeries in children, but rarely reported after oesophageal atresia repair. We report two children diagnosed with PPHH post-oesophageal surgery and the challenges of their management.

Case 1: A 2-year-old boy diagnosed with oesophageal atresia at birth, was surgically repaired requiring six oesophageal dilatations the first year of life. At 11-months of age he manifested hypoglycaemic seizures and investigations confirmed PPHH. Acarbose and diazoxide trials failed. He was managed with 17-hours continuous gastrostomy feeds. Currently, he is 28-months-old with euglycaemia on daytime bolus gastrostomy feeds and overnight 12-hours continuous gastrostomy feeds.

Case 2: A 6-month-old girl diagnosed with Wolf-Hirschhorn syndrome and tracheo-oesophageal fistula, was surgically repaired, requiring monthly oesophageal dilatations. At 5-months of age she was reported to have hypoglycaemia and PPHH was confirmed. She responded to diazoxide and continuous nasogastric tube feeds, but developed pulmonary hypertension possibly diazoxie-induced. Subsequently diazoxide was stopped and normoglycaemia was secured via 20-hours continuous gastrostomy feeds.

Conclusion: PPHH may be an under-diagnosed complication in children undergoing surgery for oesophageal atresia. These children must be monitored closely for symptoms of hypoglycaemia and if there are concerns must be screened for possible PPHH. Our cases demonstrate that continuous feeding regimens might be the only therapeutic option, until PPHH gradually lessens in intensity over time.

P2-P106

Congenital Hyperinsulinism: Clinical and Molecular Characteristics – Fluorine-18-L-Dihydroxyphenylalanine Positron Emission Tomography (F-DOPA PET) Scan Results -Treatment Responses and Short Term Outcomes of 5 Patients

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Aim: The most common cause of persistent hypoglycemia and related brain damage in infancy is congenital hyperinsulinism (CHI),due to inappropriate secretion of insülin by pancreatic β cells.The most frequent and most serious mutations are activating mutations in ABBC8 or KCNJ11 genes. Genetic analyses,which might predict the type of lesion, performed in early period and 18fdopa pet scanning are very valuable for treatment choice and follow-up of the patients.

In this study,our aim was to emphasize the importance of genetic studies and 18fdopa pet scanning,and the management of 5 CHI patients with or without known genetics who underwent different treatment strategies.

Cases: Four cases were diagnosed in the first month of life,while one case was diagnosed at fourth months.All of the patients had presented with hypoglycemic seizures. There was a history of preterm delivery in 4 cases. Four patients were large for gestational age and one had a normal birth weight.Female/male ratio was 4:1. There were consanguineous marriages between parents in three cases. While one case responded to diazoxide, three cases needed additional therapy.In one case pancreatectomy was performed due to failure of medical therapy. Four cases were scanned with 18-f dopa pet CT. In 2 cases,lesions were interpreted as focal; increased uptakes were observed in the head and body of pancreas (table). While 3 cases showed normal motor mental development,severe motor mental retardation(MMR) was observed in one case due to hypoxic encepholophathic disease. And one case diagnosed at the 4.mounth showed moderate MMR due to hypoglycemia. Genetic analyzes were performed in all cases.Mutations in ABCC8 genes

Table 1. for Abstract no P2-P106)

	Case 1	Case 2	Case 3	Case 4	Case 5
Age/gender	1.46/F	3.67/F	2.25/F	1.07/M	0.45/F
Genetic Analysis	Heterozygous mutation in ABCC8 gene	Compound heterozygote mutation in ABCC8 gene	No mutation detected	No mutation detected	Mutation in ABCC8 gene
FDOPAPET/SCAN	No lesion detected	No screening was performed	Diffuse uptake	In the pancreas head increased uptake	Focal increased uptake image of 0.5 cm in the pancreas body
Treatment	Octreotide	Octreotide Nifedipin	Octreotide Nifedipine	Diazoxide	Near total pancreatectomy

were detected in 3 cases. In 2 cases no mutation was found in the studied genes.

Conclusion: Hyperinsulinemic hypoglycemia in neonates and infants is a condition that should be urgently and effectively treated to prevent neurological compications. Molecular genetic tests and Fdopa pet scans in congenital hyperinsulinism are very valuable to decide on treatment choice and to predict the clinical follow-up.

P2-P107

Congenital Hyperinsulinism in a Child with Alagille Syndrome

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Background: Alagille syndrome (ALGS) is an autosomal dominant genetic disorder, with highly variable phenotype affecting multiple organs. Commonly presents in infancy or early childhood as cholestasis. Mutations in the notch signaling pathway ligand (*JAG1*) or its receptor (*NOTCH2*) lead to ALGS. This pathway is important for the pancreatic development. However,no cases of ALGS with Congenital Hyperinsulinism (CHI) have been reported to date.

Aim: To report an atypical case of ALGS presented with CHI.

Case report: A full-term female infant, with birth weight of 2.78 Kg, developed cholestatic jaundice and episodes of hypoglycaemia on day 3 of life. Further investigations confirmed CHI and started Diazoxide (5 mg/kg/day) along with Chlorothiazide (7mg/kg/day). She had mild facial dysmorphism with bossed forehead, prominent nasal bridge and small chin. Microarray showed monosomy of 20p11.21–p12.2 due to interstitial deletion of the short arm of chromosome 20, consistent with ALGS. The infant was discharged at 4 weeks of life on Diazoxide and 4 hourly bottle feeds. She was diagnosed with a cardiac murmur due to a patent ductus, which was subsequently closed by the age of 12 months. At six-months of age, she was noted to have hepatomegaly (2cm) with mildly raised bilirubin appeared. Diazoxide was discontinued at the age of 1 year after self-weaning of the medications. She has been on regular follow-up visits upto the age of ten years without further episodes of hypoglycaemia or hyperglycaemia.

Conclusion: ALGS is a rare inherited disease with variable phenotypic expressions. To the best of our knowledge, this is the first case of ALGS diagnosed with CHI that was Diazoxide-responsive and resolved at 12 months of age. Further work is needed to understand the mechanism of CHI in ALGS and children should be screened for CHI if any concerns regarding hypoglycaemia.

P2-P108

Severe Stress-Induced Subcutaneous and Intravenous Insulin Resistance in an Eight Year Old Boy with T1DM, Necessitating Seven Months of IV Insulin, Reversed After Psychiatric Treatment

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Background: Persistent severe insulin resistance (IR) in T1DM is infrequent, complex to handle and disabling. Genetic and epigenetic factors play a significant role in the pathophysiology of IR. This case report discusses the potential role of habitual and stress-inducing environmental factors in a school-aged boy with a neurodevelopmental disorder.

Case report: We present an eight year old boy with a three year history of T1DM (GAD positive) regulated by uneventful continuous subcutaneous insulin infusion (CSII) treatment for three years.

Though initially increased behavioral dysregulation was partly attributed to T1DM, he was diagnosed with a neurodevelopmental disorder with symptoms of autism, deficient anxiety and attention

regulation at age six. Therapy consisted of behavioral interventions and atypical antipsychotics. Shortly after start of aripiprazol, mild ketoacidosis developed. After appropriate treatment, metabolic control could only be maintained by intravenous insulin (iv) therapy. Attempts during prolonged admission and while on iv insulin to restart CSII were unsuccessful with subcutaneous (sc) insulin up to 6 U/kg/day and injections sc with Insulin Degludec, Insulin Aspart, Insuman Infusat (to exclude allergy), and Insulin Glulisin as well as addition of metformin all failed to reinstall glycemic control.

Technical problems and manipulations were excluded; carbohydrate and exercise management did not affect IR and he did not have signs of lipodystrophy or acanthosis nigricans. Extensive laboratory investigations revealed normal cortisol, catecholamine- and glucagon levels; positive anti-insulin and negative insulin receptor antibodies.

Antipsychotics, as potential trigger for IR, were discontinued; thereafter behavioral problems deteriorated despite initiation of carbamazepine treatment. Five months after onset of IR, admission to a child psychiatry inpatient unit was decided on. A 24/7 structured, behavioral approach combined with ongoing strict T1DM regulation led to a successful, lasting transfer to CSII treatment.

Discussion: In this now 10 year old boy with T1DM and a neurodevelopmental disorder we hypothesize a role for stress-induced IR. Antipsychotic treatment alterations may have initiated the onset of sc and iv IR. However, cessation of antipsychotic treatment did not re-install glycemic control; suggestive of a role for stress-induced IR. With structured behavioral approach in a child psychiatry unit combined with continuation of strict regulation of nutrition and insulin therapy the IR disappeared. He still frequently presents with ketoacidosis but not with lasting IR.

In **conclusion:** IR appeared to be at least in part stress dependent and an integrated therapeutic approach led to better behavioral as well as glycemic control.

P2-P109

A Case of Neonatal Diabetes Due to Pancreatic Hypoplasia

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Introduction: Neonatal diabetes mellitus (NDM) is a rare form of insulin-dependent monogenic diabetes mellitus (1/400,000 live births) diagnosed in the first six months of life. It can be either transient or permanent, with abnormalities in the parental chromosome 6q24 and with mutations in genes related to the ATP-sensitive potassium pump in the β-cell membrane respectively.

Aim: We describe a male infant, 2.5 months old, diagnosed with NDM and pancreatic hypoplasia.

Subjects and methods: The infant was admitted via the paediatric A&E with irritability, a two-week history of reduced feeding, and loose stools 6-10 times daily. His development was normal for age. He was the first child of healthy, unrelated parents, born at 40^{+3} weeks of gestation by caesarean section due to no progression of labour, IUGR, birth weight 2300 gr. On examination he was alert, pale, with mild dehydration, vital signs normal. Laboratory testing showed hyperglycaemia without ketoacidosis, blood glucose 919 mg /dl (51mmol/l), Na^+ 121mmol/L (NR 135-145 mmol/L), K^+ 5.6 mmol/l (NR 3.5-5.1mmol/L), pH 7.418, $HCO3^-$ 25.3 mmol/l, BE 1.3 mmol/l), HbA_1c 13.6% (NR 4-6%) (125.1mmol/mol, NR 20.2-42.1), insulin 1.6 μIU/L (2.6-24.9), C-peptide 0.449 ng/ml (NR 1.1-4.4), serum amylase 15 U/L (NR 28-100) and serum lipase 4 U/l (NR 13-60). Initially, he was treated with intravenous fluids and insulin, then with subcutaneous insulin. Diarhoea improved gradually, started gaining weight, he had normal stool on day eight after admission. Subsequently, he was started on CSII with synchronous continuous glucose monitoring (CGM). His latest HbA1c was 9.2% (77mmol/mol).

Results: Antibodies to glutamic acid decarboxylase (anti-GAD) 0.1 (<10U/ml) and insulin (IA2) 8.7 (<10U/ml) were negative, pancreatic islet cell antibodies (ICA) were found marginally positive 1.6 U/ml (> 1.05 U/ml positive). Fecal elastase was detected at very low levels (<15 grams/gr of faeces, NR >200) on two occasions. Abdominal ultrasound showed increased echogenicity of the pancreas which appeared to be hypoplastic for age; results confirmed by MRI of the abdomen. Genetic testing was negative for mutations in the KCNJ11, ABCC8 and INS genes.

Conclusions: The genetic causes of NDM in 40% of cases remain unknown. Congenital pancreatic hypoplasia may be responsible for NDM and deficiency of pancreatic exocrine function, therefore, requiring insulin therapy and pancreatic enzyme substitution.

P2-P110

Neonatal Diabetes Mellitus Caused by a Novel *GLIS3* Mutation in Twins

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Background: *GLIS3* is a transcription factor involved in the development of pancreatic β-cells, the thyroid, eyes, liver and kidneys. In the pancreas, *GLIS3* is expressed at various stages of ductal and endocrine cell development, and is a critical regulator of β-cell development and insulin expression. Mutations in *GLIS3* have been recently described as a rare cause of neonatal diabetes and congenital hypothyroidism (CH), reported in only 20 patients to date.

Case Report: Two term small for gestational age non-identical twins (male and female), were born to first-cousin parents. Both

developed marked hyperglycemia in the first 24 h of life. During their first weeks, they were diagnosed with primary CH, bilateral glaucoma, mild cholestasis, and polycystic kidneys. Regular IV insulin administration was started and continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) were initiated at 2 weeks of age. L-T_4 therapy was started on the 5th day of life and bilateral eye trabeculotomy was performed at 1.5 months. After the first month, the best diabetes control was achieved with CSII using insulin Humalog diluted 1:10 (10 U/mL). The combination of neonatal diabetes with CH, kidney cysts, cholestasis and glaucoma suggested the diagnosis of a *GLIS3* mutation; this was confirmed by molecular analysis. A novel homozygous nonsense mutation (c.2392C>T, p.Gln798Ter) located in exon 9 in both twins, and the heterozygous mutation in the parents were identified. Currently, at the age of 1 year, both twins have mild motor retardation and low weight gain. Kidney cysts have disappeared, liver function tests and intraocular pressure are normal and their thyroid function tests are controlled with L-T_4 dose of 250-300 mcg/week. HbA1c is 7.7% (male) and 8.5% (female), with a daily insulin dose of 0.4–0.5 unit/kg.

Conclusions: We report a novel *GLIS3* mutation in non-identical twins with a combination of neonatal diabetes, CH and glaucoma. We will discuss the challenges in managing neonatal diabetes, and show that the combination of CSII and CGM is the best way to achieve diabetes control in neonates. Our report highlights the importance of early molecular diagnosis for the management of, and genetic consultation in neonatal diabetes.

P2-P111

Permanent Neonatal Diabetes, Hepatic Failure and Progressive Left Hemispheric Cerebral Atrophy in a Patient with Wolcott-Rallison Syndrome: A Clinical and Genetic Study from the State of Qatar

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Background: Wolcott-Rallison syndrome (WRS) is a rare recessively inherited disorder characterized by insulin-dependent diabetes and multiple epiphyseal dysplasia. The disease is also characterized by recurrent episodes of hepatitis or hepatic failure, growth retardation and developmental regression. WRS is caused by biallelic mutations in *EIF2AK3*, encoding the eukaryotic translation initiation factor-2 kinase 3 (IEF2AK3). *EIF2AK3* regulates the synthesis of unfolded proteins in the endoplasmic reticulum and is involved in the differentiation of pancreatic islet beta cell progenitors. To date, several mutations from all over the world have been described in the *EIF2AK3* gene; however, no case report has been described from the State of Qatar.

Objective(s): To describe a complex case of WRS in a Qatari patient.

Case Report: This patient presented with permanent neonatal diabetes (PNDM) and subsequent autoimmune liver disease requiring a liver transplant, progressive left hemispheric cerebral atrophy of unknown etiology, severe seizure disorder requiring multiple anticonvulsants, sodium losing nephropathy, and EBV viremia.

Methods: All exons (1-17) of the *EIF2AK3* gene were amplified by PCR. The amplified products were then sequenced using ABI 3500XL sequencers and analyzed for sequence variations. The variations significance was determined by comparison with wild type sequences, previously reported mutations, and correlation with the eukaryotic translation initiation factor2-alpha kinase 3 protein structure.

Results: DNA analysis revealed a c.1566_1569delGAAA in exon 9 of the *EIF2AK3* gene. This four-nucleotide deletion causes a frameshift and resulting in aberrant mRNA processing. This exact change has been previously published as an *EIF2AK3* mutation. The patient is homozygous for this mutation. Analysis of DNA derived from the father and mother reveals a heterozygous *EIF2AK3* exon 9 deletion. *EIF2AK3* analysis was restricted to exon 9 and flanking sequences.

Conclusion: This is the first Qatari patient to be described with a complex phenotype of Wolcott-Rallison syndrome (WRS). The cause of the left hemispheric cerebral atrophy and the nephropathy are not known in this patient and expand the clinical phenotype of patients with WRS.

P2-P112

A Rare Case of Diabetes Mellitus Type 1 in a Child with Neurofibromatosis Type 1

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Introduction: Neurofibromatosis type 1 (NF1) is an autosomal dominant multisystemic neurocutaneous disorder characterized by an increased risk of benign and malignant tumor formation (neurofibromas, glioma and gastrointestinal stromal tumor). The incidence has been described to be around 1 in 2,500–3,500 live births, and the estimated prevalence is 1 in 4,000–5,000. Although it was first described by von Recklinghausen in 1882, the formal diagnostic criteria were published a century later, in 1987. The diagnosis can be reached based on the positive family history as well as the following clinical features: a) pigmentary abnormalities such as café-au-lait macules which usually consist the earliest manifestation, axillary or inguinal freckling and Lisch nodules, b) neurofibromas, c) distinctive osseous lesion and d) optic pathway glioma. Diabetes mellitus is rarely seen in association with NF1, as to our knowledge, there have only been reported 3 cases of NF1 and diabetes mellitus.

Case description: A 12-year-old boy, diagnosed with NF1 at the age of 4, and no other relevant personal or family history, was admitted to the hospital presenting polydipsia, polyuria, and enuresis nocturna for the last ten days. On his physical examination, he was haemodynamically stable, with multiple café-au-lait spots (>20) of 1–5 cm in diameter and one plexiform neurofibroma on his neck. Multiple subcutaneous neurofibromas were found on his abdomen palpation. Laboratory tests revealed a blood glucose level of 488mg/dL (27.1mmol/L), a glycated haemoglobin level of 9.6% and traces of ketone bodies while liver and renal function was

normal; urinalysis revealed glucosuria (3+) and ketonuria (4+). Acidosis was not detected on his blood gases analysis (pH=7.34). Insulin level was 5.4μIU/L and C-peptide was 1ng/mL. His thyroid and celiac antibodies tests were negative. Insulin treatment was initiated, and normoglycemia was maintained. His course was uncomplicated. Later, the patient underwent further investigation (abdominal ultrasonography and MRI) to search for somatostatinoma, on the one hand as possible manifestation of NF1 and on the other as likely cause of diabetes mellitus.

Conclusion: Studying the current literature, an ongoing association between NF1 and autoimmune diseases, such as juvenile arthritis, multiple sclerosis etc., is revealed. As the number of reports on the coexistence of NF1 and autoimmune diseases increases, including diabetes mellitus type 1, an association rather than a coincidence becomes more likely, but further investigation needs to be done.

P2-P113

Detection and Analysis of Glycometabolism Related Genes in Children Diabetes

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Objective: to know more about the etiology and mechanism of antibody-negative diabetes, screening MODY pathogenicity genes and deepening understanding of islet autoantibody-negative diabetes, so as to individualized precision treatment.

Methods: A total of 31 subjects with diabetes who had negative islet autoantibodies and C-peptide≥0.3 ng / ml were collected. Another group was the type 1 diabetes control group, After informed consent obtained patient history data and a detailed physical examination. Peripheral blood DNA was extracted from patients with antibody negative, and peripheral blood DNA was extracted from parents as necessary for high-throughput sequencing of glucose metabolism related genes. Sanger sequencing validation was performed on patients and their families for the possible pathogenic mutations that were screened. The relative indexes such as birth weight, fasting C-peptide, onset time, initial HbA1c, age, family history, The incidence of DKA, insulin dosage and statistical analysis.

Results:

1. In the 31 cases, 20 cases of diabetic patients detected possible related mutations, 11 patients were not detected mutation genes. There were 11 genes related to single gene diabetes mellitus, of which 3 were pathogenic variation, 1 were possible pathogenic variation, 3 were likely to be benign and 4 the pathogenicity is not clear. There were 12 genes related to susceptibility to diabetes.
2. There was a significant difference in the BMI, fasting C-peptide, DKA incidence and insulin dosage between the group with pathogenic mutation and the group with positive islet autoantibody (P <0.05). There was a significant difference in BMI, fasting C-peptide, HbA1c and insulin dosage between the group of undetected gene mutation and the group of positive islet autoantibodies (P <0.05). There was a significant difference in the BMI, fasting C-peptide, DKA incidence and insulin dosage between the group with pathogenic mutation group and undetected gene mutation group (P <0.01).

Conclusions

1. there is a single gene mutation in Islet autoantibodies negative diabetes children group. However, single-gene diabetic genetic variation may not be the main cause of antibody-negative diabetes.
2. This study found that GCGR c.118G> A p.G40S exists in Chinese patients with T2DM, considering that the locus is related to the susceptibility to T2DM in China.
3. Our study found a case of non-reported ELN nonsense mutation (G611 *), this mutation may be related to glucose metabolism.
4. This study found an unreported frameshift mutation of LIPC, which had a great effect on the protein and was related to glucose and lipid metabolism.

P2-P114

Gender Characteristics of Responsibility for Their Own Health of Adolescents with Type I Diabetes Mellitus

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Background: To achieve the compensation of type 1 diabetes, psychological factors that contain individual psychological characteristics of the patient's personality, his emotional state and responsibility for his own health are important.

Objective and hypotheses: The purpose of the study was to study the specifics of responsibility for the health of adolescents with type I diabetes of different sex, depending on the level of glycemic control (GC).

Method: We examined 60 adolescents with type I diabetes at the age of 12-18, 32 of them girls and 28 boys with type 1 DM. The experience of the disease was from 3 to 16 years (an average of 6.9 years). Half of patients had optimal (28%) and suboptimal GC (30%), 42% had high-risk GC. To diagnose the emotional state and study the psychological features of motivation for treatment, the following methods were used: the diagnosis of self-esteem of mental states according to Eysenck, the Lusher test and the questionnaire for studying the attitude to DM and its treatment.

Results: According to the results of testing, it was established that the presence of full responsibility for the state of own health among adolescents who had the optimal GC (the average level of HbA1c-6.7%) was registered in 70.6% of adolescents, of whom boys took responsibility more reliably (100% vs 28.6% for girls, p ≤0.01). Removed responsibility, completely shifting it to relatives and doctors 29.4% of adolescents, and it was only girls (71.4%). Adolescents with type 1 diabetes, with suboptimal GC (mean HbA1c-8.1%) in the majority (77.8%) took responsibility for their own health, and only 22.2% transferred it to others. On the basis of gender in this subgroup, 100% of the young men and 66.7% of the girls took responsibility for their own health, and 33.3% of the girls

shifted responsibility to others. In adolescents with insufficient GC (mean HbA1c-9.8%), a high risk of complications of diabetes in 100% of cases, regardless of gender, adolescents refused responsibility, shifting it to mother, grandmother or doctors.

Conclusion: The received information, on perception by the sick adolescent of responsibility for a condition of own health, will allow the psychologist or the doctor endocrinologist to correct directions of formation and maintenance of self-checking of type 1 diabetes mellitus.

P2-P115

Favorable Outcome Despite Prolonged Hypoglycemic Episodes Following a Massive Insulin Overdose: A Case Series

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Objective: To report on a pediatric case series of massive insulin overdose, its altered pharmacokinetics and the patients favorable outcome.

Cases and results: Case 1: 300 IU of insulin aspart were subcutaneously injected into a non-diabetic eight-year-old boy within an extended suicide. After 16 hours he was found unconscious with generalized convulsions. The initial blood glucose concentration was below detection limit. It normalized only after administration of highly concentrated glucose via a central line. Brain imaging showed no significant signs of cerebral edema. On admission, c-peptide and blood glucose were undetectable. Serum insulin concentration was 130 mU/l (941 pmol/l). Considering that the used insulin assay (IMMULITE 2000, Siemens) has a cross-reactivity with insulin aspart of only 9%, the actual serum insulin aspart concentration could have been up to 10-fold higher. Endogenous insulin secretion, as mirrored by c-peptide serum levels, started to rise after 30 hours. A more congruent insulin and c-peptide serum pattern appeared 60 hours after insulin aspart overdose. A complete physical and neurological recovery was observed.

Case 2: A seventeen-year-old diabetic girl intentionally administered herself insulin overdoses on three different occasions. A monointoxication of insulin aspart was present in the first (100-200 IU) and the second (unknown amount) suicide attempt. No cross reactivity was observed in the used insulin assay (Elecsys Insulin, Roche Diagnostics). Severe hypoglycemia was treated with intravenous glucose (5-10%) and glucagon. The blood-sugar-lowering effect of insulin aspart lasted for twelve and nine hours. The patient survived without any deficit.

Case 3: A sixteen-year-old diabetic girl was treated for her third suicide attempt by insulin overdose. She injected herself 450 IU of insulin detemir, 200 IU of insulin glargine and 450 IU of insulin aspart. Recurrent hypoglycemia was treated for about 60 hours. The patient made a full recovery.

In all cases supraphysiological doses of insulin analogues prolonged their time of activity considerably. The used test kits for insulin show diminished or no cross-reactivity to the insulin analog aspart. In non-diabetic individuals detectable c-peptide levels indicated a decreasing activity of insulin aspart. No patient sustained permanent complication from hypoglycemia. Even after a prolonged hypoglycemic coma a favorable outcome is possible.

Conclusion: Massive overdose of insulin in children is rare. Prolonged periods of severe hypoglycemia can be survived without apparent sequelae. As shown here, in children the pharmacokinetic of insulin aspart was severely altered with a significantly prolonged hypoglycaemic effect.

P2-P116

Effect of a Reduced Fluid Replacement Regimen on the Resolution of Diabetic Ketoacidosis (DKA) in Children

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Background: A substantially reduced fluid replacement regimen was introduced in the 'New' British Society of Paediatric Endocrinology Diabetes(2015) compared to 'Old'(2009) guideline for DKA management. However, data on varying fluid replacement regimens is limited and we explored this by comparing outcomes of the 2 guidelines on the resolution of DKA.

Methods: In a retrospective audit of consecutively admitted patients (age<18yrs) to 2 UK hospitals with DKA between Jan 2014-March 2017, we evaluated the resolution time of DKA defined by recovery of acidosis (pH>7.30), ketosis (blood ketones<1.0mmol/l) or bicarbonate (>18.0mmol/l). Biochemical parameters before, the nearest to 4 and 10 hours into treatment and at resolution were collected.

Results: Of 78 patients admitted, data were available for 55[transferred (n=12), data unavailable (n=11)] patients managed by the 'New'(n=23) or 'Old' (n=32) guidelines. The mean age was 10.1yrs (standard deviation ±4.1), 36 patients (65.5%) were newly-diagnosed and 15 (27.3%) had severe DKA (pH<7.1). Age, DKA severity and proportion of newly-diagnosed patients were similar in both groups. The mean fluid administration rates were substantially lower in the 'New' guideline (29.5±9.6 vs 58.1±16.8 ml/hour, p<0.0001), but frequency of fluid boluses was similar (39% vs 50%, p=0.80). Resolution time of DKA evaluated by pH ('New' vs 'Old':13.8 ±7.5 vs 16.4 ±9.6 hours, p=0.3] or ketosis (19.3 ±10.2 vs 18.7 ±9.8 hours, p=0.82] or bicarbonate levels (17.5 ±9.1 vs 20.1 ± 12.6 hours, p=0.53) were similar. The levels of glucose, Na, K, Cl and $HCO3^-$, and pH at presentation, 4 and 10 hours of starting treatment and resolution, and hypoglycaemia rates were similar. However, in mild DKA patients managed by the 'New' guideline, the time interval for glucose levels to decline to 14mmol/l was lower (5.0 ±3.7 vs 7.4 ±4.0 hours, p=0.07) and the rate of decline in effective osmolality was faster at 4 hours (8.9 ±4.4 vs 4.9 ±6.4 mosm/l/hour, p= 0.038) and at 10 hrs (2.8±1.0 vs 1.7±1.2 mosm/l/hour, p=0.032). No patients developed cerebral oedema.

Conclusions: We found that 50% reduction in the fluid replacement in DKA was not associated with significant changes in resolution time or electrolyte levels. However, decline in effective

osmolality and glucose was faster with the reduced fluid replacement. Larger studies are important to evaluate the effects on cerebral oedema.

P2-P117

Prevalence of and Risk Factors for Nonadherence to Insulin Among Paediatric Type 1 Diabetes Patients in Singapore

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Introduction: Nonadherence to insulin therapy is a significant problem worldwide, which is associated with poor health outcomes among patients with type 1 diabetes (T1D). It is important to identify the risk factors related to nonadherence to target those at higher risk of diabetic complications. In Singapore, there is a knowledge gap in understanding the risk factors for insulin nonadherence in paediatric patients with T1D.

Objectives: To assess the prevalence of nonadherence to insulin therapy and its associated risk factors among paediatric patients with T1D in Singapore.

Methods: This was a retrospective, single-centre longitudinal study conducted in KK Women's and Children's Hospital, which is the largest paediatric hospital in Singapore. Singaporean patients with T1D aged ≤18 years with ≥1 year of insulin collection from the hospital between 1st January 2012 to 31st December 2016 were included in the study. Those on insulin pumps were excluded. Patients were considered nonadherent when medication possession ratio (MPR) was less than 100%. Mann Whitney U test, t-test, and χ^2 test were used to analyse medians, means, and proportions between the nonadherent and adherent groups, respectively. Regression analysis was used to identify risk factors for non-adherence. Sensitivity analyses was performed for varying definitions of nonadherence at MPR<95% and MPR<80%.

Results: A total of 210 patients were included in the study, where patients in the nonadherent group were older and had a longer duration of diabetes since diagnosis. Gender, race, financial class and number of concurrent medications were comparable between both groups. The prevalence of insulin nonadherence among paediatric patients with T1D in Singapore was 35.7% (95% CI= 29.2%–42.6%). This decreased to 26.2% (95% CI: 20.4–32.7%) at MPR<95% and 12.4% (95% CI: 8.3–17.6%) when nonadherence was defined at MPR<80%. An increase in age and diabetes duration were associated with 22.0% (p=0.002) and 12.6% (p=0.024) increased risk of nonadherence, respectively. Patients of Chinese descent were 56% (p= 0.026) less likely to be nonadherent compared to other ethnicities. When nonadherence was defined at MPR<95% and MPR<80%, an increase in age and duration of diabetes were associated with 22.9% (p=0.001) and 27.3% (p=0.017) increase in risk of nonadherence, respectively.

Conclusion: More than one-third of the paediatric patients were nonadherent to insulin therapy, signifying a need to design targeted interventions based on the risk factors identified.

P2-P118

"What Do You Know About Your Diabetes?": A Qualitative and Quantitative Study of Teenagers and Young Adults' Understanding of Their Disease

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Background: Type 1 diabetes (T1D) in teenagers is challenging: the constraints of diabetes add up to the specificities of a delicate age; moreover, this period of life is often associated with impaired metabolic control (i.e. higher hemoglobin A1c - HbA1c). Therapeutic Patient Education (TPE) enables people with chronic diseases to manage their illness and yields benefits in both health and financial terms.

The first step of TPE approach is to make an "educational diagnosis" (ED). We decided to do it through a specific questionnaire determining what the patient knows, doesn't know or believes, and would like to know, in order to fit specific needs.

Objective: Our principal objective is to make the ED with the description of the knowledge, beliefs and topics of interest of a cohort of teenagers and young adults with T1D (11-25 years old) by analysing their responses to an original questionnaire mostly made of open-ended questions about T1D and its constraints. The secondary objective is to look for a relationship between glycemic control and the level of understanding of the multiple aspects of T1D.

Patients and methods: We displayed a questionnaire made of 35 questions including 22 open-ended questions about T1D, concerning insulin, glycemia, nutrition, sports, contraception and procreation. Patients were either hospitalized or consulting their diabetes referent when they filled the questionnaire. A control of their HbA1c was systematic the day of the consult or the first day of their hospital stay. Their free answers were then grouped into categories and enabled us to make a qualitative and quantitative analysis.

Results: 102 patients answered the questionnaire (mean age of 15.6 years, M/F 1.5:1). Median duration of diabetes was 8.2 years, 38.2% were on insulin pump therapy. The mean HbA1c of the entire group was 8.8 %. The answers highlights that only 22% of the patients know that T1D is an auto-immune disease, the most known and scared complication of diabetes is diabetic retinopathy, 52% know the utility glycemic monitoring, 18.6% think that they can't practice some sports, 15.7% wonder about their fertility and 49% fear to transmit their disease to their offspring. 56,4% would like to know more about the origin of diabetes. There is a trend, despite not reaching statistical significance, between better knowledge of items concerning the disease itself and its physiopathology and a better metabolic control, expressed as lower HbA1c levels.

P2-P119

Parental Knowledge and Attitudes Toward Diabetes Mellitus Type 1: A Cross Sectional Study

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Introduction: Type1 diabetes mellitus (T1DM) is a chronic disease characterized by absolute insulin deficiency, it's usually diagnosed in children and adolescents. According to a recent report from the International Diabetes Federation, Saudi Arabia has 14,900 children with T1DM. The incidence is increasing over the last years with prevalence rates of 48 per 100,000 in the eastern region. Parents play an important role in the management of T1DM in children. As a result, it's important to assess parents' knowledge about child diabetic care.

Objectives: assessing the knowledge and attitudes of parents of T1DM children, regarding the disease and its therapy.

Methods: Observational cross sectional study. The participants were recruited from maternity and children's hospital (MCH) in Eastern region, Saudi Arabia. Questionnaires were distributed to the parents of children with T1DM. The questionnaire focused on basic information parents should know about T1DM.

Results: A total of 120 parents completed the questionnaire. The average score of participants was 18.8±3.9 out of 26 with a range of (7-26). The major knowledge deficiencies were in various aspects including: blood glucose levels (BGL) in DKA with only (10.8%) of right answers and accepted BGL (51.7%). Hyperglycemia knowledge in general was the weakest point with only 35.8% of right answers. A significant correlation (p= 0.01) was found between total score of parents knowledge and their level of education.

Conclusions: This study provided an initial identification of the major deficiencies in parental knowledge regarding T1DM and its management. More attention should be paid to these deficiencies in future parents' education.

P2-P120

Identifying the Association of Depression and Diabetic Distress in Pakistani Patients Diagnosed with Type 1 Diabetes

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Background and aims: Depression plays an important role among patients diagnosed with Type 1 Diabetes. It is believed that diabetes distress is recognised as major psychological issue in Pakistan. Our study aims to identify diabetes distress among Pakistani children patients diagnosed with type1 Diabetes. We also aim to find out the relationship among depression, distress caused by Diabetes and glycemic control

Materials and methods: A cross sectional study was conducted in Sir GangaRam Hospital Lahore during June 2016 to October 2017. Total 80 patients diagnosed with Type1 Diabetes Mellitus were included in the study. Hb A1C levels were collected via venous puncture. A personalized health questionnaire was used to classify depression among patients. Diabetes distress scale was used to identify diabetes distress and other factors such as social distress, interpersonal distress, physician related distress, emotional distress and regimen related distress.

Results: The rate of depression was 39% among patients diagnosed with type 1 Diabetes. 8% were categorised as mild depression, 14% moderate depression and 17% with severe depression. Diabetes depression was found in 71% of the selected population. Rates of social distress, interpersonal distress, physician related distress, emotional distress, regimen related distress were 23%, 33.5%, 17.8%, 73.4% and 42.6 respectively. There was no association between depression and glycemic index.

Conclusion: Our study concludes that Diabetes distress is very common among patients with type 1 Diabetes and this is an alarming condition for Pakistani population. We need to develop and modify our management plans in order to combat this deadly distress. Mass media should be involved in order to raise awareness about diabetes distress and depression.

P2-P121

Role of Breastfeeding in Prevention of Type 1 Diabetes in Pakistan

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Background: Diabetes Mellitus is the leading cause of morbidity and mortality especially in under developed countries like Pakistan. In type 1 Diabetes, there is autoimmune destruction of β cells which is genetically transmitted. Various factors are responsible for this autoimmune process like early use of cow's milk, allergic food, absence of breastfeeding and various other factors.

Objective: Our study aims to investigate the role of breastfeeding in prevention of type 1 diabetes in an underdeveloped country Pakistan.

Research Design and Methods: A case control study was conducted in Sir Ganga Ram Hospital, Lahore from March 2016 to April 2017. Case were the patients diagnosed with Type 1 Diabetes Mellitus and controls were the siblings of affected children. Type 1 Diabetes was diagnosed according to the criteria of World Health Organisation and using ISPAD guidelines. Data on breast feeding, introduction of cow's milk, time and duration of breast feeding, prenatal care, gestational age, mode of delivery, birth weight, need for resuscitation and immunisation status were collected through the information provided by parents and health records. Date was analysed using SPSS.

Results: 100 children with type 1 Diabetes and their respective siblings were included in the study. The total study population was 200. Patients with type 1 diabetes had a shorter duration of breastfeeding usually 3-4 months. However, 38% of the patients were never breastfed in the life. The diabetic group was exposed to cow's

milk during the 3rd month of their life whereas the control group was exposed to cow's milk after the 2nd year of their life. Other parameters also exhibited that a longer duration of breastfeeding was associated with a protective effect against diabetes.

Conclusions: We concluded that breastfeeding plays a vital role in prevention of Type 1 Diabetes. It is important that future studies must identify the duration and exclusivity of breastfeeding in order to prevent diseases like type 1 diabetes.

P2-P122

A Young Type 1 Diabetic with Acute Hemichorea: Rare Central Nervous System Complications

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A 20-year old lady with poorly controlled type 1 diabetes mellitus diagnosed since 9 years old, comorbidities of hyperlipidemia and steatohepatitis as well as a history of smoking, presented with an acute 2-day history of involuntary, writhing movements of her left upper and lower limbs. Physical examination confirmed left mild hemiparesis with hemichorea-athetosis.

Emergent MRI brain demonstrated abnormal signal in the right caudate nucleus and lentiform nucleus (low T2W/FLAIR signal and high T1W signal) suggestive of diabetic striatopathy. There is corresponding marked non-ketotic hyperglycemia (?any levels) with a glycated haemogloblin (HbA1c) of 12%.

Incidentally, MR angiography brain revealed severe stenoses of both terminal internal carotid arteries with multiple collaterals, suggestive of severe bilateral Moyamoya syndrome. A hypercapnoea challenge demonstrated exhausted vasodilatory reserves with paradoxical reduction of flow velocities. Extensive investigations for the aetiology of the Moymoya syndrome that included autoimmune cerebral vasculitis, were unremarkable.

The patient was managed with aggressive glycemic control and symptomatic treatment for her movement disorder, with full resolution of her symptoms after 4 weeks. She was started on aspirin and advised for vascular bypass surgery for her Moyamoya syndrome.

Diabetic striatopathy presenting with acute hemichorea and/or hemiballimus, can occur in type 2 diabetic patients (usually female, Asian and elderly) with non-ketotic hyperglycemia. Diabetic striatopathy rarely occurs in a young patient and in Type 1 diabetes. It is postulated that chronic hyperglycemia leads to hyperviscosity, in turn causing cerebral hypoperfusion, anaerobic metabolism and reduced γ-aminobutyric acid levels. This in turn leads to increased thalamocortical activity, causing abnormal movements.

Moyamoya syndrome is a rare condition of which diabetes is a possible aetiology. Chorea is a rare presenting symptom, secondary to ischaemic dysfunction and imbalance in the complex basal ganglia circuitry.

We describe the first reported case of a young adult with poorly controlled type 1 diabetes, hyperlipidemia and smoking, who presented with acute hemichorea. Given the risk factors, our initial differential was that of a thrombotic stroke. She was eventually found to have 2 rare diabetes-related central nervous complications of hyperglycemia-induced striatopathy and severe Moyamoya syndrome, both of which could result in acute movement disorder. MRI and MRA brain are important investigations to help differentiate the three causes. Aggressive glycemic control often results in resolution of the movement disorder in diabetic striatopathy. However, it is important to ensure there are no concomitant diabetes-related vascular stenoses, that would increase stroke risk and necessitate different management.

Diabetes & Insulin P3

P3-P071

Multiple Autoimmune Association and Varied Spectrum of Presentation in Indian Diabetic Children

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Objective: To define the prevalence of autoantibodies at presentation in children with type 1 diabetes and to determine the associated comorbid autoimmune conditions in Indian pediatric patients.

Materials and Methods: Children (n = 468) diagnosed with type 1 diabetes at Indraprastha Apollo Hospital, Delhi, India for childhood Diabetes were screened for autoimmune thyroid disease (thyroid peroxidase autoantibodies [TPOAb]), celiac disease (tissue transglutaminase autoantibodies [TTGAb]) which were further confirmed by thyroid function test for thyroid disease and upper GI endoscopy and biopsy for coeliac disease.

Results: Of the 468 children, 174 had islet cell antibodies positivity, and of these, 14 (8.04%) had autoimmune thyroid disease and 7 (4.02%) had celiac disease. Two patients had autoimmune Type1 diabetes with thyroid disease and coeliac disease at the time of presentation.

Conclusions: All the associated co-morbid autoimmine conditions should be screened at the time of presentation, and followed up regularly both in the presence and absence of antibodies, as they have a variable presentation.

Early detection of commonly associated autoantibodies at type 1 diabetes onset may prevent complications associated with delayed diagnosis of these disorders.

P3-P072

Severe Hypertriglyceridemia and Multiple Autoimmune Phenomenon at New Onset Type 1 DM

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Introduction: Type 1 Diabetes is a condition associated with deficiency of insulin, which is a key regulator of carbohydrate and fat metabolism.

Most newly diagnosed type 1 diabetes present with diabetic ketoacidosis, which is a triad of hyperglycemia, ketonemia and acidosis. It usually presents with features of acidosis such as lethargy, dehydration, and tachypnea.

Case: We present a case that presented to us with a lipemic blood sample and on further workup was diagnosed with diabetic ketoacidosis with hypertriglyceridemia with multiple autoimmune phenomenon positivity.

She was closely monitored and treated as per protocol for DKA, no lipid lowering agents were give and her lipids came back by to normal levels by 96 hours of diagnosis.

Conclusion: Only 11 cases have been reported describing pediatric patients (age<18 years) with DKA and severe hypertriglyceridemia (Triglyceride>1000), on the contrary several large case series and cases have been reported in adults describing the same.

Pediatricians should be aware about complications associated with severe hypertriglyceridemia such as acute pancreatitis and cerebral edema.

P3-P073

Effects of Diabetes Mellitus Type-1 on Vitamin D Status Among Children

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Introduction: Vitamin D defciency is a common health concern among all children world wide.together with the rapidly increased prevalence of diabetes mellitus..This study was conducted to determine if diabetes is associated with increased risk of vitamin D.deficiencydy examination the influences of diabetes effecting status on specific patients disease characteristics in regardsto vitamin D level among children from saudi arabia.

Methods: All retrospective and prospective patients with proven diagnosis of type-1-diabetes following up at pediatric endocrinology clinic between Jan 2016-Dec 2017...the participants about 100 diabetic patients age 2-14 years were enrolled in the study including the age -sex-duration of the disease, symptoms and signs of vitamin D deficiency..Blood samples were collected,,,25 (0H) vitamin D together with glycosylated hemoglobin AIC level measured by high performance liquid chromatography standardized to the Dcct assay.

Results: We divided the children into three groups according to 25(oH) vitamin D level..

(1) deficiency, 25(oH) vitamin D more or equal 20 ng/ml...

(2) insfficiency, 25 (oH) vitamin D between 20-29 ng/ml...

(3) sufficiency, 25(oH) less or equal 30 ng/ml...

The outcome of the study shows that about 60 patients belong to group (1)... 25 patients belong to group (2) and 15 patients belong to group (3)...in addition to that patients belonging to group (1) have higher HbAIC in comparison to group (2) and (3)...also patients with longer duration of Diabetes are more liable to have vitamin D defieciency in comparison to the newly diagnosed..

Conclusions: Type-1 Diabetes is associated with an increased risk of vitamin D deficiency.

Patients with type 1Diabetes sustained some what disproportional relation between the control of Diabetes reflected by HbAIC and vitamin D..duration of diabetes type 1-has a negative impact on vitamin D adequacy..These finding have an important health implication giventhe increasing prevalence of type 1 Diabetes and the morbidity and mortality associated with vitamin D inadequacy..Ensuring vitamin D sufficiency throughout childhood and adolescence in this populationseems especially warranted.....

P3-P074

Association Between Prior Toxic Stressors and Development of T2DM in Adolescents

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Background: Low stress resilience in late adolescence and psychosocial traumatic events in adulthood have been linked to a higher risk of developing type 2 diabetes (T2DM) later on in life. However, limited data is available regarding whether prior stressors are related to the risk of developing T2DM in adolescence.

Objective: We sought to determine the potential association between prior toxic stressors and T2DM in adolescence.

Design/Methods: We conducted a prospective case-control study using a validated 10-question questionnaire (ACE-Q) to evaluate prior exposure to stress events in adolescents. Ten types of adverse childhood experiences were studied falling under 3 categories; household dysfunction, abuse and neglect. A score from 0 to 10 was used to quantify prior exposure to the 10 types of stressors. Eligible participants were males and females aged 15 to 21 years. Cases were diagnosed with T2DM using the ADA criteria no later than 6 months prior to their enrollment and controls did not have T2DM, but presented to our weight management clinic with a BMI z-score≥1.5, no later than 6 months prior to their enrollment. Our goal was to enroll 30 cases and 60 controls. Enrollment started in November 2016. Data on demographics (age, gender, race, socio-economic factors) and clinical outcomes (A1c, BMI) were obtained by self-report and chart review.

Results: To date, we have approached 33 cases and 30 controls. A total of 8 (24%) cases were enrolled, 4 M and 4 F, aged 15.2-20.2 years, with a BMI z-score ranging from 1.15 -2.69 and an A1c ranging from 6.3% -14.3%. In addition, 6 (20%) controls were enrolled, 2 M and 4 F, aged 15.8-20.5 years with a BMI z-score ranging from 2.08 and 2.81. The majority of cases and controls were primary English speakers (87% and 84% respectively) and had public health insurance (71% and 50%). Fifty percent of participants in both groups were Hispanic. Five cases had an ACE score of 1 and the remaining 3 had a score ranging between 2 and 5. Two controls had an ACE score of 0, three had a score of 1 and one had a score of 3. Parental separation was the most common stressor in cases (62%) and controls (100%).

Conclusion: The poor enrollment rate highlights the challenge to assess stress events in adolescence using a questionnaire. Although we are still recruiting, the small size of our sample prohibits us from drawing conclusions.

P3-P075

First 4 Cases of Neonatal Diabetes from Kazakhstan, Almaty with Proven Mutations in KCNJ11 and INS Genes

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We report 3 cases of neonatal diabetes from Kazakhstan, Almaty with the *KCNJ11* gene mutation who were successfully switched from insulin to sulphonylurea treatment and 1 case of insulin (INS) gene mutation that presented as permanent insulin dependent neonatal diabetes.

Case 1: An 1 month old girl presented with elevated glucose level, dehydation, ketoacidosis and was treated with Insulin. Hb A1c at diagnosis was 10%. Heterozygous missense mutation in the *KCNJ11* gene, exon 1, c.685G>A, p.Glu229Lys (p.E229K) was identified. At 18 months diabetes resolved. Mother has the same heterozygous missense mutation in the *KCNJ11* gene, exon 1, c.685G>A, p.Glu229Lys (p.E229K). She was treated with Glibenclamide, which has normalized her glucose levels.

Case 2: A 2 months old boy presented with elevated glucose level, dehydation, ketoacidosis and was treated with Insulin. Hb A1c at diagnosis was 11%. Heterozygous *de novo* missense mutation *KCNJ11* gene, exon 1, c.602G>A, p.Arg201 was identified. Both parents don't have this mutation. He was treated with Glibenclamide which has improved his glucose level.

Case 3: A 3 months old boy presented with elevated glucose level, dehydration and was treated with Insulin. Hb A1c at diagnosis was 9%. Heterozygous de novo missense mutation *KCNJ11* gene, exon 1, p.Gly53Asp (p.G53D), DNA c.158G>A was identified. Both parents don't have this mutation. He was treated with Glibenclamide which has improved his glucose level

Case 4: A 1 month old girl presented with elevated glucose level, dehydration and was treated with Insulin. HbA1c at diagnosis was 9%. Heterozygous mutation in *INS* gen c.64G>C p.A22P was identified. Both parents don't have this mutation. She continues to have insulin dependent diabetes

Conclusion: Genetic testing of neonatal diabetes can change treatment and prognosis. Heterozygous missense mutations such as p.Glu229Lys, p.Arg201His, p.Gly53Asp in the *KCNJ11* gene can present as transient or permanent neonatal diabetes. Missense mutaiton p.A22P in the *INS* gene can present as permanent neonatal diabetes.

P3-P076

First 2 Cases of Monogenic Diabetes (MODY) from Kazakhstan, Almaty with Proven Heterozygous Mutation in Hepatocyte Nuclear Factor 1-Alpha (HNF1A) Gene

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Background: It is important to make correct diagnosis of monogenic diabetes or MODY in children. Most of the patients are misdiagnosed with diabetes type 1 or type 2 and undergo unnecessary treatment with insulin or oral medications. We report first 1 case of MODY with heterozygous mutation in HNF1A gene when Insulin treatment was changed to sulphonylurea treatment and 1 case of compound heterozygote of glucokinase (GCK) gene and HNF1A gene mutations.

Case 1. An 11-year-old girl presented with diabetes with HB A1c 10.4%. Mutations HNF1A p.Q170E and p.R171Q were found in her case, MODY 3. Gliclazide was initiated and insulin therapy was stopped. Her glucose level improved. Mother and aunt have the same mutations, HNF1A p.Q170E and p.R171Q and were treated with Gliclazide oral sulphonylurea that normalized glucose level. MGM, MGF, 6 sisters and 1 brother have diabetes. Analysis of HNF1A is pending in the other cases of this family. We report first 1 case of MODY with heterozygous mutation in HNF1A gene in Kazakhstan, in which Insulin treatment was succesfully stopped and changed over to oral sulphonylurea therapy.

Case 2. A 7-year-old girl presented with diabetes with Hb A1c 6.8 % at diagnosis. Heterozygous mutation p.Ser433Ala (c.1296delC) in GCK gene and Heterozygous mutation in HNF1A gene p.Thr190Ala (c.568 A>G) were found. Her glucose control has been well controlled by diet so far, similar to other cases of MODY-2 secondary to GCK gene mutations. Mother has diabetes with Hb A1c 7.5%, her gene analysis is pending.

Conclusion: The confirmation of the MODY diagnosis results in a personalized treatment, discontinuation of unnncessary insulin treatment. Children with diabetes and negative ß-cell antibodies, positive family history of diabetes need to be screened for MODY in Kazakhstan. In this population the frequency of known MODY cases can be increased with genetic analysis at diagnosis

P3-P077

Achievement of Therapy Targets in Children and Adolescents with Type 1 Diabetes Mellitus at the "Diabetes School"

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Aim: The work was initiated to assess efficacy of training and achievement of therapy targets in children and adolescents with type 1 diabetes mellitus in "Diabetes Schools".

Method: The five-day training course was conducted in "Type 1 Diabetes School" at the Scientific-Research Institute of Cardiology and Internal Diseases, Kazakhstan Public Health Ministry (Almaty). The training was conducted by means of a structured program containing all appropriate sections. Before and after training course all participants were tested with a questionnaire containing 30 key questions for self-control. On the basis of the findings children and adolescents with type 1 diabetes mellitus were divided into groups. 54 of 80 children and 38 of 57 adolescents were preliminary trained, 26 children and 19 adolescents got no training. Carbohydrate metabolism was assessed according to the level of glycemia (laboratory and self-monitoring with the Akku-check Nano swab). DCA Vantage Siemens (USA) was used to measure glycated hemoglobin (HbA1c) by means of latex agglutination inhibition. Certified by the National Glycohemoglobin Standardization Program this method became the reference one. It helps demonstrate the predicting role of HbA1c level as a criterion for assessment of chronic glycemia and achievement of therapy targets in children and adolescents with type 1 diabetes mellitus.

Results: Frequency of target HbA1c level (≤ 7.5%) achievement in the trained patients was 68%. Among children who got no preliminary training target HbA1c level was found in 12%. Among trained adolescents 58% achieved compensation. The target HbA1c level was found in 11% of adolescents who got no training.

Conclusion: Frequency of target HbA1c level (≤ 7.5%) achievement was found in 68% of children with type 1 diabetes mellitus having received preliminary training at "Diabetes School" to be significantly higher ($p<0.001$) than the one in the group of patients who got no preliminary training (12%). Among adolescents target HbA1c level achievement was observed in 58% of the trained patients to be significantly higher ($p<0.001$) as compared with those who got no preliminary training (11%). Better compensation and higher frequency of target HbA1c level achievement in children as compared with those among adolescents confirms the role of family in the type 1 diabetes mellitus control.

P3-P078

Characteristics of MODY-GCK Diabetes in Children and Adolescents in Siberia

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The purpose: To identify the clinical features of MODY-GCK diabetes which we need to follow of this group of patients.

Materials and methods: We examined 35 patients under the age of 18 years with impaired carbohydrate metabolism. Inclusion criteria were: diagnosed carbohydrate metabolism disorder or diabetes mellitus (DM), normal weight, family history of diabetes, no antibodies, normal or slightly decreased C-peptide level for at least 2 years, absence of ketoacidosis. We diagnosed MODY-GCK diabetes during the molecular genetic testing (direct automatic sequencing) of glucokinase gene. All patients had a full clinical examination, blood samples for biochemical research, determination of C-peptide and TSH, antibodies to b-cells, GAD, microalbuminuria, abdominal ultrasound, heart and thyroid ultrasound, examination of ophthalmologist.

Results: We identified MODY-GCK in 15 patients (43%). Patients with MODY-GCK were 7 boys (47%) and 8 (53%) girls, median of age of onset was 8 years [1;17]. 12 (80%) of 15 patients with MODY-GCK had not clinical manifestations of disorders of carbohydrate metabolism at the time of debut. All patients had fasting hyperglycemia and 2 hours after a meal - a small increase in blood glucose levels. Overweight and obesity were not detected in any patient.

1 (7%) patient had diabetic peripheral neuropathy. 2 (13%) patients had thyroid pathology, 5 (33%) - the presence of allergic reactions, and 1 (7%) - a disease of the gastrointestinal tract among the comorbid conditions. 2 (13%) patients use small doses insulin (now doctors are trying to transfer them to sulfonylureas), 1 (7%) - oral hypoglycemic agents (before diagnosis of MODY he use insulin) and 12 (80%) - a balanced diet.

13 (87%) patients with MODY-GCK diabetes had targets levels of HbA1c, C-peptide level was below the reference values, anti-b-cells were not detected.

Conclusions:

1. MODY-GCK diabetes had oligosymptomatic onset, soft flow, good compensation of carbohydrate metabolism, no complications.

2. Most patients with MODY-GCK achieve carbohydrate metabolism targets by diet, with confirmation of this type of diabetes it is possible to try to transfer patients from insulin to tablets which improves the quality of life and reduces the cost of diabetes.

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P3-P079

Clinical Case of MODY-GCK Diabetes: Heterogeneity of Course Among Relatives from One Family

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We described a family in which MODY-GCK was detected in 6 people and its course varied.

Materials and methods: The diagnosis of GCK-MODY was verified by the proband and his relatives on the basis of direct automatic sequencing and sequencing by Sanger.

Results: Proband - a boy of 12 years, diabetes mellitus (DM) type 1 is diagnosed at the age of 11 years. He felt polydipsia, polyuria. Body weight was normal, he has not any diseases and complicates of DM. Antibodies to b-cells, GAD were negative, level of C-peptide was 250 pmol/l (normal ranges: 298-2350 pmol/l), HbA1c – 7,4%, prevalent fasting glycemia, postprandial increased to 9.3 mmol / l. He was treated by insulin glargin 6 U and aspart 10 U/day, had frequent hypoglycemia.

When diagnosing diabetes in the boy we examined his sister, 10 years. DM was diagnosed, she had not any complaints. She had diagnosis DM type 2. Body weight was normal, she has not any diseases and complicates of DM. Antibodies to b-cells, GAD were negative, level of C-peptide was 290 pmol/l (normal ranges: 298-2350 pmol/l), HbA1c – 7,1%, prevalent fasting glycemia. She was treated by diet.

Also diabetes was diagnosed in the grandmother of a proband in 40 years, use oral hypoglycemic drugs, does not have diabetic complications; in proband's father, 38 years, when we examined all relatives, he had not complaints, use diet; in fathers brother in 35 years, he had frequent viral infections and was examined, use oral hypoglycemic drugs; his son (cousin of proband), was diagnosed in examination, use diet. All patients had fasting hyperglycemia, normal body weight, C-peptide level was normal, antibodies to b-cells and GAD were absent. The *GCK* gene was studied given the strong family history of diabetes and clinical characteristics. A heterozygous mutation c.752T>C:p.M251T in the *GCK* gene was diagnosed in all six patients (proband, sister, they father, fathers brother, his son, a grandmother).

The conclusion: This case shows a different clinical course, the use of different hypoglycemic therapies (diet, oral medications and insulin) in relatives of one family with MODY-GCK diabetes.

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P3-P080

Clinical and Biochemical Characteristics of Familial Type 1 Diabetes Mellitus (FT1DM) Compared to Non-Familial Type 1 DM (T1DM)

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Introduction: The clinical and genetic characteristics of T1D cases with and without affected family members have been previously studied with varying results. Some investigators found a similarity of presenting features whereas others reported significant differences between the two groups.

Patients and Methods: This was a cross sectional descriptive study to determine the clinical presentation and prevalence of beta cell autoimmunity (Anti GAD, anti-islet cell and anti-insulin antibodies), thyroid function (FT4, TSH) and anti-thyroid peroxidase antibody (ATPO) and anti-tissue transglutaminase (ATT) in a cohort of children and adolescent (aged 6 months -16 years) with FT-1DM (n= 111), FT1DM was defined as having 2 or more persons affected per family (parent-offspring or sib-pair) and compare them with those for children with non-familial T1DM (n = 431) at their first presentation at HMC, Doha, Qatar from 2002 - 2016

Results: FT1 DM was more prevalent in boys versus girls (58.5: 41.5 respectively) whereas the prevalence of T1DM did not differ between genders. FT1DM occurred relatively early in childhood (40.7% before the age of 4 years and 72% before 9 years of age). T1DM occurred relatively later in life (80 % after the age of 4 years and 40 % after the age of 9 years). 35.2% of FT1DM presented with acidosis versus 32.5 % of T1DM. The prevalence of anti-GAD antibodies = 70.2 % in FT1DM versus 75.5% in T1DM. Anti-islet Ab were detected in 53.4 % of T1DM and 72.5% of FT1DM. Anti-insulin AB were detected in 40.4 % of T1DM and 31.6% of FT1DM. The three antibodies together were high in 18.4 % of T1DM and in 16.7 % of FT1DM. Anti TPO were detected in 27.2% of T1DM and 35.5% of FT1DM. Hypothyroidism (FT4 < 11.5) was detected in 10.6% of T1DM and 2.9% of FT1DM. Subclinical hypothyroidism was diagnosed in 7.3% of T1DM and 2.2% of FT1DM. 22.7 % of T1DM and 28.2% of FT1DM had high anti TPO with normal thyroid function. ATT IgA were high in 5% of T1DM and 19.8% of FT1DM whereas ATT IgG were high in 4.4 % of T1DM and 15.4% of FT1DM.

Comments and conclusion: It appears that FT1DM is slightly more prevalent in boys versus girls and it occurs earlier in childhood compared to T1DM. Clinical and subclinical hypothyroidism were more prevalent in T1DM versus FT1DM. ATT antibodies were more prevalent in the FT1DM versus T1DM. The genetic background may explain many of these differences.

P3-P081

Prevalence of Beta-Cell Antibodies and Associated Autoimmune Diseases in Children and Adolescents with Type 1 (T1DM) Versus Type 2 Diabetes Mellitus (T2DM) in Qatar

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Introduction: Type 1 diabetes (T1DM) is an autoimmune disease with abnormal immune responses to specific β-cell autoantigens, resulting in insulin deficiency. Children and adolescents with T1DM may also develop organ-specific autoimmunity. The most frequently reported disorders are thyroid dysfunction and celiac disease. There are limited previous studies on the prevalence of associated autoimmunity, especially multiple, in children with T1DM.

Aim: The present study reports the prevalence of prevalence autoantibodies and thyroid dysfunction in a cohort of children with T1DM and T2DM.

Patients and Methods: This was a cross sectional descriptive study to determine the prevalence of beta cell autoimmunity (Anti GAD, anti-islet cell and anti-insulin antibodies), thyroid function (Free thyroxine (FT4) and TSH) and anti-thyroid peroxidase antibody (ATPO) and anti-tissue transglutaminase (ATT) in a cohort of children and adolescent (aged 6 months-16 years) with T1DM (n= 431) and T2DM (n = 59) checked at their first presentation at Hamad General Hospital pediatric Diabetes Center, Doha, Qatar over 5 years period from 2012 - 2016.

Results: The prevalence of anti-GAD antibodies = 75.5 % in T1DM and 29.3% in T2DM. Anti-islet Ab were detected in 53.4 % of T1DM and 29.4% of T2DM. Anti-insulin AB was detected in 40.4 % of T1DM and 58.3% of T2DM. The three antibodies together were high in 18.4 % of T1DM and none of T2DM. Anti TPO was detected in 27.2% of T1DM and 34.6% of T2DM. Hypothyroidism (FT4 < 11.5) was detected in 10.6% of T1DM and 10% of T2DM. Subclinical hypothyroidism was diagnosed in 3.5% of T1DM and 8% of T2DM. High anti-TPO was detected in 27.2% of T1DM and 34.6% of T2DM. 22.7 % of T1DM and 23.1% of T2DM had high anti-TPO with normal thyroid function. ATT IgA was high in 5% of T1DM and 8.7% of T2DM whereas ATT IgG was high in 4.4 % of T1DM and not detected in any patient with T2DM. Mucosal biopsy proved the diagnosis of celiac disease in 9 out of 12 patients with positive ATT IgA and IgG antibodies.

Conclusion: We report a high prevalence of associated autoimmune abnormalities in our patients with T1DM and T2DM. These data strengthen the argument for routine screening of all children and adolescents with T1DM and T2DM for other autoimmune disorders particularly the thyroid function and increased anti-TPO and ATT antibodies.

P3-P082

Clinical Presentation and Autoimmune Markers in Children and Adolescents with Familial Type 1 Diabetes Mellitus (FT1DM) and Familial Type 2 Diabetes Mellitus (FT2DM)

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Studies support the existence of a genetic contribution to both type 1 and type 2 diabetes, and additionally suggest a relationship between both types of diabetes. The rapidly growing worldwide epidemic of type 2 diabetes has been partially explained by obesity and the sedentary lifestyle. However, familial factors also seem to play a major role in the pathogenesis of type 2 diabetes.). The fact that type 1 and type 2 diabetes cluster in families suggests that some patients may even have a "double form" of diabetes.

Objective: To report the clinical presentation and autoimmune markers of children and adolescents with FT1DM and FT2DM

Patients and Methods: All children with onset of FT1DM and FT2DM 2-16 years of age registered between 2012-2016 were studied. We those who had one or more first-degree relatives (parents and siblings) with T1DM (FT1DM) (n = 108) and those with one or more first-degree relatives with type 2DM (FT2DM) (n =13). The clinical presentation and biochemical data including the prevalence of beta cell autoimmunity (Anti GAD, anti-islet cell and anti-insulin antibodies(ICA), thyroid function (Free thyroxine (FT4) and TSH), anti-thyroid peroxidase antibody (ATPO) and anti-tissue transglutaminase (ATT) at their first presentation were recorded, described and compared.

Conclusion: Children with FT2DM had a significantly high prevalence of ICA, anti-GAD and ATPO antibodies. In addition, they did not have ketosis at their first presentation with hyperglycemia. This presence of autoimmune markers in a good number of our patients with FT2DM point out to a probable familial-genetic mixture between FT1DM and FT2DM.

P3-P083

Real–world Clinical Evolution of Type 1 Diabetes Patients on Twenty Years

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Introduction: Type 1 diabetes mellitus (T1DM) is a chronic disease with important complications.

Objective: Describe clinical characteristics, metabolic control and comorbidities of our pediatric diabetes population.

Table 1. (for Abstract no P3-P082)

Familial Diabetes	FMT1DM	FMT2DM
Anti-GAD	70.21%*	0%
ICA	72.5%*	42.8%
Anti-insulin AB	31.57%	50%*
Anti GAD +ICA2	56.5%*	0%
Free T4 (<11 pmol/L)	2.94%*	0%
TSH (5.6–10 U/ml)	3%	8.3%*
TSH (>10 U/ml)	0.99%	8.3%*
ATPO (>100 IU/ml)	35.5%	30%
ATPO (>100 IU/ml)+ Normal TFT	28.26%	20%
ATPO (>100 IU/ml)+ hypothyroid (T4 <11 pmol/L) or TSH >10U/ml)	7.7%	0%
ATPO (>100 IU/ml)+ (TSH 5.6–10 U/ml)	2.2%*	0%
ATPO (<100IU/ml) + hypothyroid (T4 <11 pmol/L or TSH >10U/ml)	1.1%	10%*
ATT IgA>10U/mL	19.8%*	0%
ATT Igg >10U/mL	15.4%*	0%
PH <7.3	35.21%*	0%
HCO3 <15	30.85%*	0%
ketosis	60%*	0%
Females	41.51%	38.5%
Males	58.50%	61.6%
0to 4 years	40.7%	0%
5 to 9 years	31.48%	0%
10 to 14 years	27.78%	100%*

* p< 0.05.

Table 1. (for Abstract no P3-P083)

	Total	Onset 1996–2005	Onset 2006–2016	p value
Age onset (years)(%)				
<5	25.14	26.2	16.9	p 0.02
5.1–9.9	32.62	30.4	55.41	p0.001
10–15	39.32	43.4	27.69	p 0.001
Clinical presentation(%)				
Ketoacidosis	37.7	41.2	33.3	p 0.001
Hyperglicemia with ketosis	47.7	48.71	44.4	ns
Hyperglicemia	14.4	10.09	21.5	p0.001
A1c Hbat onset	10.84 (2.48)	10.7 (2.53)	10.94 (2.56)	ns
Peptide C ng/ml(meanSD)				
Basal	0.70 (0.5)	0.75 (0.64)	0.61 (0.44)	ns
Post- glucagón	1.28 (0.08)	1.35 (1.28)	1.08 (0.6)	p 0.04
Insulin treatment(%)				
Multiple injections	78.04	84.41	67.7	
ISCI	21.96	15.59	32.30	
Follow up (years) (mean)	6.86 (1–15.75)	8.5 (2–15.75)	5.83 (1–11.9)	p 0.001
A1c Hb (% median during evolution)				
NPH	7.50	7.5	7.5	ns
Long acting -insulin analog	7.65	7.8	7.65	ns
ISCI	7.32	7.3	7.30	ns

Methods: T1DM patients diagnosed from 1996-2016 were included. Celiac and thyroid disease screening were analized. Clinical and biochemical data were compared during evolution. SPSS.21 for statistical study.

Results: 187 patients (55,6 males) were follow at least one year and 40 during more than 10 years. Mean age at onset 8,57 (0,5-15) years. (Table 1) There were no diferrences between age at onset and clinical presentation. A1cHb is lower and residual function is significant higher in those diagnosed at onset on hyperglycemia (p<0,05). 12,2 % were negative for islet antibodies at clinical presentation. During evolution, 2 patients were MODY, one Wolfram syndrome and 3 developed other autoinmunities. 7,9% were still negative for inmunology All were on basal-bolus treatment, with rapid insulin analogs. From 2006, 42 patients were on ISCI. 7,48% were diagnosed for celiac disease by biopsy. Mean age 8,57 (3,9). 14,43% had thyroid disease, mean age 11,74(3,5). In 68,5% of patients mean A1 cHb were <7,5%. Severe hypoglycemia in 2,3% without differences between treatment. 6,4% developed intermittent microalbuminuria with no differences with A1C Hb but with duration of disease (Median 13 vs 6,5 years (p0,01)). No arterial hypertension nor retinopathy were detected.

Conclusions: CAD presentation reduce with time. High prevalence of associated diseases that demostrates the need for screening. Low complications with good metabolic control in most of patients. It ´s neccesary to re-evaluate negative inmunological patients for an etiological diagnosis.

P3-P084

Diabetic Capilaropathy: A Case Report

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Uncontrolled diabetes mellitus is a disease with a wide range of systemic complications. Eye complications may seriously threaten quality of life. Diabetic retinopathy is the most frequent diabetic ocular complication. However, diabetic capilaropathy is a little known condition of diabetic retinopathy. It is an acute optic disc edema and/ or macular edema; due to an acute hyperglycaemia.

Method: We present a case of a diabetic 14-years-old female with diabetic capilaropathy.

Results: A 14-year-old female with poor control of type 1 diabetes mellitus who suddenly shows loss of visual acuity associated with headache. Valued in ophtalmology, She presents a decrease in visual acuity associated with bilateral optic disc and macular edema. visula evoked potencials, electroneuroretinogram and macular optical tomography are initially altered.

The initial study with blood test, chest X-ray and cranial computerized tomography is normal. The study continues with lumbar puncture, obtaining normal opening pressure cerebrospinal fluid and normal cytochemical and microbiological analysis. Finally, tuberculin skin test, quantiferon and cranial MRI are normal too. Metabolic control of diabetes is optimized by insulin therapy. After optimizing the treatment of the diabetes, a good evolution of visual acuity is observed with clinical normalization. Finally, macular optic coherence tomography and eye fundus tests are normalized.

Conclusions:

1. Poor blood glucose control may generate systemic and ocular complications.
2. Although the most well-known ocular complication is diabetic retinopathy, there are other ocular complications derived from poor diabetic control, such as diabetic capilarophaty.
3. The optimization of the treatment with insulin, can improve the diabetic capilaropathy.

P3-P085

A Sibling Case of Wolfram Syndrome with Diabetes Mellitus Diagnosed Within 10 Months in Early Childhood

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Introduction: Wolfram syndrome (WS) is a rare progressive neurodegenerative disease that shows autosomal recessive inheritance characterized by diabetes insipidus, diabetes mellitus (DM), optic nerve atrophy and deafness. WFS1 gene encoding a protein, wolframin, which is essential to the function of the endoplasmic reticulum, is identified as main causative gene of the disease. We report here a sibling case suspected WS with insulin-dependent DM and optic atrophy in early childhood.

Case 1: A 7-year-old boy with no family history of DM and eye disease was referred to our hospital for a positive glucose urine test in elementary school and hyperglycemia. He showed mild diabetic ketoacidosis (DKA). Postprandial glucose and HbA1c levels were 11.8 mmol/l and 10.7%, respectively. Autoantibodies to GAD, insulin, IA-2 and ZnT8 were all negative. The peak C-peptide reactivity (CPR) level after glucagon stimulation was low as 1.32 ng/ml (normal:>3) and he was treated with multiple daily injection of insulin. On an ophthalmologic examination after the diagnosis of DM, atrophy of his optic nerve was revealed.

Case 2: younger brother of Case 1] After two-month episode of nocturnal enuresis at the age of 5 years and 8 months, he showed hyperglycemia of almost 10-20 mmol/l measured by his mother using his brother's blood glucose meter. It was only 10 months after his brother's diagnosis of DM. Postprandial glucose and HbA1c levels were 11.8 mmol/l and 9.5%, respectively. Any islet associated autoantibodies were negative. The peak CPR level after glucagon stimulation was 2.73 ng/ml and multiple daily injection of insulin was started. He was also pointed out mild optic atrophy by an ophthalmologic examination.

Discussion/Conclusions: WS was not suspected at first when Case 1 developed insulin-dependent DM. But only after 10 months, his brother also presented insulin-dependent DM without autoimmune response in addition to optic atrophy, so WS was strongly suspected. It is common that DM is the first symptom of WS patients diagnosed around at 10 years old, and other abnormal symptoms occur subsequently. At the moment, they do not show achromatopsia, visual acuity lowering, diabetes insipidus

and other neurological or psychiatric symptoms. But since symptoms of WS are progressive, careful observation and follow-up of the patients are needed to note onset rapidly. Genetic diagnosis of WS may be important for the choice of appropriate treatment, the welfare improvement of the patients and the development of future therapy.

P3-P086

Continuous Subcutaneous Insulin Infusion in Children and Adolescents: Analysis of Initial and Follow Up Basal Rates

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Objective: Initiation of continuous subcutaneous insulin therapy (CSII) requires an appropriate basal rate profile. Although different approaches exist; there is a lack of evidence-based recommendations, especially in young children. Our aim was to show how the % of basal rates change at the end of first year of therapy when basal rates are equally distributed at the start of therapy.

Materials and Methods: In this survey, 129 CSII patients were analyzed. Patients were divided into four age groups: <5 yr (n = 27), 5 to < 8 yr (n = 20), 8 to <12 yr (n=33), 12 to <15 yr (n = 28), 15 to < 18 yr (n=16) and > 18 yr (n = 5). Basal insulin requirement and diurnal distribution were evaluated at the initiation of pump therapy and in the first year.

Results: Basal insulin requirement did not differ between the beginning of therapy and first year (Table 1). In every age group basal insulin (U/kg) circadian insulin profiles were different except in the group 12 to <15 yr.

As a result, at the start of pump therapy basal rates should be designed according to circadian rhythm.

Table 1. Basal rates according to age groups at the beginning and first year (for Abstract no P3-P086)

	Basal İnsulin beginning U/kg	1 st Year Basal insulin U/kg	p
0–5 yr n:27	0.41±0.88	0.26±0.68	0.13
5–8 yr n:20	0.29±0.12	0.30±0.09	0.50
8–12 yr n:33	0.31±0.13	0.32±0.09	0.27
12–15 yr n:28	0.33±0.08	0.35±0.09	0.34
15–18 yr n:16	0.32±0.10	0.34±0.11	0.43
>18 yr n:5	0.22±0.05	0.24±0.06	0.5
p[a]	0.006	0.002	

p, basal and first year change; pa, change according to age groups.

P3-P087

Prevalance of Fatty Liver in Patients with Type 1 Diabetes Mellitus Attending Diabetes Clinic at Alexandria University Children's Hospital

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Background: Type 1 diabetes mellitus (T1DM) - related hepatopathy is not uncommon and tends to be more prevalent among children with poor glycemic control. Recent studies suggest that fatty liver disease may be more common in T1DM than previously thought.

Aim: The aim of this work was to determine the frequency of hepatopathy in patients with type 1 diabetes mellitus attended diabetes clinic at Alexandria university children's hospital (AUCH) and it's relation to the state of glycemic control and lipid profile.

Methods: Study was carried out on 70 patients diagnosed with type 1 diabetes mellitus attended diabetes clinic at AUCH. All were subjected to the following: History, full detailed physical examination, Anthropometric measurements: Height standard deviation (SD) score and body mass index (BMI) percentile were calculated using Centers for Disease Control (CDC) 2000 growth charts, Liver enzymes (ALT&AST), Liver function tests (albumin and prothrombin time), Lipid profile: total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides, HbA1C and transabdominal ultrasonography by using scoring system for detection of fatty infiltration of the liver.

Results: In the present study, the mean duration of diabetes was 6.5 ± 2.2 years. About (51.4%) of the patients were using premixed insulin therapy. Hypercholestremia, hypertriglyceridemia, high LDL and low HDL were found in (24.3%, 17.1%, 8.6% and 4.3%) of the patients 8respectively. (62.9%) of patients were with poor glycemic control. More than half of the patients had been found to have fatty liver (52.9 %).

Conclusion: A high rate of fatty liver among the patients was found and it was related to patients with poor glycemic control.

P3-P088

The Triad of Obesity, Acanthosis Nigricans and Diabetes Mellitus in a Newly Diagnosed Adolescent; Is this Type 1 Or Type 2 Diabetes Mellitus?

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Introduction: The incidence of type 1 and type 2 diabetes mellitus in children and adolescent has been on the rise for the last decades. While the reasons behind these are not known, one possible explanation for the emergence of type 2 diabetes in children is the increase of obesity and decreasing physical activity. Adolescents are at the cross roads between childhood and adulthood and that makes classification of their diabetes mellitus at presentation a diagnostic challenge.

Objectives/Aims: To describe the clinical presentation, diagnosis and management of an obese adolescent boy who was newly diagnosed with diabetes mellitus and to categorize it according the current standard classifications.

Method/Case: We present a 16 years old boy who first presented to the emergency department with dizzy spells and lethargy after school. Upon rapid assessment in the emergency department, he was noted to have the following features; obesity with body mass index (BMI) of 32 kg/m2, acanthosis nigricans in the nape of the neck and arm pits, gynaecomastia but no abdominal striae, moon face or buffalo hump. He was noted to have dehydration, elevated blood glucose, with readings of 17 mmol/L and positive urine ketones. A diagnosis of diabetes ketoacidosis (DKA) was made and he was treated in accordance with the standard protocol. Following the resolution of DKA, he was discharged home on vildagliptin/metformin. However, he was admitted 3 days later in a state of DKA. Following that admission, a possibility of type 1 diabetes mellitus in was entertained and the c-peptide and the auto-antibody screen was done.

Results: His blood investigations revealed the following: the C-Peptide; 455 pmol/L (normal range 364- 1655 pmol/L), HbA1c of 12.1%, Anti-glutamic acid Decarboxylase (GAD) Antibody >2000 IU/mL(Positive)(normal range 0-10 IU/mL), Islet cell Antibody (pancreas IFA)-positive, Anti-IA2 Antibody <10.00 IU/ml(Normal Range 0–20 IU/mL), Gluten IgE-Negative (<0.10) KU/L(Normal Range 0–10 KU/L), Gluten IgA (anti gliadin)-0.40 U/ml (Normal Range 0–10 U/mL)

Discussion/Conclusion: In view of obesity, acanthosis nigrans and normal C-Peptide levels, type 2 diabetes mellitus was initially considered. Positive auto-antibodies and failure of oral hypoglycaemics makes type 1 diabetes mellitus likely in that obese adolescent. We conclude that classification of diabetes mellitus in obese adolescents is challenging and clinicians should consider all possibilities at diagnosis.

P3-P089

A Female Patient with Atypical Diabetes Features, Showing Heterozygous Mutations on G6PC2 (Glucose 6 Phosphatase, Catalytic Subunit 2). Does Explain All Clinical Manifestations Or Is It Only Polymorphism?

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Introduction: Determing diabetes subtypes and classification is not clear for every patient and diagnosis can be difficult. Here in, we have found a quite interesting mutation on G6PC2 gene in a girl, 10 years old, showing atypical diabetes characteristics.

Case: A girl who was first diagnosed with obesity for 9 years and 7 months. In this time blood lipid levels and fasting glucose were in normal range. And she was admitted to endocrinology department due to asemptomatic hypergisemia at 11 years old. Keton was negative. There was no significant symptom except mild weight faiure. In her first physical examination; weight 54 kg(>99P) and height 146,7 cm(>99P) pubertal stage was Tanner 3. Random glucose was 363 mg/dl and insulin 3,76 ıu/ml c peptide was 1 ng/ml. HAb1c level was %10. Other biochemistry tests and hormonal profile were normal. Anti GAD level was 3 ıu/ml (<1). Firstly type 1 DM was diagnosed and insuline has been started but after 3 years her insulin requirment was still 0,4 u/kg/day and insulin resistance findings were noted. So genetic analyses was sent. A mutation was detected on G6PC2 gene. İt was known as glucose sensor (GCK) regulator and no mutation on this gene causing monogenic diabetes up to date

Conclusion: It is known that this gene does not cause monogenic diabetes that is prone to type 2 diabetes and is generally active in fasting blood sugar regulation. So we treat patients as type 1 diabetes but some patients who can show the characteristics of all types of diabetes. With advanced genetic tests, diabetes classification can be made more clearly.

P3-P090

Clinical and Laboratory Features at the Onset of Childhood Type 1 Diabetes Mellitus in the Nortwest Region (Trakya) of Turkey

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Aim: To describe the clinical pattern and laboratory characteristics at presentation of a group of children with type 1 diabetes mellitus living in the Northwest region (Trakya) of Turkey.

Methods: The clinical and laboratory data of a total of 315 children who presented with newly diagnosed type 1 diabetes mellitus during a 12 year period (2006-2018) were retrospectively analyzed based on hospital records. The data were assessed by gender and age subgroups (≤5, 6-10, ≥11 years).

Results: There were 161 boys (51.1%) and 154 girls (48.9%) with a mean age of 8.7± 4.1 years. The age distribution was categorized as 0-5 years: 92 (29.2%), 6-10 years: 118 (37.5%) and 11-18 years: 105 (33.3%). The patients were mostly diagnosed at aged 6-10 years but this difference was not significant. Mean duration of symptoms was 26.2±34.3 days. Although a shorter duration of symptoms was reported in younger cases (aged 0-5 years), no significant difference was determined. The seasonal distribution of onset was as follows: 78 (24.8%) occurred in spring, 56 (17.8%) in summer, 84 (26.7%) in autumn and 97 (30.8%) in winter. The seasonal difference was statistically significant ($p<0.05$). Family history revealed type 1 DM in 12.4 % (n=39), type 2 DM in 53.3% (n=168). One hundred and sixty two (51.4%) of all patients presented with diabetic ketoacidosis (DKA), 122 (38.7%) with ketosis and 31 (9.8%) with hyperglycemia. The frequency of DKA was not significantly different between the gender and among the three age groups. Mean blood glucose level was 430.7± 152.7 mg/dl and mean HbA1C level was 13.8 ±6.5. HbA1c levels did not differ by gender but was significantly lower in 0-5 aged group ($p<0.05$). The prevalence of anti-thyroid peroxidase (TPO) anti-endomysium antibodies were 6.3% and 5.1% respectively, while there was no difference between gender in all groups, but anti-TPO was significantly lower in young patients ($p<0.05$).

Conclusion: These findings indicate that nationwide educational campaigns about the symptoms of type 1 diabetes in children are needed to provide early recognition and to avoid more severe types of presentation.

P3-P091

Clinical and Epidemiological Features of Children with Type 1 Diabetes

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Introduction: The world health organization has adopted diabetes as the most important health problem because of its increasing frequency and complications. Determination of changes in patient profile over the years due to type 1 diabetes (T1DM), the most common type of diabetes in childhood, is an important point in the follow up observation and treatment of diabetes.

Aim: To determine the epidemiological and clinical characteristics of children and adolescents with T1DM diagnosis and to evaluate the change over the course of time.

Method: The files of 631 patients diagnosed with T1DM between 1990 and 2017 in Gazi University Faculty of Medical Hospital Pediatric Endocrinology Department were examined retrospectively. The gender of the cases, age of diagnosis, season of diagnosis, complaint of admission, duration of symptoms, laboratory and physical examination findings as the time of admission, family history of diabetes mellitus, accompanying autoimmune diseases and chronic complications were recorded. The cases were divided into three groups according to the years of diagnosis (1990-2000, 2001-2010 and 2011-2017).

Results: 309(49%) of the cases were females while 312 (51%) were males with a mean age of 8.7± 4.2 years. Diagnosis is most common in winter and autumn seasons. The most common referral complaints were polyuria (93.1%), polydipsia (94.1%) and weight loss (58.8%). There was an increase in nocturia complaints in respect to years. (p=0.035).Family history of diabetes mellitus was found to be 15.7% for T1DM and 53.6% for T2DM. 47.7% of the cases were diagnosed of diabetic ketoacidosis (DKA), 29.7% of hyperglycemia and 22% of ketosis. In patients with familial T1DM the rate of incidence of DKA in admission was low (p=0.001). It was found that the recurrence rate was significantly higher in females compared to males (p = 0.001). The recurrence rate of DKA was 12.9% and decreased when evaluated according to years (p< 0.001). Hashimoto's disease was 20.4%, Celiac disease was 5.6%, nephropathy was 9.6% retinopathy and neuropathy was 0.9%.

Conclusion: It was discovered that T1DM cases were diagnosed mostly in winter and autumn seasons, the diagnosis peaked at ages 6-10 and puberty age group and 41.7% of them were diagnosed with DKA. This study contains cases that were referred to our hospital in this context, there is a need for extensive studies to be done nationwide to have enough knowledge about T1DM epidemiology.

P3-P092

Predictors of Optimal Glycemic Control in Children with Diabetes Mellitus Type 1 Receiving Pump Insulin Therapy

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Objectives: To study predictors of target levels of glycosylated hemoglobin (HbA_1c) in children with diabetes mellitus type 1 (DM1), receiving pump insulin treatment.

Materials and Methods: 64 children (27 girls, 46 adolescents) with diabetes mellitus type 1 (mean age 12.8±3.5 years, disease duration 4.46±3.1 years, daily insulin dose 0.82±0.24 units) receiving pump insulin treatment for 2.46±1.43 years were studied. The results of questionnaire were assessed, including using the main technical features of the pump (bolus advisor, bolus type, temporal basal velocity, computer data analysis), archive data of the pump, HbA_1c values.

Results: The satisfaction of dosage device use was high, reaching 98,6% (p<0,001). Parents' participation in this therapy type was low - 57,8% (p=0,4).

In the studied group, the mean HbA_1c value was 8.08±1.46% irrespective of gender (girls, 7.73±1.05%, boys, 8.32±1.64%, p=0.1), puberty status (children, 7.6±1.0%, adolescents 8.27±1.6%, p=0.1) and the time of pump installation (since DM1 diagnosis 7.96±1.62%, with DM1 duration, 8.27±1.0%, p=0.55).

In the majority of cases (46/64, 71.9 %) the children were using less than 3 main pump functions (mean, 1.04±0.73), as reflected by the mean HbA_1c value - 8.49±1.46%, while in 7 (10.9%) using 3 and more basic pump functions (3.43±0.53) this value has reached the target range and was 7.2±0.44% (p=0.0126).

Combination of continuous blood glucose monitoring with pump insulin therapy was used in 11 (17,2%) patients. The mean HbA_1c value in this group has reached the target level and was 6.78±0.7% (p=0.001).

Conclusion: While the treatment satisfaction of dosage device use was high (98,6%), the treatment compliance for this therapy type remains low (10,9%). Parents' responsibility for pump insulin treatment administration is insufficient and was 57,8%. Using three or more basic pump technical functions and the combination of its use with continuous blood glucose monitoring helps to achieve target glycosylated hemoglobin levels in children with DM1.

P3-P093

Symptomatic Cerebral Infarction: A Rare Complication of Diabetic Ketoacidosis

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Diabetic ketoacidosis (DKA) is accompanied by intracerebral complications from 0.3% to 1%. Cerebrovascular events account for 10% of intracerebral complications.

Our aim is to present a case of symptomatic cerebral infarction as a serious complication of DKA and draw attention to the management of DKA treatment.

A 3.5-years-old male patient was referred to our department with DKA for further evaluation and treatment. Before coming to our center, insulin and sodium bicarbonate bolus had been given before adequate hydration.

On examination, he was extremely dehydrated and had a fluid deficit of 10%. The score in the Glasgow Coma Scale was determined as 7. He was lethargic and tachypneic with Kussmaul's breathing. His respiratory rate was 36 breaths per minute, pulse was 136 per minute and axillary temperature was 36.7°C. The activity of the deep tendon reflexes was normal and the Babinski sign was negative bilaterally.

Laboratory investigations showed serious acidosis (pH: 7.04; HCO3: 3.8 mmol/L; pCO2: 11 mm Hg), hyperglycemia (plasma glucose: 194 mg/dL) and ketonuria, Serum sodium concentration was found to be 139 mmol/L and potassium 3.1 mmol/L. HbA1c was 10.9% (4.8%–6.0%).

The patient was monitored in the pediatric intensive care unit. The fluid treatment plan was made for 36 hours. Rehydration with 0.9 % saline was started (10 mL/kg/h for the first 1 h), followed by continuous intravenous infusion of a 5% glucose solution containing 100 mEq/L sodium chloride, 40 mEq/L 7.5% potassium chloride. Insulin infusion was started with 0.05 U/kg/h. Capillary blood glucose was monitored hourly; electrolytes, urea, and blood gases were repeated with an interval of 2 h.

His DKA was resolved about 24 h after the admission. Subcutaneous insulin therapy was started with an adequate caloric diet for diabetic people.

On the second day, left-sided hemiparesis and increased deep tendon reflexes and positive Babinski reflex on the left side were detected. Magnetic resonance imaging (MRI) of the brain showed right sided fronto-parieto-occipital infarction. After 3 months of follow-up, the neurological findings of the patient who was on physical therapy program were improved.

Finally, a well rehydration strategy in the first hours of therapy is crucial in reducing the neurological complications. Since it may be mortal, particularly high-risk and severe cases of DKA should be treated with child endocrinology specialists and, if possible, treated under the conditions of the pediatric intensive care unit.

P3-P094

Our Clinical Experiences in Type 2 Diabetes

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Background: Type 2 diabetes is a heterogeneous disorder characterized by the defective of insulin, which can not progressively compensate for insulin resistance, due to the influence of environmental factors on the basis of genetic susceptibility. Hyperglycemia, which starts with insulin resistance, is thought to show toxic effects (glucotoxicity) on β cells and ultimately impairs beta cell function., Although many factors play a role in etiology, obesity is the most common cause. Type 2 diabetes is more common in girls than boys.

In this article, we present etiology and clinical features of type 2 diabetic cases followed-up in our clinic, and share treatment and follow-up approaches.

Cases: A total of 16 patients (12 female, 4 male) with type 2 diabetes mellitus who admitted to our clinic were included this study. The causes of admission, family history, hormonal and biochemical evaluation, and the treatments were recorded for all patients. 37.5% of patients had presented with typical symptoms of diabetes and 0ne of the patients presented with severe symptoms such as hyperosmolar nonketotic coma, 12.5% applied with infection symptoms (stress hyperglycemia) and other patients were asymptomatic. One patient referred with cataract. The family history was positive in 11 patients and all patients were obese and/or overweight except for one patient. Acanthosis was also detected in half of the patients. Approximately 70% of patients require insulin treatment.

Conclusion: Type 2 diabetes is an insidious disease and rare in children. Because of this, the diagnosis can be delayed. Here we discussed the cases of heterogeneous clinically confronted type 2 diabetes: two cases of hyperosmolar nonketotic coma, one with diabetic ketoacidosis, one with ketosis, one with cataract, and 8 asymptomatic patients. Family history was positive for majority of children and type 2 diabetes was especially associated with obesity. In spite of heavy insulin resistance, acanthosis was seen in half of the patients, which is another case showing clinical heterogeneity in the patients. In conclusion, in children with obesity, especially if there is family history, type 2 diabetes should be considered even in absence of clinical symptoms.

P3-P095

The Relationship Between Serum Levels of C-Peptide and the Age, Body Mass Index, and Insülin Doses in Newly Diagnosed Type 1 Diabetic Children

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Background and aim: C-peptide is an important indicator of endogenous insulin release. Our aim was to investigate the association of serum C-peptide levels with age, body mass index (BMI) and insulin doses in newly diagnosed type 1 diabetic (DM1) children.

Metods: The patients with newly diagnosed DM1 were enrolled the study and classified as DM1A and DM1B. Clinical and laboratory findings of all the patients were recorded. Daily insulin doses, BMI and its z score were calculated. Fasting and two hours after the meal serum samples were obtained for C-peptide levels. The statistical analyses were performed using the SPSS.

Results: Although serum C-peptide levels of DM1B patients were higher (fasting and postprandial 0.53 ± 0.80 ng/ml and 0.98 ± 1.29 ng/ml, respectively) than those of DM1A patients (fasting and postprandial 0.41 ± 0.39 ng/ml, 0.43 ± 0.36 ng/ml, respectively), we found only significant difference in postprandial C-peptide levels between the groups ($p < 0.05$). There was a significant positive correlation between both fasting and postprandial C-peptide levels and age, BMI, and BMI z score ($p < 0.001$). There was no significant correlation between serum C-peptide levels and insulin doses.

Conclusions: C-peptide levels might be affected by body fat and age as well as pancreatic beta-cell function. It is known that body fat is to be related to insulin resistance. However, there are only a few studies evaluating the effect of BMI on C-peptide levels in children with DM1. We found a strong correlation between serum C-peptide levels and BMI and its z score. Therefore, it is important to evaluate serum C-peptide levels according to age and BMI while performing clinical assessment and differential diagnosis

P3-P096

Serum Trace Element Levels in Children Presenting with Diabetic Ketozis and Diabetic Ketoacidosis: A Longitudinal Controlled Study

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Objective: There have been very few studies, with contradictory results, on the serum trace elements in children and adolescents presenting with diabetic ketosis and diabetic ketoacidosis due to type-1 diabetes mellitus. The objective of this longitudinal controlled study was to determine serum trace element status including selenium (Se), zinc (Zn), copper (Cu), manganese (Mn), chrome (Cr), and cobalt (Co) in type-1 diabetic children and adolescents presenting with diabetic ketosis and diabetic ketoacidosis and to compare them with that of healthy controls.

Materials and Methods: Thirty eight children and adolescents with diabetic ketosis and diabetic ketoacidosis, aged 3 to 17 years, and 38 similar ages - and the same sex-matched healthy controls were participated in the study. Serum hemoglobin A1c, free thyroxine (FT4), thyroid stimulating hormone (TSH), creatine kinase (CK), and trace elements including Se, Zn, Cu, Mn, Cr, and Co were measured. Blood gases were determined and whole blood analysis was performed. All patients were evaluated at the diagnosis (visit 1), 10-15 days after diagnosis (visit 2), three months after diagnosis (visit 3), and six months after diagnosis (visit 4).

Results: The mean serum Se and Zn concentrations in diabetic patients at each visit were higher than those in healthy controls. No correlations were found between the serum Se and Zn levels and others parameters.

Conclusion: The serum Se and Zn levels of diabetic children and adolescents during six months after diagnosis are noticeably higher compared to those of healthy controls. Long term prospective and controlled studies are necassary.

P3-P097

Evaluation of Relation Between Diabetic Education Levels of Type 1 DM Child/Adolescent and Parents and Metabolic Control

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Introduction and Aim: The education of the diabetic patients and their parents is an important phase of diabetic treatment. It is accepted in general that good control in diabetes is not possible without enough knowledge and experience about diabetes. In this study it is aimed to evaluate the relation between diabetic education levels of type 1 DM child/adolescent and parents and metabolic control.

Material and Method: The study included the patients and their parents who refered to Pediatric Endocrinology clinic and followed at least for 1 year with diagnose of Type 1 DM. Children over 11 years old and their parents performed questionary form which aims to evaluate diabetes knowledge level and daily diabetic management. They had 20 questions, every right answer had 10 points, and diabetes knowledge point (DKP) was measured. Patients had physical examination and anthropometric measures, HbA1c levels in last 1 year used to evaluate metabolic control. HbA1c level <%7.5 was good, %7.5-9 was mild, >%9 was bad in metabolic control.

Results: Mean age of 42 patients (27 girl/15 boy) was 11.6±4.1 (1.6-18.6) years. 69% of patients (n=29) were pubertal. Mean diabetes duration was 4.8±3.3 (1-15) years and mean HbA1c levels

were 8.2±1.4% (5.9-12.3%). Metabolic control was evaluated as good in 33.3% (n=14), mild in 38.1% (n=16), bad in 28.6% (n=12). 69% of parents (n=29) evaluated their own diabetes knowledge as good, 16.7% (n=7) as very good and 14.3% (n=6) as mild. When they were asked for usage of diabetes knowledge in management of disease 47.6% of parents (n=20) answered as always, 35.7% (n=15) as often, 9.5% (n=4) as sometimes and 7.1% (n=3) as rarely. DKP of patients was 134.3±35.9 (73-200), of parents was 133.6±25.3 (69-189). No relation was detected between HbA1c levels and patient and parents DKP (p=0.279, p=0.963, respectively). HbA1c levels observed to decrease when usage of diabetes knowledge in management of disease increases, but no statistically difference found (p=0.418). The most important factors affecting HbA1c levels were diabetes duration (p=0.010) and frequency of blood glucose measures (p=0.028).

Conclusion: In this study no relation was found between patients and parents diabetes knowledge levels and metabolic control. It is considered that usage of knowledge in management of disease has impacts on metabolic control but there are more important factor affecting metabolic control.

P3-P098

A Case of Childhood Type 1 Diabetes Mellitus Who Developed Granuloma Annulare

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Introduction and Aim: Granuloma Annulare (GA) is a granulomatous dermatitis of unknown etiology with numerous associations, consisting of a single or multiple small lesions (of nodular or papular shape)with annular configuration, usually localized on dorsal surfaces of the feet or hands and over other bony prominences; it is clinically painless and not pruriginous. Granuloma annulare has rarely been reported in childhood, and its association with type 1 diabetes mellitus (T1DM) and other chronic systemic diseases such as autoimmune thyroiditis or rheumatoid arthritis has been reported. We present this report because of the very rare existance of T1DM together with GA.

Case: A 8 years and 9 months old girl who is followed for 1.5 years with the diagnose of T1DM and receiving analogue insülin treatment complained of skin eruption in ankles. Eruptions were first noticed during initial DM diagnose and repeated every hyperglisemia periods. Physical examination was normal, except erythematous annuler lesion with atrophic focal areas replacing in left foot dorsum and ankle and erythematous lesion replacing in lateral of right lateral malleol. HbA1c was 7.9%, anti-nuclear antibody was positive. Hystopathological examination of biopsy from lesion revealed normal epidermis, increased mucin accumulation and nekrobiosis areas with significant borders and surrounding histiocytic infiltration in mid and deep dermis. These findings were diagnosed as granuloma annulare.

Results: The relationship of GA to T1DM is controversial. Although a clear mechanism remains stil unknown, prolonged exposure to high glucose levels could contribute to expression of this skin manifestation. Clinicians must take into consideration an association of GA in patients with T1DM to avoid unnecessary medical investigations and/or inadequate pharmacological treatment.

P3-P099

Case Report: De Novo Mutation of FOXP3 Causing Mild Phenotype of Immunodysregulation, Polyendocrinopathy, Enteropathy, X-Link Syndrome

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Immune dysregulation-polyendocrinopathy-enteropathy-X-linked syndrome (IPEX) is caused by mutations in the gene that encode for the transcription factor FOXP3. IPEX is a rare, often fatal disease. However, several cases present later onset, mild forms or less common clinical manifestations. We report a case who had de novo mutation of FOXP3 causing neonatal diabetes but without other features of IPEX syndrome. An 8 days old male, late preterm at 36 weeks, low birthweight 2200gr, hospitalization for diabetic ketoacidosis and sepsis. After diabetes, he had mild dermatitis. There was no significant family medical history. He was treated with actrapid/ insulatard and eosin 2%. The DNA analysis at the University of Exeter Medical School found mutation at exon 12 of FOXP3 gene c.1190G>A, p.(Arg397Gln). The FOXP3 missense variant p.(Arg397Gln) was not detected in his mother's DNA sample. IgE level were high. Autoimmune antibodies were negative except anti-RNP positive.

P3-P100

Is There a Relationship Between Immune-Mediated Type 1 Diabetes Mellitus and Congenital Rubella Infection?

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Congenital rubella infection is a transplacental infection that can cause intrauterine growth retardation, cataract, patent ductus arteriosus, hearing loss, microcephaly, thrombocytopenia and severe fetal injury. It has been shown that type 1 diabetes mellitus develops in 12-20% of patients with congenital rubella infection and disorder in oral glucose tolerance test is observed in 40%.

A 13-year-old male patient presented with complaints of new-onset polydipsia, urination, and weight loss. From 3 months old, he was diagnosed with patent ductus arteriosus in pediatric cardiology department and he was found to have neurosensory hearing loss from birth. On physical examination, weight was 42.7 kg (25-50p), height was 153.2 cm (25-50 p), head circumference was 46 cm (< 3p), 2/6 cardiac murmur and hearing aid

were present. Blood glucose was 619 mg / dl, urine ketone was +3, blood gas shows metabolic acidosis, insulin was 4,1 IU / mL (2-18) and serum C-peptide level was 1.23 ng / mL (1,1-4,4). HbA1c value was 15.9%, anti insulin antibody was 0.78 U / mL (0-0.5U), anti-GAD was 22.8 U / mL (< 1U / mL) and islet cell antibody was positive. Intravenous fluid and insulin therapy was started according to the degree of dehydration with the diagnosis of immune-mediated type 1 diabetes mellitus. Subcutaneous insulin therapy was switched to 1.2 units / kg / day after the patient's metabolic acidity was corrected and blood glucose regulation was achieved. Immune-mediated type 1 diabetes was thought to be associated with congenital rubella infection due to patent ductus arteriosus, microcephaly, and neurosensory hearing loss following a febrile and rash illness of the mother during pregnancy.

Immune-mediated type 1 diabetes mellitus associated with congenital rubella infection should be assessed and followed up with a multidisciplinary approach. Early diagnosis and appropriate treatment will prevent the development of complications.

P3-P101

Changes in Glycemic Control After Switching from NPH & RI to Insulin Glargine & Lispro in Children with Type 1 Diabetes Mellitus (T1DM)

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Background & objective: It has been reported that glycemic control gets better in children with T1DM on insulin glargine and lispro when compard to patients on NPH and RI. This study was conducted to see the changes of glycemic control after switching from insulin glargine and lispro (GLAR/LIS) to NPH and RI (NPH/RI) in Korean children with T1DM.

Materials & Methods: We studied 14 patients who were diagnosed with T1DM in Kyungpook National Children's Hospital, and who switched insulin from NPH/RI to GLAR/LIS. HbA1c, body mass index(BMI), insulin requirement, self-monitoring blood glucose and frequency of hypoglycemic episodes were compared between the two periods which were on NPH/RI or GLAR/LIS for one year before and after switching insulin. Their medical records were reviewed retrospectively.

Results: Change of HbA1c was not significant when compared NPH/RI to GLAR/LIS period (8.5±1.72 vs 8.3±1.87%, p=0.575). BMI (kg/m2) and insulin requirement (IU/kg) were significant neither (23.3±6.73 vs 24.1±6.45, and 1.17±0.51 vs. 1.26±0.48, p=0.300 and p=0.168). Self-monitoring blood glucose (mg/dL) for one month before and after switching insulins showed significant changes in morning and evening fasting blood glucose (191.07±88.47 vs 107.07±89.86, p=0.024, and 175.83±47.75 vs 122.07±58.51, p=0.020, respectively). The range of deviation of self-monitoring blood glucose at 3:00 AM and morning fasting time tends to be more narrow in the GLAR / LIS period. The frequency of hypoglycemic episodes were significantly higher in the NPH/RI period compared to GLAR/LIS period (20% vs.4.6%, respectively, p<0.05).

Conclusions: Unlike the previous reports, there was no significant change in HbA1c, body mass index and insulin requirement in GLA/LIS period. However, the frequency of hypoglycemic episodes were lower in GLAR/LIS period. Further large-scaled studies are necessary.

P3-P102

When Type Mody II Diabetes simulates Type I Diabetes

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Introduction: Mutations of the GKN gene are the most common cause of Mody diabetes. MODY II typically results in mildly elevated fasting blood sugar, without noticeable diabetes, maintaining good metabolic control without treatment.

Clinical Case: A 4.5 years old female infant, was referred due to presenting polyuria, polydipsia and fasting hyperglycemia of 126-130mg/dl and 2 hours post-intake blood glucose level of 150-220mg/dl

She was born by normal delivery and was symmetrical IUGR, her weight and height in the 25th percentile.

Family History: Her mother was diagnosed with gestational diabetes, controlled by diet. One year later, she was diagnosed with Type I Diabetes requiring insulin treatment. Maternal grandmother was diagnosed with Type II Diabetes requiring at the beginning oral antidiabetics.

Laboratory work:

-Fasting glucose level: 121 and 130mg / dl, Insulin level: 3.8mUI / ml, C-Peptide : 0.4ng/ml, Hemoglobin A1C level: 6.2%

- thyroid hormones were normal and Thyroid antibodies negative

-GOTT: basal glycaemia 99mg/dl, after 2 hours: 220mg/dl.

-Negative diabetes antibodies (Anti-GAD, Islet, insulin autoantibodies)

-Inmunoglobulin A <5mg / dl and IgG& IgM: normal

- Coeliac blood test: negative

-Urine test: Negative microalbuminuria. Not glucosuria.

- HLA typing test: Not compatible with Type I Diabetes

-Mody Molecular Study II: Negative sequencing of exons 1 to 10 as well as flanking zones of the GCK gene.

Evolution: Treatment with diet was performed. At the first year of evolution she presented with clinical signs of polyuria, polydipsia, fasting and post-intake hyperglycemia greater than250 mg/dL with HbA1C of 7.2%, following which she started treatment with a low dose of glargine insulin (3 units daily) and immediately her glycaemia normalized and clinical symptoms disappeared,

Conclusions: MODY Diabetes does not usually require treatment, however its clinical spectrum overlaps with features of both type 1 and type 2 diabetes, thus presenting a diagnostic challenge.

The clinical symptoms in our patient are justified due to suffering deletion in all exons from 1 to10.

Early diagnosis is important to remove insulin treatment and to administer the most appropriate type of therapy. Nevertheless, the fundamental goal is a clinical and personalized follow-up of the patient.

P3-P103

Epidemiological Study and Analysis of Type 1 Diabetes Comparing Patients with and Without Ketoacidosis in the Last 5 Years

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Type 1 diabetes(T1DM) in childhood is a highly prevalent disease, with incidence oscillating around 17.6/100000.However, incidence is higher in some communities (25.5/ 100000), as it is in the case that concerns us.Diabetic ketoacidosis (DKA) is a complication usually recorded in25-40% of cases but has been as high as55% in studies of children under 5 years old.(T1DM) is an associated autoimmune disease to other precursor autoimmune pathologies.

Objective: To compare the clinical, epidemiological and associated comorbidities in patients with type 1 DM.Establish differences between (DKA) with and without onset, as well as severity of said (DKA).

Material and Method: Observational, descriptive and analytical retrospective study of patients diagnosed with (T1DM), between January2013 and December2017. The variables sex, age, HBA1c, Insulin, C-peptide, severity of DKA, place of origin, levels of25-OH-Vitamin D, season, autoimmunity, breastfeeding, diseases associated with the onset, establishing two periods to compare 2013-2015, versus 2016-2017. We have stratified the DKA according to age groups:0-5 years, 5 -10 years, 10-14 in order to analyze if the incidence was higher in children under 5 years, as reflected in the literature.Data was analyzed through SSPS20.0

Results: 101 children were diagnosed, the population is parity with respect to sex(53.5%F vs 46.5% M).The mean age was 8.03 years, DKA (8.1 +/- 3.8) versus NO DKA (8.2 +/- 3.7).The average HBA1C was 10.98%, there were no significant difference between time periods, neither between patients with or without DKA. 70% of cases of severe DKA in 2016-2017 were older than 5 years. In the first period, 68.9% were referred from ambulatory, versus 43% in the second period (P <0.05).Significant differences were observed in patients who were referred from the emergency department between both periods 13.3% versus 30%.There were significant differences in patients with KAD referred from ambulatory in the second period 37.8%, versus 55% in the first period (P <0.05).They presented diabetes antibodies (positive antiGAD 31.6%, positive ICA 8.9% and positive Antithyrosine-phosphatase 36,7%, and Antiinsulin 50%.The average evolution to diagnosis was 2.8+/- 1.2 weeks.There were significant differences in both groups of patients (with and without KAD) in both periods, related with the season of the year at diagnosis,autoinmunity, coeliac disease and breastfeeding(P <0.05).

Conclusions: We believe that the promotion of diabetological education programs, awareness and clinical recognition, is fundamental since it would allow early diagnosis and corresponding decrease of the number of serious complications.

P3-P104

The Frequency of Diabetic Ketoacidosis Hospitalization in Siberian Children and Adolescent

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Introduction: Diabetic ketoacidosis is a frequent reason for hospital admission of children with newly diagnosed diabetes and the most frequent cause for hospitalization of children with poorly controlled diabetes.

Aim: To evaluate the frequency of diabetic ketoacidosis (DKA) hospitalization for pediatric patients and resources for its decrease.

Methods: Subjects included children <19 years who hospitalized with DKA in the pediatric diabetes care units during one year. The study entry criteria were venous pH <7.30 and/or bicarbonate <15 mmol/l and ketonuria. Patients were treated with fluid replacement and insulin infusion. The patients were analyzed according to demographic data, clinical and laboratory findings.

Results: One hundred and twenty four DKA patients (72 boys and 52 girls) were hospitalized during the study period. Pediatric DKA accounted for 1739 hospital days (median length of stay 14 days). 38 children (30.6%) were with new-onset diabetes. The frequency of DKA at onset of diabetes was equal 92%. The risk of presenting with DKA was the highest among patients <5 years old. 86 patients were with early diagnosed diabetes and duration of disease from 2 months to 12 years. Compared with single episode DKA, recurrent DKA (46.2%) was highest among children with poorly controlled diabetes, prepubertal and adolescent boys, children with difficult family circumstances.

Conclusion: The carried out research was shown high frequency of DKA at onset of diabetes, recurrent DKA among adolescent boys and children with difficult family circumstances. Opportunities exist to reduce DKA hospitalizations for children with diabetes with clinical and policy interventions targeted to this population.

P3-P105

Monogenic Diabetes Cause by Mutation of the Gene HNF–1A

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Introduction: The MODY diabetes (Maturity Onset Diabetes of the Young) belongs to monogenic alterations group, the mutation of the gene HNF-1α is the most common and present an

autosomal dominant inheritance that causes dysfunction of the Beta pancreatic cell and alteration in the reabsorption of glucose to renal level, with age of variable presentations, it often leads to a misdiagnosis as type 1 diabetes mellitus.

Description of the Clinical Case: Present in a 3-Year-old patient that debuts with hyperglycemia without ketosis, that has being catalogued as type 1 diabetes mellitus, therefore it initiates treatment with insulin (basal- bolus) with low dose (0.3UI/Kg/day) and continuous monitoring system of glucose, being relevant in her clinical history the presences of antibodies negative and the low requirements of exogenous insulin after 2 years of evolution, with HbA1 6,5 %. The genetic study showed a mutation of the gene HNF-1a in heterocygosis c.62 C> G before described. With these findings, the treatment began with sulfunilureas to (0.07mg / kg / day) up to the maximum dose recommended (1.5mg / kg / day) without therapeutic awaited response.

Conclusions: We are with a patient that is showing a mutation of the HNF-1α gen located at the region of the promoter in heterozygosis c.62 C>G of early beginning, leaving in evidence that this entity has a wide variability, not only in the age of beginning but in the response to the treatment with sulfunilureas.

P3-P106

Reversibility of Early Acute Diabetic Neuropathy (DN) in Adolescents with Type 1 Diabetes Mellitus (T1D)

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Introduction: Diabetic neuropathy (DN) is a common complication of type 1 diabetes mellitus (T1D) with significant morbidity in adulthood. The association between DN with long term poor metabolic control is well established. However, acute painful DN may present early in the course of the disease and may be reversible.

Case presentation: A female adolescent, aged 12 years, with a T1D duration of 9 months, presented with acute metabolic derrangement (HbA1c:11%) due to eating disorders. She reported omission of meals and insulin doses in an attempt to reduce her weight. The patient complained of numbness and burning sensation in the limbs. Nerve conduction studies (NCS) were indicative of demyelinating deficits in sural and peroneal nerves, which improved within 2 years, with a progressive decline in HbA1c values (7.6%) and the resolution of the eating disorder by psychiatric support.

Additionally, an adolescent boy (age: 16 years, T1D duration: 2.5 years), presented with painful DN in the lower limbs, during a period of dramatic deterioration of his metabolic control. During a 4 month period HbA1c values increased from a previous mean of 6.2% to 9.5%. NCS depicted demyelination in sural and peroneal nerves. His symptoms resolved and the electrophysiological parameters normalized with intensive follow-up and improvement of HbA1c within 6 months (HbA1c:7.2%).

Conclusions: Acute DN may present in adolescent patients with T1D, early in the course of the disease and may be also associated with eating disorders. Nevertheless, the symptoms and electrophysiological findings can be reversed with the achievement of optimal metabolic control. However, long-standing hyperglycemia can cause permanent nerve impairment. Intensive follow-up is needed to assure that adolescents with T1D maintain a near normoglycemic profile, in order to prevent or even reverse the evolution of DN.

P3-P107

The Value of Continuous Hemodiafiltration in Rescuing Children with Severe Diabetic Ketoacidosis

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Objective: To explore the value of continuous hemodiafiltration in rescuing children with severe diabetic ketoacidosis.

Method: Two children with severe diabetic ketoacidosis were studied in regard to clinical manifestation,laboratory examination and treatment and of the relevant literature was reviewed.

Result: Case 1 was a girl of 13 years 5 months old,who was diagnosed as "Type 1 diabetes mellitus,Diabetic ketoacidosis and Acute kidney injury(3stage)".After fluid infusing and blood sugar lowering with insulin,the metabolic acidosis could not be corrected. The girl was in a coma state with acute kidney injury.After Continuous hemodiafiltration (CHDF), both DKA and kidney injury was corrected. Case 2 was a girl of 2 months 8 days old,who was diagnosed as "Neonatal diabetes mellitus,Diabetic ketoacidosis and Hyperglycemic Hyperosmolar State".The diabetic ketoacidosis was corrected and the hyperglycemia and hyperosmotic state was improved after CHDF.

Conclusion: CHDF is of great clinical value for saving patients with severe DKA, hyperglycemic hyperosmolar status, or renal failure.It is worthy of promoting.

P3-P108

Psychosocial Risks, Comorbidities and Health Events During the Follow-Up of Children and Adolescents with Type 1 Diabetes

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Background: Psychosocial factors and health events are important for patients with chronic diseases such type 1 diabetes (TD1).

Objective and hypotheses: The aim was to explore the psychosocial factors, health events and comorbidity found at diagnosis and during the follow up of children and adolescents with type 1 diabetes. Also to analyze the association between socioeconomic status and glycaemic control.

Method: Medical charts of children between 2-18 years old with type 1 diabetes were reviewed. All of them were type 1 diabetic patients followed by the Paediatric Endocrinology team in our hospital from 2010 to 2017. Diabetes care includes: 1 week of hospitalization at diagnosis, diabetological education, 5-6 outpatient visits per year, and phone or email support. Insulin regimen: 52 children with basal- bolus, with rapid-acting and long-acting insulin analogues, 3 children using continuous subcutaneous insulin infusion (CSII). All were instructed in carbohydrate counting. 18 (32.72%) children used continuous glucose monitoring system (CGMS).

Results: Fifty five TD1 children (19 girls (34.54%) and 36 boys); mean age at diagnosis 93.36 +- 44 months, (range 21- 198); months of follow up were 61.41 +-41.83 (range 1-168); 38 children were Spanish and 17 immigrants (30.90%), most from Morocco or Romania. Prediagnostic diseases were: 2 celiac disease, 2 thyroiditis, 2 IgA deficiency, 1 Down síndrome, 1 viral miocarditis, 3 preterm, 2 twins and 1 triplet. Six (10.9%) children had relatives with DM1 and 7 (12.72%) with tyroid autoinmunity. Diabetic ketoacidosis was found in 17 debuts (30.09%). Mean HbA1c at diagnosis was (11.2%+- 2.45) (range 5.3-16.2%). Mean Anti-GAD was 198 +-528 (range 0-2500).

Follow up: Mean last HbA1c was (7.8% +- 1.25) (range 5.4-11.5%); 9 (16.36%) severe hypoglycemia occurred; 19 (34.54%) children were hospitalized after the debut (ketoacidosis, severe hypoglycemia, poor control or infectious diseases). In 8 cases (14.54%), family collaboration was insufficient; 8 (14.54%) children had poor school adjustment, and 2 has learning impairment (Down symdrome, limbic encephalitis). 12 (21.81%) adolescents had psychiatric or psychosocial problems. One girl had autoimmune limbic encephalitis with psychosis, intellectual disability and refractory epilepsy that improved with IV immunoglobulin.

Six (10.9%) children had dyslipemia; 5 (9.09%) celiac disease;

7 (12.72%) thyroiditis (5 hypothyroidism); 6 (10.9%) microalbuminuria; none ocular involvement; 2 pancreatitis and 1 atrophic gastritis. Weight and height development were normal except 1 short stature and 5 overweigth.

High socioeconomic status, not be an immigrant and CGMS, were significantly associated with better glycaemic control.

P3-P109

Clinical Profile and Outcome of Diabetic Ketoacidosis in a Tertiary Care Teaching Hospital of a Developing Country

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Objectives: Diabetic Ketoacidosis (DKA) is a dreaded complication and due to a paucity of studies on Paediatric DKA from India, we studied its clinical profile and outcome over the last 03 years

Methods: A retrospective chart review was used to obtain demographics, clinical presentation and various laboratory parameters on presentation of DKA in children less than 12 yrs of age.

Results: See Tables 1-3**.**

Conclusions: The mean age, sex and anthropometric parameters did not differ significantly. Laboratory parameters or the incidence of complications also did not differ significantly. However, the mean time of resolution is significantly higher in the new-onset group (p-value<0.01).

Table 1. Demographic parameters of study cases (n = 20) (for Abstract no P3-P109)

Variables	DKA in New–Onset DM (n=11) Mean (95%CI of Mean), OR n (%)	DKA in Diagnosed DM (n=9) Mean (95%CI of Mean), OR n (%)	All DKA cases (n=20) Mean (95%CI of Mean), OR n (%)	P-value
Age (years)	8.5 (6.8–10.2)	9.2 (6.8–11.5)	8.8 (7.5–10.1)	0.616^{NS}
Age groups				
5–10 years	7 (63.6)	4 (44.4)	11 (55.0)	0.653^{NS}
10–12 years	4 (36.4)	5 (55.6)	9 (45.0)	
Male Sex	6 (54.5)	1 (11.1)	7 (35.0)	0.070^{NS}
Anthropometry				
Height (cm)	122.6 (112.7–132.6)	121.2 (113.6–128.8)	122.0 (116.1–127.9)	0.810^{NS}
Weight (kg)	20.3 (16.7–23.9)	19.2 (16.3–22.0)	19.8 (17.6–21.9)	0.597^{NS}
BMI (kg/m^2)	13.7 (11.2–16.1)	12.9 (12.3–13.6)	13.3 (12.1–14.6)	0.568^{NS}

NS – Statistically not significant.

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Table 2. The clinical outcome of study cases (n=20) (P3-P109)

Glycaemia				
Blood Glucose (mg%)	542.4 (468.6–616.1)	537.4 (490.9–583.9)	540.1 (498.6–581.7)	0.906^{NS}
HbA1C (%)	12.6 (11.7–13.6)	12.2 (11.3–13.1)	12.4 (11.8–13.0)	0.460^{NS}
Urine Ketones				
Moderate	3 (27.3)	5 (55.6)	8 (40.0)	0.343^{NS}
Severe	7 (63.6)	4 (44.4)	11 (55.0)	
Highly Severe	1 (9.1)	0	1 (5.0)	
pH	7.15 (7.05–7.25)	7.19 (7.14–7.25)	7.17 (7.11–7.22)	0.390^{NS}
HCO3	9.0 (6.3–11.7)	10.5 (8.5–12.5)	9.7 (8.1–11.3)	0.358^{NS}
Sodium	140.1 (135.0–145.2)	137.8 (133.7–141.9)	139.0 (135.9–142.1)	0.450^{NS}
Potassium	4.2 (3.7–4.8)	4.7 (3.8–5.7)	4.5 (3.9–4.9)	0.292^{NS}
Chloride	105.4 (100.9–109.9)	106.4 (101.4–111.5)	105.8 (102.8–108.9)	0.720^{NS}
Time for resolution	31.6 (24.8–38.5)	18.4 (13.9–22.9)	25.7 (20.7–30.7)	0.003**

NS – Statistically not significant.

Table 3. Associated complications (P3-P109)

UTI	0	3 (33.3)	3 (15.0)	0.206^{NS}
Pneumonia	1 (9.1)	1 (9.1)	2 (10.0)	
Cerebral edema	2 (18.2)	0	2 (10.0)	
Other	0	1 (9.1)	1 (5.0)	

NS – Statistically not significant.

P3-P110

Diabetes Mellitus, Autoimmune Hemolytic Anemia, Hepatosplenomegaly and Lymphadenopathy: A Rare Association in Chinese Children

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Objectives: To report a case of concomitance of diabetes mellitus, autoimmune hemolytic anemia, hepatosplenomegaly and lymphadenopathy in a 7-year girl.

Methods: Retrospective review of medical records of a patient with multiple autoimmune diseases followed at the Departments of Endocrinology and Metabolism, Children's Hospital of Fudan University. This rare case was undergoing whole exome sequencing.

Results: This girl 2 year was diagnosed with hepatosplenomegaly and lymphadenopathy due to symptoms. When she was 7 years old, she was diagnosed with diabetes due to symptoms, laboratories work up and multiple dose injection insulin therapy was started. Her sister died of diarrhea during infant period. Her Hemoglobin fluctuated between 95 and 123 g / L with positive autoantibodies ANA and ANCA. Her family history was very unique. Her brother was diagnosed with neonatal diabetes and died of diarrhea at the age of one-month. A compound heterozygous mutation (p.E22X and p.Q114X) was found in exons 1 and 3 of the *IL2RA* gene.

Conclusions: This case report showed that a compound heterozygous *IL2RA* mutation contributed to autoimmune phenomena in this Chinese child.

P3-P111

Type 1 Diabetes and Central Precocious Puberty a Rare Association

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Introduction: In girls, precocious puberty is defined as the sign of secondary sexual characteristics occurring before the age of 8 years in Caucasian girls.

Type 1 diabetes (T1D) is a rare association with precocious puberty. We discuss through this case, the involvement of type 1 diabetes mellitus in the

onset of early puberty from a review of the literature.

Observation: We report the case of precocious puberty in a 6-year-old girl followed for T1D since the age of 3,5 years, the T1D was well-balanced under insulinotherapy.

At the age of 6 years, the child presented signs of precocious puberty. Clinical examination revealed a Tanner stage III for breast development and Tanner stage III for pubic hair development with statural advance of more than 2 SD. The LHRH test was for central precocious puberty, and brain MRI had no abnormal lesion or tumor posing the diagnostic of central precocious puberty. Under LHRH analogues,we noted a regression of bilateral mammary hypertrophy, the standardization of the speed of growth and regression of signs of estrogenic impregnation on pelvic ultrasound.

Conclusion: Precocious puberty and type 1 diabetes is rare association. The relationship between these two pathologies has not been determined.

P3-P112

Diabetic Ketoacidosis Among Egyptian Children with Type 1 Diabetes: 3-Years Study

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Introduction: Diabetic Ketoacidosis (DKA) is one of the acute complications of type 1 diabetes. It is a life-threatening condition that varies in severity and prognosis from patient to another. In Egypt, there is no available data about the socio-demographic characteristics as well as the DKA severity determinants among children

Objective:

1. To identify demographic, clinical and laboratory variables of pediatric patients diagnosed with DKA at Suez Canal university medical center through three years;
2. To identify the determinants of DKA severity among Egyptian children

Methods: We conducted a retrospective study from medical records of children and adolescents presented with DKA at emergency department of a Suez Canal university pediatric hospital between 2014 and 2016. DKA severity was categorized as mild, moderate, or severe. Data collected obtained demographic, clinical and laboratory variables. Multivariate regression analysis was applied to identify determinants for of DKA severity.

Results: From a total of 86 DKA patients, Females (61.6 %) were almost twice number of males (38.4%). one-third of patients (31.4%) have a positive family history of diabetes. More than 65% were newly diagnosed to have type 1 DM at admission. The most frequently presented symptoms at admission were vomiting, polyuria, and abdominal pain. mean HbA1c was 10.6 ±2.24 and mean random blood sugar at admission was 431 ±108 mg/dl. Blood gases parameters at presentation showed that mean pH was 7.18 ±0.15 and mean bicarbonate was 11.04 ±4.5. mean sodium and potassium levels were 136 ±10.5 and 3.9 ±0.68, respectively. Regarding symptoms, vomiting presentation was found to be significantly different among grades of DKA (p=0.041). There were also statistically significant differences in HbA1c (p=0.019), pH (p<0.01), bicarbonate (p<0.01), and sodium level (p=0.02) among different grades of DKA. Multivariate analysis showed that DKA severity isn't associated with any of demographic, clinical or laboratory variables.

Conclusion: Although we couldn't find potential determinants of DKA severity in our sample; vomiting, serum sodium, and HbA1c can be possible predictors for further wide-scale study.

P3-P113

Fructosamine Level in Type 1 Diabetes Mellitus Children Performing Ramadhan Fasting

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Background: Ramadan fasting may influence metabolic control in Type 1 Diabetes Mellitus. Fructosamine is an accurate metabolic control in a short-term period. Comparison of fructosamine between intensive and conventional insulin regimen in T1DM children has not been widely studied.

Objective: To compare fructosamine level between intensive and conventional insulin regimens during Ramadan Fasting in T1DM.

Methods: Observational analytic study was conducted in endocrine-outpatient-clinic Dr.Soetomo hospital during Ramadan 2013 and 2015. Inclusion criterias were T1DM in children performed Ramadan fasting before, and already diagnosed >6 months before the study. Exclusion criterias were severe hypoglycemia < 3 months before the study, recurrent hypoglycemia(blood glucose levels<65mg/dl), hyperglycemia with diabetic ketoacidosis (DKA) < 3months before study conducted, hospitalized patients, kidney and liver disease and severe malnutrition. Fructosamine was evaluated 3 times (one week before, in the middle and at the end of Ramadan fasting). Daily blood glucose monitoring, DKA events, and hypoglycemia episodes were observed. Patients were divided into 2 groups: group 1 given intensive-treatment (Detemir, short-acting insulin) and group 2 conventional (intermediate, short-acting insulin).

Results: Twenty-four T1DM fasting children were included. Fourteen were girls, mean age 14.92(range 9-18) years. Nine children in group 1 and 15 children in group 2. Duration of illness was 4.48(range1-9) years. Mean of fructosamine before Ramadan:518.5(254-757)µmol/L, middle:502.8(276-745)µmol/L, and at the end of Ramadan:495.3(267-743)µmol/L (P>0.05). Comparison of Fructosamine level between groups before (497.1vs.531.2 µmol/L,P=0.5), middle (458.2vs.529.6 µmol/L,P=0.1) and at the end of Ramadan(467vs.512 µmol/L,P=0.4) were not significant(P>0.05). Most subjects(91.6%) had hyperglycemia without DKA with a mean of frequency 17.3 times. Neither symptomatic hypoglycemia nor DKA was found in this study.

Conclusions: Fructosamine level during Ramadan fasting between intensive and conventional insulin regiments were similar. Type-1 DM fasting children did not experience symptomatic hypoglycemia or DKA.

Keywords: fructosamine, metabolic control, T1DM, ramadan fasting,insulin

P3-P114

Metformin Therapy Ina Lean Adolescent Girl with Prediabetes Dysglycemia Treated: Good Response

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Background: Metformin (dimethylbiguanide) is the most widely prescribed treatment for children with T2DM. Long term controlled studies are still required to assess its effect on prediabetes dysglycemia in children

Case presentation: A 13-year-old lean adolescent girl presented to PEC with a day history of difficult breathing associated with dry cough. No history of fever, abdominal pain, vomiting or change in bowel motion. She had a 10 months' history of excessive water drinking and polyuria and mild weight loss. She had a family history of bronchial asthma and T2DM (both parents' families). Examination revealed: RR= 34 /min, HR= 123b/min, BP 130/80 mmHg, BMI 20kg/m2. She did not have acanthosis nigricans or goiter. The diagnosis of atypical pneumonia was entertained and treated. Lab showed hyperglycemia, BG = 16.2mmol/L, PH = 7.35, HCO3= 19.7 mmol/L. Repeated lab revealed: Blood glucose (BG) 28.5 mmol/L, PH 7.19, HCO3 = 11 mmol/L and PCO2 = 28.7mmol/L. She was started on insulin infusion therapy and IV Fluid therapy as per DKA protocol. Further labs showed HbA1C=5.7%, plasma insulin = 239 uU/mL (High), C-peptide = 14.68 ng/mL (High). Acidosis and glycemia was corrected in 12 hours. Follow up of her BG readings for 3 days, without insulin therapy, were: (Before breakfast = (5.1- 6.1 mmol/L), before lunch (5.2- 7.2 mmol/L) and before dinner (5.5- 8.9 mmol/L). SBGM showed postprandial hyperglycemia (7.7- 9.4mmol/L). OGTT (using 75 g Dextrose) showed fasting BG = 5.4mmol/L, and 2hrs BG = 7.9mmol/L with fasting insulin level = 15.2mU/mL. HOMA-IR was 3.7. Anti-GAD antibodies were undetectable. Continuous glucose monitoring (CGMS) tracing showed glucose peaks up to 11.7 mmol/L 1hour after meals. 18% of the time her glucose was > 7.8 mmol/L and 82% between 3.9-7.8 mmol/L. Metformin 500mg BID was prescribed with lunch and dinner. The table shows the average (mean) of her BG (mg/dl) readings by glucometer before versus after Metformin therapy.The mean BG readings decreased by a mean of = 1.1 mmol/L (20 mg/dl) after Metformin therapy.

Conclusion: Metformin successfully corrected dysglycemia in a lean adolescents with prediabetes.

P3-P115

Association Between Thyroid Stimulating Hormone and Hemoglobine A1c in Type 1 Diabetes Mellitus Children

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Background: Type 1 Diabetes Mellitus children are at risk to suffer from thyroid dysfunction. The association between thyroid stimulating hormone and hemoglobin A1c is still controversy.

Objective: To determine the association between thyroid stimulating hormone and hemoglobin A1c in type 1 Diabetes Mellitus children.

Methods: We conducted a cross sectional study from January - June 2017 in pediatric endocrine outpatient clinic dr Soetomo Hospital. Subjects were Type 1 DM children aged 7 until <18 years old. Exclusion criterias were diabetes ketoasidosis, previously diagnosed thyroid problems and patients hospitalized in PICU.

Results: 34 patients included in the study. Nineteen (54.3%) were male, mean of age was 11.3 years old. Mean of duration of diabetes was 3 years, mean of thyroid stimulating hormone was 3.76mIU/L. The lowest was 0,033 mlU/L and highest 45,300 mlU/L. There were 2 male patients with high TSH level, 25 and 45 mIU/L respectively. These patients then follow up for FT4 and we have normal FT4. So we diagnose patients as subclinical hypothyroidism. The association of duration of diabetes and Thyroid stimulating hormone was r_s=-0,068; p=0,703 (p>0,05). The association of thyroid stimulating hormone and hemoglobin A1c was r_s = -0,017; p=0,925 (p>0,05).

Conclusion: There wasn't any association between thyroid stimulating hormone and hemoglobin A1c in T1DM children.

Keywords: thyroid stimulating hormone, hemoglobin A1c, type 1 diabetes mellitus children.

Table 1. (for ABstract no P3-P114)

Mean BG	Fasting	B lunch	A 2 hrs*	B dinner	A 2 h
Before Metformin	5.5	6.0	6.8	6.8	8.2
After Metformin	4.9	6.7	5.4	5.8	6.5
Difference	-0.6	0.6	-1.4	-1	-1.7

*After Metformin 500 mg dose. B = before, A– = after.

P3-P116

Monogenic Diabetes in 2 Years and 4 Months Old Girl: Is It DEND?

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Background: Monogenic forms of diabetes are still rare and not well understood. Their prevalence accounting for 1–4% of pediatric diabetes cases. Several genes encoding proteins important to β-cell function or regulation have been identified that lead to monogenic diabetes. However, awareness of these conditions may be lacking, and screening for them genetically is not routinely undertaken due to lack facility.

Objective: To report a case diagnosis and management of monogenic diabetes and DEND in 2 years and 4 months old girl.

Case: Two years four months old girl, BW 8.4 kg (< -3 SD), BH 79 cm (< -3 SD), came to emergency department of Dr. Soetomo General Hospital. She referred from private hospital with DKA, pneumonia, seizure and loss of consciousness (GCS 113). In the past 2 months she has polydipsia, polyuria, polyphagia and loss of weight. Abdominal pain and difficulty of breathing were found in the past 4 days before admission. She has developmental delay such as motoric delay, speech delay and has involuntary movement too. Laboratory examination revealed BS 477 mg/dL; pH 7.32; HCO3 9.8; ketone 4.8; HbA1c 4.7; c-peptide 1.35 (1.1-4.4 ng/ml). Treatment with Glibenclamid and novorapid can control BS within normal limit.

Conclusion: The girl was diagnosed DEND using criteria developmental delay, epilepsy and diabetes. To confirm diagnosis of DEND needs genetic mutation testing.

Keywords: Monogenic diabetes, DKA, DEND

P3-P117

Compliance for Monitoring of Glycemic Control in Children with Type 1 Diabetes

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Background and Aims: To estimate attachment of children with type 1 diabetes to self-control of blood glucose with help of automatically data processing system of glycemic control.

Method: We have checked 54 patients with first type diabetes at the age 14 ± 3, 4 years old (32 males, 22 females), divided into two age groups: from 0 to 14, and 15-18 years old. There were 54 glycemic checking with help of automatic system of the analyzing self-monitoring results quantity of self-control of blood glucose per 24 hours estimated based on last. The compliance self-monitoring index was calculated (quantity of the tests done/quantity of the recommended tests (5)*100%). Compliance index more than 90% has considered acceptable.

Results: Median quantity of average checking are 4,3 [3,2; 5,3] a day, median compliance index is 85 % [64;106], average value of HbA1c 8, 1 % ± 1,8, shows insufficient compliance in total group.

Median quantity of average checking in girls' cases are much higher (Me 4,8 vs 3,6, p=0,04), either the compliance self-monitoring index too (Me 96, 3 vs 72,9 %, p=0,03).

In two age groups - from 0 to 14, and 15-18 years old, median quantity of average checking (Me 4,4 [3,6; 6] vs 3,7 [2,6; 4,7]), p=0,08, and the compliance self-monitoring index (Me 87,2% [73; 116] vs 74% [51; 93,2]), p=0,09 didn't differ significantly. But in group 0-14 years old average HbA1c value 7, 6 % ± 1,1 is much lower, than in 15-18 years old group -average HbA1c value 8, 6 % ± 2,1.

Patients with HbA1c <7,5% (21/54, 39%), (average HbA1c value 6,7%±0,5) have better glycemic control. Median quantity of average checking is 4,7 [3,6; 6,1], median compliance index is 93 % [73;122], than patients with HbA1c ≥7,5% (33/54, 61%), (average HbA1c value 9%±1,8) - median quantity of average checking is 3,9 [2,6; 4,6], p=0,05, median compliance index is 78 % [52;92], p=0,04.

Conclusion: Automatic system of the analyzing and estimation of the glycemic control gives opportunity to estimate the compliance of self-monitoring tests in first type diabetes in children and shows satisfactory to self-monitoring skills. However, girls' cases were better than in boys' cases. Optimal management of type 1 diabetes in elder group presumably depends not only on frequent blood glucose monitoring, but other factors, such as puberty, stress, eating disorder, adult supervision too.

P3-P118

Ketogenic Diet in a Child with Diabetes and Global Developmental Delay

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Effective management of Type 1 diabetes can be challenging

We would like to discuss the management of a 7 year old boy with Type 1 Diabetes, Lissencephaly and global severe developmental delay with medically refractory epilepsy who was introduced to and managed on a Ketogenic diet to try and improve his seizure control

He is non mobile and non-verbal and purely gastrostomy fed. He has diagnoses including;

Lissencephaly and band heterotopia, absent corpus callosum, microcephaly, cortical visual impairment, severe global developmental delay and medically refractory epilepsy not controlled on multi drug therapy

His Diabetes was managed prior the ketogenic diet with rapid acting insulin aspart via an insulin pump with Continuous glucose monitoring, sensor augmented pump therapy

His Diabetes control was satisfactory as evidenced by his HbA1c of 53mmol/mol in October 2017

As his seizure control was worsening a classical ketogenic diet therapy was proposed.

He was started on a diet that would provide 930Kcal and 24 grams protein,90-60 grams Carbohydrate and 52-60 grams LCT fat.

Gradually introduced over many weeks it was proposed to maintain his blood ketones between 2-3 mmol

This presented many challenges including identifying and differentiating ketosis which was diet induced and appropriate but identifying diabetic ketoacidosis (DKA) which would be fatal if untreated.

We did weekly venous blood gases to check his blood pH to see if rising ketone levels would affect his pH and blood gas as there was very little data available in the literature regarding this on a patient out of an intensive care setting

Blood ketones between 2-3 mmol were attained by week 5 of diet.

His blood gases remained stable and non-acidotic

We established that maintaining blood ketones between 2-3 mmol consistently did not make him acidotic on the blood gas

We continued with his ketotic diet for the next 4 months with no improvement of his seizures.

Therefore the diet was gradually discontinued.

His diabetes control improved during this time with the recent HbA1c being 45mmol/mol

This patient demonstrated the challenges in delivering ketogenic diet to a patient with Type 1 Diabetes and global developmental delay and inability to communicate

P3-P119

A Rare Cause of Severe Anemia in a Patient with Type 1 Diabetes

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Introduction: Anemia in children is still quite common, sometimes it is a secondary symptom of another rare disorder. Rendu-Osler-Weber disease, a genetically determined haemorrhagic diathesis, is characterized by the occurrence of vascular malformations leading to bleeding from the nose, skin and mucous membranes and to various internal organs. Diagnosis facilitates the occurrence of the disease in relatives of the first degree, however, due to the progressive nature of vascular anomalies (full phenotypic expression of the disease > 30 years of age), the diagnosis rarely occurs before 18 years of age.

Case report: We present a case of a boy with type 1 diabetes with severe anemia due to chronic epistaxis. The boy has been repeatedly hospitalized because of poorly controlled disease as a result of many years of neglect in self-control. For the same reason, the boy came to the local clinic in December 2016. In lab tests carried out at that time: HbA1c-10.3% and glucose records indicated numerous errors in insulin therapy, failure to comply with the diet. In routinely performed morphology - features of microcytic, non-pigmented anemia (Hb-7.6g/dl, Ht-29.7%, E-5.73mln/h, MCV-51.8fl, MCH-13.3pg, MCHC-25,6g/dl) and extremely low levels of iron with the absence of clinical symptoms beyond the marked pallor of the skin. In an in-depth interview, the boy has been feeling well, very active - regularly going to the gym, recurrrent nasal bleeding occurs for many months, appearing spontaneously or with minor nasal injuries, besides no other symptoms occur, and also nicotinism. Positive family history for Rendu-Osler-Weber disease in mother and sister was observed. Consulted by an ENT specialist - no signs of active bleeding - conservative treatment was recommended. Due to the deepening of disorders due to heavy epistaxis up to min. Ht 25%, Hb 6.4g%, he required transfusion of RCC, intravenous iron administration. Diagnostic procedures in the direction of vascular malformations has been extended to include imaging examinations - abnormalities in the MR of the head, abdominal and chest CT were not confirmed. As a result of the applied therapy, gradual suppression of bleeding and normalization of the RBC parameters were obtained. Unfortunately, further outpatient control indicates irregular application of the recommended therapeutic procedure - periodic recurrence of nose bleedings and reduction of iron level.

Conclusions: Rendu-Osler-Weber disease is one of the very rare causes of anemia. Lack of the patient cooperation may contribute to exacerbating the course of the disease.

P3-P120

Oral Gliclazide (A Sulfonylurea) Monotherapy Is Effective and Safe in the Management of T2DM in Children: A Case Report

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Introduction: Most of the oral medications available for treating type 2 diabetes (T2DM) have not been studied in children. T2DM in pediatric patients is usually treated with metformin and insulin. The use of other oral antidiabetic drugs is not clearly delineated in T2DM in children although potentially useful.

Case Report: A 13 year- old girl, presented with polyuria, polydipsia and weight loss (5 kg) for 2 weeks before presentation. Her Weight = 65.7 kg, Height = 152 cm (15th percentile) and BMI = 27 (>97th percentile). She had acanthosis nigricans but no goiter. Laboratory work up revealed Blood glucose = 27mmol/l, HbA1C = 11.6 %, insulin level 14.4 uU/ml (n= 2.0 - 23.0 uU/ml) and C-peptide= 1.15 ng/ml (n= 0.78- 5.19ng/ml). OGTT using 75 g of dextrose showed:

T2DM) was diagnosed. She was initially started on s.c insulin (basal/bolus regimen) (0.6 units/kg/day). After 6 months her HbA1C dropped to 5.9 %. Her weight increased to 70 kg. Another Dialectologist investigated the effect of oral Gliclazide 60mg once daily. OGTT on Glyclazide showed FBG = 6 mmol/L and 2h = 7.8 mmol/L. Insulin was stopped and patient started on 60 mg Gliclazide PO daily. Her BG pre meals as following: before breakfast before lunch (6.3-6.1mmol/L) and before lunch (6: 6.7 mmol/L)

Table 1. (for Abstract no P3-P120)

	Glucose (mmol/L)	C peptide (ng/ml)
0-hr	6.3	1.4
2-hrs	15.5	7.37

and before dinner (6-6.6 mmol/L). Her HbA1c continued to be 5.9: 6.2% in subsequent visits for 1 year. No hypoglycemia or other side effects was reported during this period. Her weight remained the same during the full year (70 kg).

Comment: Sulphonyl urea (Gliclazide) offers safe long-term control similar to insulin in our adolescent with type 2DM.

Conclusion: More studies are required to assess the efficacy and safety of its use in large cohort of children with type 2 DM.

P3-P121

Pediatric Stroke as the Presenting Symptom of New Onset Diabetes Without DKA

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Introduction: Neurologic symptoms, such as cerebral edema, stroke, and extrapontine myelinolysis, are rare in pediatric patients with type 1 diabetes mellitus (T1DM) in the absence of severe diabetic ketoacidosis (DKA) or chronically poor glycemic control. Ischemic or hemorrhagic stroke may account for 10% of intracerebral complications of DKA. DKA increases the risk for neurovascular compromise by several proposed mechanisms, including dehydration, hyperosmolarity, tissue hypoxia and acidosis. Neurologic complications of hyperglycemia in adult patients without DKA are reported frequently; however, there are rare reports of hyperglycemia without DKA and stroke in the pediatric population.

Case: We present the case of a ten year old, premenarchal, previously healthy, thin African American female, who presented to the emergency department with a two day history of right facial droop and right hemiplegia. Imaging showed an acute right thalamic ischemic stroke without vascular defects. An incidental finding of hyperglycemia (initial blood glucose 217 mg/dl, 12mmol/L) led to the diagnosis of new onset T1DM with a hemoglobin A1c of 8.4%, positive GAD-65, ICA512, insulin autoantibodies. She did not have ketosis (bicarbonate of 24mmol/L, negative urine ketones) and her screening for prothrombotic conditions was negative. Family history was negative other than a brother with sickle cell trait. She was treated with multi-dose insulin injection therapy. She returned to her neurologic baseline gradually over the subsequent year without stroke recurrence to date, two years later, despite suboptimal glycemic control due to nonadherence.

Discussion: Stroke at T1DM presentation is rare, especially in pediatric patients and in the absence of DKA. We are aware of only one other report of stroke in a child at diagnosis of diabetes without concurrent DKA, who had thiamine-responsive megaloblastic anemia that may have contributed to her clinical presentation. Hyperglycemia has been implicated in stroke risk but typically in association with concurrent comorbidities such as severe acidosis, metabolic syndrome, and dehydration.

Our case does not prove causality, but raises questions about the impact of recent onset hyperglycemia on stroke risk in pediatric patients. Therefore, we propose that diabetes care providers should consider early screening for stroke symptoms in pediatric patients with diabetes (including those without DKA), as prompt diagnosis and treatment of stroke decreases morbidity and mortality.

P3-P122

Challenges In Educating New Onset Type 1 Diabetes MellitusPatients: Can The Use of a Tablet be The Answer?

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Background: Educating patients and families on the management of Type 1 Diabetes Mellitus(DM) has always been a challenge. Some endocrinologists educate patients and families with new onset Type 1 DM in the inpatient setting, while others have tried to do this process as an outpatient given the changes in the limits of inpatient coverage. Given the challenges in the education process, we must find new and innovative ways to educate patients and families efficiently in order to equip them with the necessary skills to be successful in the management of Type 1 DM. In a world of smartphones and tablets as the mainstay of communication and sources of information, medical professionals can integrate these devices into the education of patients and families. Use of such a platform can make patients and families be more independent in the education process of newly diagnosed Type 1 DM patients.

Objective: To study whether the use of a tablet platform as an adjunct in the education of patients and families with newly diagnosed Type 1 DM could lead to improved understanding of diabetes management, leading to better HbA1C improvement, less hypoglycemia, as well less phone calls to the office.

Methods: We will randomize new onset Type 1 DM diabetes patients, so that 50% will only receive traditional diabetes education by nurses and the other 50% will recieve the tablet and traditional diabetes education. For the patients and families who will receive the tablet, the tablet will contain an education system with modules that teach the various aspects of Type 1 DM care. Each module will have a pre-test to assess the user's knowledge prior to viewing the modules. The modules have slides that models a lecture on the topic, as well as a video reviewing the topic. Following this, there will be a post-test to assess the user's knowledge. We will then compare patients and families who receive the tablet versus those that do not. The follow-up measures that will be compared consists of improvement in HbA1C, incidence of hypoglycemia and phone calls to the office. We will also survey the patients and families about the tablet education process.

Results: To be ascertained.

Conclusions: Our hope is that the patients and families using the tablet platform will become more comfortable with the management of Type 1 DM, which will result in better Hba1C improvement, less hypoglycemia and less phone calls to office.

P3-P123

AID-GM System (Advanced Intelligent Distant – Glucose Monitoring) to Monitor Health Status and Metabolic Control of Young People with Type 1 Diabetes

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Aim of the study: In type 1 diabetes, it is well recognized that collecting additional information about diet, physical activity, health status, stress and any patients' everyday behavior, is crucial to evaluate accurately metabolic control and therapeutic prescription adherence. The aim of this study is to test AID-GM (Advanced Intelligent Distant – Glucose Monitoring) a web-based platform, able of collecting automatically patient generated health data (PHGD) coming from different sources (blood glucose sensors, activity trackers, vocal messages, etc).

Methods: Thirty young TDM1 patients (over 11 years), under multiple daily injection therapy and using a FGM sensor (FreeStyle Libre®, Abbott Diabetes Care, Alameda, CA) will be overall enrolled. To determine time spent walking and sedentary time, a Fitbit device will be delivered. AID-GM will be used to automatically collect and share data coming from these sensors and provide several advanced analysis and visualization tools. Moreover, a mobile app will be used by patients to record vocal messages reporting any relevant health information. An automatic tool will extract the information from messages and store them into the system database. Finally, the system is able to automatically detect specific temporal patterns in single or group of patients' data, like for example *rebound effect* and *dawn effect*. The temporal analysis can be focused on specific time frames (e.g. days of the week, moments of the day, etc).

Results: The application is easy to use by both patients and care providers. It offers several functionalities such as: 1) rapid integration of clinical and health related data and sharing between patients and physicians, without having to use paper-based diaries; 2) active on-line inspection and analysis of real-time generated data for health status monitoring and prevention/prediction; 3) active monitoring of treatment outcomes (even remotely); 4) health-related data access. Finally, a potential usage of the platform will be in the context of clinical research trials running in realistic day-by-day settings.

Conclusions: the platform supports effectively home care supplying every information and analysis tools useful to increase knowledge about the factors influencing the patient's glucose metabolic control. Using the platform, it will also be feasible to design observational clinical trials collecting PHGD at low cost with long follow-up with the aim of deriving model-based indexes of glucose metabolism and increasing the insight on basic mechanisms underlying diabetes disease.

P3-P124

Continuous Glucose Monitoring Results of Our Cases with MODY Type 2 Diabetes

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Introduction: The most common type of diabetes in childhood is type-1 diabetes. The group of diabetes called MODY (maturity-onset diabetes of the young) is rarer. Mutations that occur in glucokinase gene cause disruption in the perception of the resultant glucose level and, consequently, impaired insulin release, leading to the development of MODY-2. In this case, resulting hyperglycemia is usually at a mild, non-progressive level and does not require insulin therapy. For this reason, medical treatment is rarely recommended for the patients.

In our clinic, we performed continuous glucose monitoring (CGM) in MODY-2 patients who were diagnosed by genetic analysis. With this study, we aim to reveal the presence of hyperglycaemic periods in a day.

Method: CGM was performed for 6 days in 8 patients who were followed up in Erciyes University Pediatric Endocrinology Clinic and identified mutation related to MODY-2 in GCK gene. The attending symptoms, the age of diagnosis, and the laboratory values were recorded.

Findings: Four of the patients were female and four were male. Two of the patients were admitted to the hospital with complaints of drinking too much water and frequent urination, while 2 were admitted with stress-induced hyperglycemia. The other 4 patients were initially not symptomatic and hyperglycemia was detected on screening tests for different reasons. At least one of the parents of all patients had blood glucose levels above normal ranges. The mean age of the patients at the time of diagnosis was 10.4 (2.81-17.08). The laboratory evaluation at the time of diagnosis and during CGM are summarized in Table 1. 2 of the patients initially received short-course insulin treatment and none were using insulin at the time of the evaluation.

Conclusion: Patients diagnosed with MODY-2 may be either symptomatic or asymptomatic at the beginning. Although the HbA1c values of the patients were generally below 7.5, all patients showed a glucose elevation of about 50% and a high blood sugar value of 0.1-3% in relation to lifestyle and nutritional status. As can be seen from these patients, as long as they do not obey certain rules, they will not develop symptoms during the day but will have high sugar levels that can cause damage in the future similar to that caused by other types of diabetes. We think that continuous glucose monitoring may be useful for awareness and reminding the importance of lifestyle change.

P3-P399

Family Investigation and Clinical Phenotype Analysis of Type A Insulin Resistance Syndrome

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Objective: To study a large Chinese family with Type A Insulin Resistance Syndrome (TAIRS)and the members' clinical phenotypes. Explore their genotype-phenotype relationship between environmental factors and hereditary features,

Methods: 19 members of the family were investigated for their past history, dietary habits and living habits. PCR and Sanger sequencing were applied to detect mutations of the INSR gene among 6 core members from the Pedigree. Besides,fasting blood glucose and insulin were measured or oral glucose tolerance test was performed among the 6 members.

Results: (1) A heterozygous mutation C.3614C>T (p. P1205L) of the INSR gene was identified in 4 members from the core members,and the inheritance mode of the family was consistent with the autosomal dominant according to the pedigree. (2) The phenotypes of 4 members were prominently heterogeneous: the probands showed hirsutism, acanthosis nigricans, severe insulin resistance, diabetes; while the other 3 had no hirsutism or acanthosis nigricans,the father and the grandpa only showed impaired fasting glucose, while her little aunt was still healthy. (3) Phenotypic heterogeneity was associated with insulin levels, but not with environmental factors. Conclusion The C.3614C>T mutation underlies the disease in this pedigree. This mutation has not been reported in China. The gene mutation has phenotypic heterogeneity, the latter is associated with insulin levels.

Key words: Type A Insulin Resistance Syndrome, INSR gene, Mutation, Family survey

P3-P403

Epidemiology, Demographic Criteria and Risk Factors in Type 1 DM Egyptian Children; A Single Center Study

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Introduction and Objectives: Type 1 DM is a chronic metabolic disease. Its incidence is rising worldwide. We studied demographic criteria, risk factors and epidemiology of children with type 1 DM attending our diabetes control clinic..

Methods: This cross sectional study was conducted over 3214 children between 1-18 years who are diagnosed with type 1 diabetes and following up in DEMPU clinic, Cairo university children's hospital. Between April 2017- April 2018 all patients who attended the diabetes follow up clinic were included. History taking including age, age at diagnosis, gender, place of birth and living, consanguinity, family history, order of index case, socioeconomic status, vitamin D administration, feeding in first 6month, time of weaning, mode of presentation, complications of DM and receiving diabetes education. Thorough clinical examination including anthropometric measures, assessment of diabetes complications and/or comorbidities. Thyroid profile, microalbumine in urine, TTG, mean lipid profile, mean HbA1c during the preceding year were recorded from files.

Results: The mean age was 10.7 ±3.65 years, 48% females and 52% males. Consanguinity was positive in 37% of cases. 64% of cases had positive family history of a first degree member with diabetes. The order of index case was highest for the 2nd childe (33%). Mean diabetes duration was 40 months (range= 1-95 months). 89% of cases hadn't receive vitamin D supplements (p=0.01).70% were exclusively breast fed while 7% had early introduction of cow milk<12 months. 58% presented with DKA and required ICU admission for a mean of 12.8 hours ±4.2. Highest rate of presentation occurred in winter (45% p=0.02). Full course diabetes education was delivered to 74% of the patients and their caregivers. Regarding measurements, mean height SDS and weight SDS were 0.32±2.6 and 0.38±1.2 respectively. Mean HbA1c during follow up was 8.2 ±1.8%. Logistic regression statistics study used in this study to come out the most labile risk factors for type 1 DM. the study used the HbA1c level as an indicator for the risk factor. The study confirmed cow milk introduction before 1 year as a statistically significant risk factor (p <0.0001).

Conclusion: proper community awareness regarding type 1 DM to lessen the DKA at presentation. Improve vitamin D status among children, encourage exclusive breast feeding for the 1st 6 months and prevent cow milk intake before the age of 1 year.

P3-P407

Degludec Versus Glargine in Pediatric and Adolescent Patients with Type 1 Diabetes

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Introduction: To optimal glycemic control without hypoglycemia must be the aim of insulin treatment for all patients with type 1 diabetes (T1DM). Despite the advantages of the basal-bolus insulin regimens with MDI, hypoglycemia presents a major barrier in achieving desirable blood glucose levels. Degludec is a new basal insulin analog with longer half-life and lower variability.

Objective: To investigate the differences between long-acting insulins glargine and degludec, in real-life study in pediatric and adolescent patients with T1DM.

Materials and methods: This observational, retrospective study enrolled 19 patients with T1DM. They were on basal bolus therapy with Glargine administered once daily and pre-prandial insulin boluses. Blinded CGM (Medtronic iPro 2®) was chosen to monitoring glucose values. Glucose data obtained by CGM during treatment with Glargine and 3 months after switching to Degludec were compared. Each patient serves as a self-control. Data were analyzed by several indexes:

HbA1c, total insulin dose, basal/bolus ratio, average glucose and SD, fasting mean glucose, time in range (70-180 mg/dl), time

in hypoglycemia (<70 mg/dl, <54 mg/dl), time in hyperglycemia (>180 mg/dl, >250 mg/dl), hypoglycemia episodes and glucose variability (coefficient of variation (CV), MAGE, MODD and CONGA). Stastistical processing was performed using IMB SPSS Statistic 19. T Student test for paired samples.

Results: Nineteen patients with T1DM (10 boys, 9 girls, age 8-19, with an average duration of T1DM of 7 years, were on basal-bolus therapy with Glargine once a day and preprandial fast acting insulin boluses.

Reason of switching: hypoglycemia or variability.

Overall glucose control was the same between the two treatments, and HbA1c did not change after switching from Glargine to Degludec (7.05±0.7% vs 7.01±0.7%). Total daily insulin requirement was reduced in 10 patients, dependent on basal insulin.

Looking at hypoglycemia (n=16), a statistically significant increase in fasting mean glycemia was observed (120.4 vs 151.2, p=0.08). Time spent by patients in hypoglycemia (<54 and <70 mg/dl) was not statistically different between Glargine and Degludec.

Current tratment with Degludec, episodes of hypoglycaemia are reduced (11 vs 8, p=0.09).

Switching from Glargine to Degludec did no change in terms of daily glycemic variability, despite CONGA index with a significant increase.

Discussion: The potencial limitation of this study is the small sample size, but it shows that Degludec is effective as Glargine in glycemic control, without differences in glucose variability, and might be advantageous in patients with risk of hypoglycemia.

P3-P416

A Rare and Unexpected Cause of Diabetes in Childhood

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Background: Pancreatogenic diabetes is rare in children.The prevalence is 5-10% of all cases of diabetes in the developed world. The underlying pathophysiology is destruction of islet cells by pancreatic inflammation.

Case: A 15-year old previously healthy boy presented with polyuria, polydipsia, abdominal pain and loss of weight (LOW) over several weeks.Family history revealed a three-generational history of diabetes including reported type-1 (T1DM) and type-2 diabetes mellitus (T2DM).On examination he had mild epigastric tenderness, with moderate dehydration. His initial blood tests showed hyperglycaemia and high HbA1C.

Table 1. (for Abstract no P3-P416)

Test	Result	Normal range
Random blood glucose (BG)	18.8 mmol/L	<4–7
HbA1c	90 mmol/mol	<20–42
Amylase	185 IU/L	<25–125
Blood ketones	0.1 mmol/L	<0.3

An oral glucose tolerance test (OGTT) showed baseline BG (7.3 mmol/L) and c-peptide (274 pmol/L) both rising after 2-hour (BG 18.8mmol/L and c-peptide 498pmol/L).Diabetes autoantibodies (Islet cell, Islet antigen 2, and Glutamic acid decarboxylase) were negative.The results confirmed diabetes but not conclusive of either T1DM or T2DM.He was started on subcutaneous insulin (Glargine and NovoRapid®).Next generation sequencing for all known monogenic diabetes genes was negative.

In the following weeks the patient complained of possible symptoms of gastric outlet obstruction (GOO) with on-going central abdominal pain, LOW (8kg over 6 weeks), early satiety and pain on eating larger portions.A repeat amylase was very high (415 IU/L) and an abdominal MRI revealed a large pancreatic pseudocyst with pancreatic duct disruption.This confirmed diabetes secondary to chronic pancreatitis - also referred to as type 3c diabetes mellitus (T3cDM) or pancreatogenic diabetes.

Bloods for fat soluble vitamins (A,D and E) confirmed vitamin D deficiency, and he was commenced on vitamin D supplementation.His clotting profile was normal. Following endoscopic drainage of the pseudocyst his symptoms of GOO quickly resolved. His insulin requirement is slowly weaning.Further tests looking at genetic causes for idiopathic pancreatitis (SPINK1 and PRSS1 genes) were negative.

Discussion: T3cDM is a complex condition which unlike T1DM or T2DM is often complicated by co-morbidities such as malabsorption and malnutrition.It is mis-diagnosed as T2DM in over 87% of patients.Making the diagnosis of T3cDM is important in order to appropriately manage both the exocrine and endocrine pancreatic insufficiency.

Patients with T3cDM require insulin therapy more urgently than those with T2DM.Hence early pancreatic imaging is recommended in suspected cases.Avoiding alcohol and smoking will reduce pancreatic inflammation.Oral pancreatic enzyme supplementation may be required.

P3-P417

Study of Children with Type 1 Diabetes Mellitus of Long Duration Attending Alexandria University Children's Hospital

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Background: Type 1 diabetes mellitus (T1DM) is a complex metabolic disorder typically diagnosed in childhood and characterized by insufficient insulin production.

Diabetic complications are still a major concern as they constitute the main cause of morbidity and mortality in diabetic patients despite the advances in T1DM treatment. Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers; and autonomic neuropathy. Abnormalities of lipoprotein metabolism are often found in patients with diabetes.

Aim: The aim of this work was to study children with type 1 diabetes mellitus of long duration, attending the diabetes clinic of AUCH; with regard to adequacy of treatment and presence of complications.

Methods: This study was conducted on fifty children and adolescents with type 1 DM of long duration ≥5 years, attending the diabetes clinic of the AUCH. We investigated the presence of diabetic complications and their relation with the glycemic control, duration of diabetes and the age at diagnosis. All the patients were subjected to full history taking, physical examination and laboratory and radiological investigation (HbA1c, eGFR, microablumnuria, complete liver profile, lipid profile, celiac antibodies, thyroid profile, ultrasound abdomen, fundus examination and echocardiography) nerve conduction study to indicated cases.

Results: There was a significant correlation between last HbA1c and the presence of diabetic nephropathy in our cases (decreased eGFR and microalbuminuria). The use of basal bolus insulin was associated with good glycemic control and this was statistically significant.As regard the presence of fatty liver, diabetic retinopathy, lipodystrophy, there was no significant relation between last HbA1c and them. About the associated autoimmune diseases, Celiac disease was present in 10% of cases while 12% of them found to have hypothyroidism.

Fat, Metabolism and Obestiy P1

P1-P093

Functional Characterization of Novel and Known Genetic Variants in the Leptin Receptor (LEPR) Gene of Two Patients with Morbid Obesity

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Background: The leptin signaling cascade is a crucial regulator of satiety and energy homeostasis in the hypothalamus, comprising extracellular leptin binding to its receptor, phosphorylation and nuclear translocation of STAT3 (signal transducer and activator of transcription 3) and consecutively the generation of a central satiety signal via neuropeptide secretion. We identified three variants in the extracellular domains of the *LEPR* gene in two children with severe early-onset obesity and hyperphagia: a compound heterozygous deletion (*p.Y411del*) and missense mutation (*p.W664R*) in patient 1; and a heterozygous missense mutation (*p.R612H*) combined with two polymorphisms in patient 2. Whereas the *p.W664R* variant has been described in one obese patient with a homozygous mutation, the *p.Y411del* variant is completely unknown so far.

Objective: We investigated the functional impact of the detected variants as a potential cause for the severe obesity in our patients.

Material and methods: HEK293 cells were transfected with plasmids encoding either wildtype or mutant (*p.Y411del, p.W664R* or *p.R612H,* respectively) leptin receptor. *LEPR* expression and signaling following leptin stimulation was assessed via immunoblot and quantitative PCR analysis of cell lysates. Cell surface expression of the leptin receptor variants was evaluated with flow cytometry.

Results: Wildtype and mutant leptin receptors were expressed in HEK293 cells at comparable levels. Phosphorylation of STAT3 after leptin stimulation was absent in cells expressing the *p.Y411del* and the *p.W664R* variant, but only mildly reduced in cells with the *p.R612H* mutation.

Similar results were obtained, when mimicking (compound) heterozygous leptin receptor expression with combined *p.Y411del* and *p.W664R* expression or a variant receptor in combination with wildtype receptor.

Furthermore, we confirmed cell surface expression of leptin receptor variants by FACS analyses with only mild reduction in the expression of mutant leptin receptors.

Conclusion: For the first time, we detected a functional impact for the novel leptin receptor variant *p.Y411del*, as well as for (compound) heterozygous expression of the *p.W664R* variant, thus making it a likely cause for the early onset obesity in patient 1. The heterozygous *p.R612H* variant, however, appears unlikely to explain the phenotype of patient 2 from our experimental analyses.

P1-P094

Association of Single Nucleotide Polymorphisms in *TNFA*, *PNPLA3*, *ADIPOQ* and *APOC3* Genes with Obesity and Non-Alcoholic Fatty Liver Disease in North Indian Adolescents

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Background: Polymorphisms in several genes may be associated with a higher risk of obesity and non-alcoholic fatty liver disease (NAFLD).

Objective: To examine the association of single nucleotide polymorphisms (SNPs) -238G>A, -1031 T>C and -863 C>A of Tumor Necrosis Factor- α (*TNFA*) gene; rs738409 C>G of patatin-like phospholipase domain containing 3 (*PNPLA3*) gene; +276 G>T and +45 T>G of Adiponectin(*ADIPOQ*) gene and 455 T>C and 482 C>T of apolipoprotein C3 (*APOC3*) gene with obesity and NAFLD in north Indian adolescents.

Methods: In this case control study, 214 overweight/ obese adolescents aged 10 to 16 years and 86 healthy lean adults were enrolled. Ultrasonography was used to diagnose NAFLD and grade its severity. Body mass index, waist circumference, fasting plasma glucose, AST, ALT, and lipids were measured in the adolescents and controls; and serum insulin, adiponectin, apolipoprotein C3 and tumor necrosis factor-α (TNF- α) only in the adolescents. Genotyping was done for -238 G>A, -1031 T>C and -863 C>A of *TNFA*; rs738409 C>G of *PNPLA3*;+276 G>T and +45 T>G of *ADIPOQ*; and 455 T>C and 482 C>T of *APOC3* genes. The frequency of hetero- and homozygous variant genotypes of the SNPs were compared among the overweight/ obese adolescents as a whole, and among the subgroups without NAFLD, with mild NAFLD and with moderate or severe NAFLD, with the lean adult controls.

Odds ratios (OR, and 95% CI) for various genotypes in subjects in comparison to controls was calculated using multinomial logistic regression.

Results: NAFLD was present in 62.5% of the subjects, with the disease being mild, moderate and severe in 40.4, 18.8, and 3.3%, respectively. Variant (i.e., heterozygous and homozygous combined) genotypes of SNPs -1031 T>C and -863 C>A of *TNFA* gene were associated with overweight/ obesity with OR of 2.47 (1.46–4.18) and 2.52 (1.45–4.35), respectively. Wild genotype of +276 G>T of *ADIPOQ* gene was associated with overweight/ obesity with OR of 2.58 (1.40-4.75). The SNP 455 T>C of *APOC3* was associated with overweight/ obesity with OR of 2.00 (1.11–3.61). The SNPs 455 T>C of *APOC3* and rs738409 C>G of *PNPLA3* were associated with moderate or severe NAFLD with OR of 5.04 (1.62–15.67) and 2.39 (1.09–5.28), respectively.

Conclusions: The study provides useful insight into the contributory role of genetic polymorphisms in the pathogenesis of predominantly lifestyle related conditions of obesity and NAFLD.

P1-P095

Variation of Circulating Brain-Derived Neurotrophic Factor According to Gender, Body Mass Index and Metabolic Syndrome Parameters in Adolescents

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Background: Brain-derived neurotrophic factor (BDNF) plays a role in the central regulation of energy balance and has been associated with body mass index (BMI).

Objective: The aim of this study was to investigate potential differences in serum BDNF concentrations in adolescents by gender and BMI, as well as possible correlations of circulating BDNF with the adolescents' characteristics of metabolic syndrome.

Methods: Study participants included adolescent males and females, aged 12-20 years, who presented to the Centre for Adolescent Medicine and UNESCO Chair on Adolescent Health Care of the First Department of Pediatrics, from May 2016 to May 2017. Exclusion criteria included diabetes mellitus, other severe chronic disorder, chronic medication use and pregnancy. Anthropometric parameters (weight, height, waist and hip circumferences), blood pressure and fasting serum levels of glucose, triglycerides, high-density lipoprotein were measured and body mass index (BMI) was calculated for each study participant. Serum BDNF concentrations were measured by ELISA using the R&D Systems Quantikine ELISA kit. The sensitivity was 20 pg/mL, the intra-assay precision ranged from 3.8% to 6.2% and the inter-assay sensitivity ranged from 7.6% to 11.3%. Student's *t*-test and Pearson και Spearman correlations were used for statistical analysis.

Results: A total of 60 adolescents (31 boys, 29 girls), 12-19 years (mean age ± SD 14.1 ± 1.7 years) with BMI of 14.7-37.4 Kg/m^2 (mean ± SD 24,5 ± 6.6 Kg/m^2) participated in the study. Boys had significantly (P=0.019) higher BDNF serum concentrations (mean ± SD 23,376.5 ± 5,746.1 pg/mL) than girls (mean ± SD 19,189.3 ± 7,574.1 pg/mL). Adolescents of normal weight had significantly (P=0.001) lower BDNF serum concentrations (mean ± SD 18,554.0 ± 7,627.2 pg/mL) compared to the adolescents with overweight or obesity (mean ± SD 24,324.6 ± 4,783.1 pg/mL) and this difference was attributed to the girls. Statistically significant correlations across the study sample were found between BDNF serum concentrations and HDL (r_p=-0.421, P=0.001), triglycerides (r_s=0.377, P=0.003), waist circumference (r_p=0.394, P=0.002), hip circumference (r_p=0.266, P=0.042) and systolic blood pressure (r_p=0.299, P=0.023).

Conclusion: Serum BDNF concentrations appear to vary according to sex, BMI and metabolic syndrome parameters in adolescents. These findings need to be confirmed by future studies of larger adolescent populations.

P1-P096

Kisspeptin and the Genetic Obesidome

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Background: Kisspeptin (encoded by the *KISS1* gene in humans), originally described as a puberty onset regulating neuropeptide, is involved in many homeostatic systems, including nutrition status, glucose homeostasis, locomotor activity, etc. Thus, in today's obesity epidemic, kisspeptin is gaining increasing interest as a research target.

Aim: To construct an updated interactome of genetic determinants of obesity, including the kisspeptin signal transduction pathway.

Methods: Kisspeptin and obesity-related genes or gene products were extracted from the biomedical literature (Geronikolou 2017, Styne, 2017, Nead 2015, Huyene 2015, Schaaf 2013, Ckallis 2013, Mead 2007, Krude 1998). The interactions among the obesity-related genes or gene products, were generated and visualized by employing STRING v10 (Szklarczyk et al., 2015), with a high confidence interaction score of 0.7-0.97.

Results: The intermediate nodes predicted that KISS1 and KISS1 receptor are connected directly to the luteinizing hormone receptor (LHR), the gonadotropin-releasing hormone receptor (GNHR) and, indirectly, through them to propiomelanocortin,

glucagon, leptin and/or proprotein convertase subtilisin/kexin-type- 1. This interactome contains 46 nodes of gene- gene products of known and/or predicted interactions.

Conclusions: Our proposed updated obesidome includes kisspeptin and its connections to the genetic determinants of obesity. The gonadotropin-releasing hormone receptor, glucagon and proopiomelanocortin genes were identified as major "hubs" of the the obesidome, providing novel insights into body's energy homeostasis and an explanation for the earlier onset of puberty in obese girls.

P1-P097

Circulating Exosomal miRNAs Involved in the Pathogenesis of Children Nonalcoholic Steatohepatitis

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Background: The incidence of children non-alcoholic fatty liver disease (NAFLD) increased rapidly paralleled with the global burden of obesity and diabetes. Although most patients are nonalcoholic fatty liver, there are still a small part of them will progress to nonalcoholic steatohepatitis (NASH), fibrosis and cirrhosis. However, the diagnosis of NASH is based on the highly invasive tissue biopsy, so reliable circulating biomarkers are urgently needed. Exosomal miRNAs have attracted attention to provide further insights into NASH, and it may serve as biomarkers of children NASH.

Methods: Circulating exosomes were isolated from children diagnosed as NASH (n=3) and age matched health control (n=3) according to the protocol of Ribo^{TM} Exosome Isolation Reagent (for plasma or serum). Illumina HiSeqTM 2500 was performed to analyze the differential expression of exosomal miRNAs between the two groups. Bioinformatics analysis was applied to identify the molecular signature differences and search for potential biomarkers.

Results: Exosomes were validated by NTA and flow cytometry (CD81 and CD63). With Illumina HiSeqTM 2500, 40 miRNAs were differentially expressed ($|\log2(\text{fold change})| \geq 1$, $P<0.05$). Among which, miRNA122 was up-regulated while miRNA133a-5p was down-regulated most significantly. Gene Ontology (GO) annotation analysis showed these miRNAs involved in biological process, cellular components and molecular function. Pathway analysis revealed that PI3K–Akt signaling pathway, pathways in cancer and MAPK signaling pathway were significantly correlated with NAFLD.

Conclusions: 40 differentially circulating exosomal miRNAs were identified between NASH and health control group, which may involved in the pathogenesis of NASH and can be used as a potential biomarker for diagnosis of children NASH.

Keyword: Circulating exosomes, miRNA, Children, Nonalcoholic steatohepatitis

P1-P098

Placental Fatty Acid Profile, DNA Methylation and Adverse Metabolic Outcomes in the Offspring at School Age

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Background: The placenta plays a key role in regulating fatty acid (FA) transport from maternal to fetal circulation. An unfavourable FA profile in the placenta, reflecting an inadequate nutritional status during pregnancy, may cause changes in placental DNA methylation and negatively affect fetal growth and metabolic health of the offspring.

Objectives: We aimed to study the association of an unfavourable placental FA profile with placental DNA methylation of specific genes related to pre and postnatal growth and their correlation with metabolic parameters of the offspring at school age.

Methods: In a prenatal cohort of 81 pregnant-newborns pairs, placental FA profile was determined by gas liquid chromatography and DNA methylation of *C19MC, ZNF331* y *IGF2/H19* placental imprinted domains was determined by pyrosequencing. Newborns were followed up until school age (6 years) and metabolic (lipid profile, glucose, HbA1C, insulin resistance) and anthropometric (weight, BMI, body composition) parameters were assessed.

Results: An unfavourable FA profile [increased levels of saturated FA (SFA) and omega-6 and decreased levels of omega-3] was associated with hipomethylation of *C19MC* and hypermethylation of *ZNF331* and *IGF2/H19* genes (all $p<0.05$). Such unfavourable FA profile was also associated with increased visceral fat, total fat mass, glucose and HbA1C (all $p<0.05$) in the offspring at age 6 years and was a risk factor for increased visceral fat (odds ratio: 2.5; 95% CI: 1.2-5.9).

Conclusion: The placental FA profile associated with DNA methylation of specific genes related to pre and postnatal growth and metabolic parameters of the offspring at school age. Such FA profile may be used to identify those newborns at higher-risk to develop metabolic diseases later in life.

P1-P099

Association of Serum Fibroblast Growth Factor 21 and Irisin with Insulin Sensitivity Markers and Serum Lipids in 12-Year-Old Children

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Background: Among other cytokines, the hepatokine fibroblast growth factor 21 (FGF21) and the myokine irisin have been considered potential biomarkers for insulin sensitivity (IS). In adult studies, both of them have been found elevated in insulin resistant states.

Objective And Hypotheses: Our aim was to study whether serum FGF21 and irisin associate with markers of insulin sensitivity (IS) and serum lipids in 12-year-old children.

Methods: A total of 192 children (109 girls) were studied at the mean age of 12.25 years (range 12.01-12.73). Seventy eight of them had been born appropriate for gestational age (AGA), 70 small for gestational age (SGA), and 44 from preeclamptic (PRE) pregnancies as AGA. Fasting serum FGF21, irisin, insulin, HDL cholesterol (HDL-C), triglycerides, high-sensitivity (hs)-CRP, gamma-glutamyltransferase (GGT) and leptin were measured. IS was estimated by Quantitative Insulin Sensitivity Check Index (QUICKI).

Results: The means of serum FGF21 and irisin did not differ between the sexes or between the children born SGA, AGA or from PRE pregnancies ($p>0.05$ for all). In the whole study population, serum FGF21 had a positive association with irisin (beta=0.630, p=0.001) and negative associations with leptin (beta=-0.262, p=0.024) and HDL-C (beta=-0.602, p=0.043) [general linear model (GLM) analysis adjusted for sex, pubertal developmental stage, age- and sex-adjusted BMI, birth weight SDS and maternal PRE pregnancy history]. Apart from FGF21, serum irisin associated positively with insulin (beta=0.341, $p<0.001$), hs-CRP (beta=0.072, p=0.003), GGT (beta=0.536, p=0.003) and triglycerides (beta=0.154, p=0.041), and negatively with QUICKI (beta=-2.516, p=0.001). In a ROC curve analysis, irisin was able to weakly discriminate the children in the lowest QUICKI tertile [area under the ROC curve (AUC) 0.624 (95% CI 0.541-0.708), p=0.005], whereas neither irisin nor FGF21 could identify the children with the highest TG/HDL-C ratio.

Conclusion: In 12-year-old children, serum irisin was associated with triglycerides and markers reflecting reduced IS, whereas FGF21 was associated negatively with HDL-C and leptin independently of BMI. In ROC curve analyses, irisin could weakly distinguish the children with the lowest IS, whereas neither irisin nor FGF21 could detect the children with markers of dyslipidemia.

P1-P100

Serum Catestatin Levels in Obese Children and Adolescents

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Objectives: The obesity in population of children and adolescents is one of the biggest public health problems in word today. Early childhood obesity with cluster of metabolic disorders (insulin resistance, impaired glucose tolerance, dyslipidemia and hypertension) are risk factor for cardiovascular morbidly and mortality later in life. Catestatin is a Chromogranin A derived peptide which reduces hepatic/plasma lipids, plasma insulin, improves insulin sensitivity, reduces hypertension and inhibits obesity in murine models. In humans, there were few studies published witch showed level of catestatin is significant risk factor for hypertension in adult patients. To our knowledge, this the first report of serum level of catestatin in obese children and adolescents.

Methods: The study included 71 obese children and adolescent with body mass index z score > 2 and control group of 25 healthy non obese children and adolescents. Anthropometric assessment (height, weight, BMI, waist circumferences and blood pressure) and fasting laboratory assessment (glucose, insulin, lipids and catestatin) parameters were measured. Obese subjects were dived in two groups depending on the presence of metabolic syndrome, which was defined by IDF criteria.

Results: There was no significant difference in age (13.78 ± 2.26 vs. 13.48 ± 2.08 years, $P = 0.532$), gender (38 (53.5%) male and 33 (46.5%) female vs. 12 (48%) male vs. 13 (52%) female, $P = 0.635$) and pubertal status between obese and control group. Catestatin was significantly lower in obese subjects (10.57 ± 5.13 vs. 13.49 ± 6.18 ng/mL, $P < 0.05$). When we divided obese subjects in two groups with and without metabolic syndrome catestatin was significantly lowest in subgroup of obese children and adolescents with metabolic syndrome (8.52 ± 3.89, $P < 0.05$). Catestatin negatively correlated with both diastolic (r=-0.24, $P < 0.05$) and systolic (r=-0.23, $P < 0.05$) blood pressure.

Conclusions: In conclusion, this study demonstrated that obese children and adolescents had significantly lower catestatin levels in comparison with age and gender matched controls.

P1-P101

Circulating MOTS-C Levels Are Decreased in Obese Male Children and Adolescents and Associated with Insulin Resistance

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Background and Aims: A novel bioactive peptide, mitochondrial-derived peptide (MOTS-c), has recently attracted attention as a potential prevention or therapeutic option for obesity and type 2 diabetes mellitus (T2DM). MOTS-c profiles have not yet been reported in human obesity and T2DM. We aimed to determine circulating MOTS-c levels in obesity and explore the association between MOTS-c levels and various metabolic parameters.

Methods: In this case-control study, 40 obese children and adolescents (27 males) and 57 controls (40 males) were recruited in the Hubei Province of China in 2017. Circulating MOTS-c levels were measured using enzyme-linked immunosorbent assay (ELISA), clinical data (e.g., glucose, insulin and lipid profile) were recorded, and anthropometric measurements were performed. Finally, we investigated correlations between MOTS-c levels and related variables.

Results: MOTS-c levels were significantly decreased in the obese group compared with the control group (472.61 ± 22.83 ng/mL vs. 561.64 ± 19.19 ng/mL, $p < 0.01$). After classification by sex, MOTS-c levels were significantly decreased in obese male children and adolescents compared to their counterparts (465.26 ± 24.53 ng/mL vs. 584.07 ± 21.18 ng/mL, $p < 0.001$), while they were comparable between the obese and healthy female subjects (487.89 ± 49.77 ng/mL vs. 508.85 ± 38.76 ng/mL, $p > 0.05$). Further, MOTS-c levels were negatively correlated with body mass index (BMI), BMI standard deviation score, waist circumference, waist-to-hip ratio, fasting insulin level, HOMA-IR, and HbA1c in the male cohort.

Conclusions: Circulating MOTS-c levels were decreased in obese male children and adolescents and correlated with markers of insulin resistance and obesity. Although the role of MOTS-c as a treatment for obesity and diabetes in humans will requires further investigation, it is possible that a decline in MOTS-c might be a biomarker of insulin resistance during childhood obesity.

P1-P102

Plasma Adropin Levels Are Associated with Lipid Characteristics Amongst Children with Obesity

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Objective: This study is to evaluate the association among plasma adropin, leptin, lipopolysaccharide-binding protein (LBP) levels and lipid characteristics in children with obesity.

Methods: This was a cross-sectional study of children with obesity ranging from 5.5 to 12.5 years old, and age- and gender-matched children with normal weight were collected as control. Height, weight, waist circumference and hip circumference of all the participants were measured. The waist-to-hip ratios (WHR) were calculated. Plasma lipid characteristics including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-c) and low density lipoprotein cholesterol (LDL-c) were detected by standard methods, and plasma adropin, leptin and LBP levels were measured using the ELISA method.

Result: 39 children (18 females and 21 males, 9.70±1.71 year-old) with obesity and 29 age- and gender- matched normal weight children (16 females and 13 males, 8.98±1.98 year-old) were collected. Compared with the control group, the TG levels of obesity group were significantly higher and the HDL-c levels were significantly lower (1.18±0.58 vs. 0.75±0.19 mmol/L, 1.43±0.29 vs. 1.77±0.32 mmol/L, respectively, both $p<0.05$). The plasma adropin levels of obesity group was significantly lower than control group (2.59±0.57 vs. 4.27±1.25 ng/ml, $p<0.05$), and the plasma leptin levels of obesity group was significantly higher than control group (2324.82±1467.40 vs. 491.65±344.10 pg/ml, 38.87±10.79 vs. 31.24±14.34 ng/ml, respectively, both $p<0.05$). Among the children with obesity, Pearson correlation analysis showed plasma adropin levels were negatively correlated with TC and LDL-c ($p<0.05$), plasma leptin levels were positively correlated with TC ($p<0.05$). There was no association between plasma adropin levels and leptin/LBP ($P>0.05$).

Conclusion: Children with obesity had lower plasma adropin and higher LBP levels, which were associated with lipid characteristics, suggesting adropin and LBP may be involved in lipid metabolism. The role of adropin in the development of obesity is still not clear, and further studies are needed especially for children.

P1-P103

Associations of Non-High-Density Lipoprotein Cholesterol with Metabolic Syndrome and Its Components in Korean Children and Adolescents: The Korea National Health and Nutrition Examination Surveys 2008–2014

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Background: In this study, we aimed to investigate the relationship between single-gender Korean references for non-high-density-lipoprotein cholesterol (non-HDL-C) and metabolic syndrome (MetS) in childhood.

Methods: A total of 5,742 Korean children aged 10-18 years who participated in a national survey were included. The subjects were classified into three groups based on single-gender non-HDL-C levels as follows: <120 mg/dL (desirable), ≥120 and <150 mg/dL (borderline high), and ≥150 mg/dL (high).

Results: Males in the borderline high non-HDL-C group had odds ratios (ORs) of 2.86 (95% confidence interval, 2.30-3.56) for elevated triglycerides (TG), 1.73 (1.08-1.79) for reduced high-density lipoprotein cholesterol (HDL-C) and 1.73 (1.08-2.78) for MetS compared with males in the desirable non-HDL-C group after adjusting for covariates. Males in the high non-HDL-C group had ORs of 1.65 (1.14-2.41) for elevated blood pressure (BP), 6.21 (4.27-9.05) for elevated TG, and 3.29 (1.49-7.26) for MetS compared with males in the desirable non-HDL-C group. Females in the borderline high non-HDL-C group had ORs of 3.03 (2.43-3.76) for elevated TG, 1.63 (1.13-2.35) for reduced HDL-C, and 4.53 (2.47-8.31) for MetS compared with females in the desirable non-HDL-C group. Females in the high non-HDL-C group had ORs of 1.43 (1.00-2.04) for elevated BP, 6.36 (4.45-9.08) for elevated TG, and 7.64 (3.65-15.96) for MetS compared with females in the desirable non-HDL-C group.

Conclusions: Our results suggest that in a Korean population, a non-HDL-C level of 120 mg/dL for males and 150 mg/dL for females is the threshold between borderline high and high risk for MetS.

P1-P104

Chromosomal Deletions at Chromosome 16p11.2 Associated with Severe Early-Onset Obesity- 3 Additional Patients

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Deletions at 16p11.2 have been reported to be associated with obesity, intellectual disability and various malformations. There are variations in phenotypes associated with deletions of different sizes in this region. Some deletions encompass the *SH2B1* gene encoding an adaptor protein involved in leptin and insulin signalling which is believed to be causal for the early-onset obesity of these patients who in addition show a developmental delay (see patient 1). Deletions at 16p11.2 not affecting *SH2B1* are also frequently associated with obesity: the recurrent microdeletion of ~ 593 kb is in addition associated with developmental delay, intellectual disability, and/or autism spectrum disorder (see patient 2). In addition, there are patients with even larger deletions not affecting *SH2B1* partly overlapping with the recurrent microdeletion (see patient 3). So far, it is unknown which genes in those deletions not affecting *SH2B1* are responsible for the obesity.

Patient 1 is a 10-year old girl with developmental delay, aggressive behaviour, ADHD and muscular hypotonia. Early-onset obesity started at the age of 3 years with steadily increasing BMI up to 30.3 kg/m^2 (+2.8 SDS) at the age of 10 years. In this patient a *de novo* ~232 kb deletion (hg19 chr16: 28.819-29.051 Mb) was found, affecting *SH2B1*.

Patient 2 is a 15-year old boy with psychomotor retardation, hypothyroidism and reflux nephrophathy. Extreme early-onset obesity started at the age of 2 years with increasing BMI to 54.4 kg/m^2 (+3.65 SDS) at the age of 14. In this patient a ~598 kb deletion at position hg19 chr16: 29.580-30.177 Mb was detected (without affecting *SH2B1*). His parents have not been analysed.

Patient 3 is a 18-year old boy with developmental delay, mild abnormalities of the heart and a pylorus hypertrophy. Early-onset obesity started at the age of 4 years resulting in a BMI of 47.6 kg/m^2 (+3.8 SDS) at the age of 18. In this patient a *de novo* ~1.138 Mb deletion at position hg 19 chr16: 28.996-30.134 Mb was detected (without *SH2B1* deletion).

In order to extend the spectrum of the associated phenotype, we added 3 more patients with different deletions at 16p11.2 and early-onset obesity to the small group of published cases. Further investigations of the deleted genes are necessary to gain a better understanding of the potential mechanism of weight regulation.

P1-P105

Effect of a Melanocortin-4 Receptor (MC4R) Agonist, Setmelanotide, on Obesity and Hyperphagia in Individuals Affected by Alström Syndrome

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Background: Alström syndrome (AS) is a rare genetic ciliopathy characterized by severe early-onset obesity, hyperphagia, retinal dystrophy, hearing loss, and cardiomyopathy. Rodent studies suggest that cilia play an important role in the leptin-MC4R pathway, which regulates energy balance and body weight. Setmelanotide, a peptide agonist of the MC4R, has led to weight loss in individuals affected by other rare genetic obesity disorders resulting from dysfunction in this pathway.

Objective: Report preliminary data on body weight, hunger scores, and safety from a Phase 2 proof of concept study of setmelanotide in individuals affected by AS.

Methods: Individuals age ≥12 years with a confirmed diagnosis of AS are eligible to enroll in this ongoing study. Setmelanotide is administered daily by subcutaneous injection with dose titration every 2 weeks up to 3.0 mg. Adults losing ≥5 kg and adolescents losing ≥4 kg during the titration and maintenance periods are eligible to continue treatment for a total of 52 weeks. Body weight, hunger assessments, BP and HR are assessed at each visit. Skin and physical examination plus metabolic, endocrine, hematologic and pharmacokinetic testing are also conducted.

Results: As of 31 March 2018, one 12-year-old male AS patient received setmelanotide at 0.5 mg and titrated up to 2.0 mg after 6 weeks in the study. At baseline, weight was 78.6 kg, BMI was 27.8 kg/m^2 (98th percentile for age and sex), mean daily highest hunger rating was 5.5 out of 10. At a dose of 0.5 mg, hunger rating dropped to 3.7, and at a dose of 1.5 mg, hunger rating dropped to 3.0 and remained stable through week 26. After 26 weeks of treatment, body weight was 62.5 kg (20.5% reduction), BMI was 21.8 kg/m^2 (85th percentile). Clinical assessment of Dykens hyperphagia score was 31 (out of 55) at baseline and 11 after 26 weeks. Setmelanotide was well tolerated by this individual. Adverse events included mild injection site reactions and increased pigmentation of the skin/nevi. There were no clinically significant changes in blood pressure, vital signs or laboratory evaluations.

Conclusions: In this preliminary data set for one individual affected by AS treated with setmelanotide, marked reductions in body weight and hunger score were observed. The safety profile is consistent with other studies in rare genetic obesity disorders, including the related genetic ciliopathy disorder, Bardet-Biedl syndrome. These findings support continued evaluation of setmelanotide in AS and other rare genetic obesity disorders.

P1-P106

Towards a Greater Understanding of the Pathophysiology of Obesity: Hypothalamic Obesity as a Model of Dysregulation of Appetite and Metabolic Homeostasis

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Introduction: Hypothalamic obesity (HyOb) is a rare form of treatment-resistant morbid obesity associated with congenital or acquired hypothalamic damage. Its pathophysiology is incompletely understood, with weight gain being attributed to hyperphagia and hyperinsulinaemia. We sought to compare the physiology of various plasma appetite-regulating hormones in HyOb and "simple" obesity (Ob) to improve our understanding of both forms of obesity and identify novel therapeutic targets.

Methods: Oral glucose-stimulated serum insulin and plasma oxytocin concentrations, and fasting concentrations of serum leptin, plasma α-MSH, BDNF, acylated ghrelin, AgRP and copeptin were measured by internally validated ELISA in obese (BMI≥+2 SDS) and lean children with hypothalamic damage (HyOb and HyLean) and Ob and Lean controls. Hyperphagia was quantified using the Dykens' Hyperphagia Questionnaire Score (DHQS).

Results: Participants (50 HyOb, 29 HyLean, 24 Ob, 19 Lean; 49.2% female) were of mean age 11.3±3.9 years at testing with a mean BMI SDS of 2.8±0.6 and 0.4±1.4 in the obese and lean groups respectively. DHQS did not significantly differ between HyOb and Ob participants (median DHQS 24 (17-34) vs. 24 (18-31), p=0.7), but both were significantly more hyperphagic compared to Lean controls (DHQS 17 (12-21), p=0.007 and 0.03 respectively). DHQS was positively correlated with fasting insulin (ρ=0.3, p=0.001), leptin (ρ=0.3, p=0.004) and BMI SDS (ρ=0.3, p<0.001) regardless of aetiology. Participants with a higher BMI SDS had higher insulin (R=0.4, p<0.001) and leptin (R=0.8, p<0.001) concentrations, but lower concentrations of acylated ghrelin (R=-0.3, p=0.045) and AgRP (R=-0.3, p=0.002). Lower fasting acylated ghrelin (β=-1.2 (95% CI -1.8 to -0.56), p=0.001) and αMSH (β=-0.2 (95% CI -0.4 to -0.02), p=0.04) concentrations were independently associated with more rapid BMI SDS changes at one year. Hormone concentrations did not significantly differ between HyOb and Ob subcohorts, but HyLean participants exhibited intermediate insulin, leptin and αMSH concentrations between HyOb and Lean controls despite normal BMIs, with 10/15 (66.7%) showing a BMI SDS increase over one year, and one patient developing impaired glucose tolerance.

Conclusion: There are no differences in appetite-regulating hormone concentrations or the degree of hyperphagia in HyOb and Ob, with peripheral anorexigens being compensatorily increased, and central and peripheral orexigens being suppressed. The association between lower central anorexigen concentrations (αMSH) and more rapid weight gain independent of baseline BMI requires further investigation. HyLean patients exhibit early hormone dysregulation and require careful follow-up as they remain at risk of HyOb.

P1-P107

Serum Uric Acid Level and Its Association with Metabolic Syndrome in Korean Adolescents

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Background: Elevated serum uric acid (UA) levels are associated with metabolic syndrome (MS), cardiometabolic risk factors (CMRFs) and non-alcoholic fatty liver disease (NAFLD) in adults. However, little is known about usefulness of UA to predict MS in adolescents. As the prevalence of obesity among pediatric population has been increasing, it is important to know the factors associated with the CMRFs to prevent future development of diabetes and cardiovascular disease.

Objective: We aim to evaluate the association between serum UA level and MS and CMRFs among Korean adolescents.

Methods: Data collected from the Korea National Health and Nutrition Examination Survey in 2016 were used, which was a nationally representative cross-sectional data. A total of 548 subjects (males 268, 48.9%) aged 13-20 years were included in this study. They were classified into tertiles of serum UA levels (T1, lower tertile, T2 mid-tertile, T3 upper-tertile) according to sex. Prevalence of MS and CMRFs including alanine aminotransferase (ALT) was compared by tertiles of UA.

Results: The mean UA was higher in males than females (6.3 ± 0.1 mg/dL vs. 4.6 ± 0.1 mg/dL; $p < 0.001$). BMI z-score, waist circumference, waist-height ratio, total cholesterol and non-HDL-cholesterol were significantly higher as T3 of UA in both sexes. Moreover, systolic blood pressure, triglyceride, ALT increased and HDL-cholesterol decreased in males. In T3 of UA, the prevalence and odds ratio increased significantly in abdominal obesity (23.3%; OR 3.1, 95% CI 1.5-6.4), elevated triglyceride (27.3%, OR 2.6, 95% CI 1.4-4.6), low HDL-cholesterol (18.3%; OR 4.7, 95% CI 1.9-11.3), elevated ALT (18.3%; OR 3.4, 95% CI 1.5-7.8), obesity (33.6%; OR 4.9, 95% CI 2.1-11.6) and MS (11.3%, OR 3.1, 95% CI 1.1-8.5), compared with T1 of UA. Proportion of participants with ≥ 3 CMRFs were 4.0% in T1, 5.6% in T2, and 11.3% in T3 ($p = 0.003$).

Conclusions: In this national cross-sectional study, we found that serum UA level is associated with MS, its components and marker of NAFLD in Korean adolescents. Serum UA level could be used as an important marker to predict MS in adolescents.

P1-P108

More Than a Gut Feeling: Preliminary Evidence Supporting a Role for Lifestyle Habits in Shaping the Intestinal Microbiota in Childhood and Adolescence

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Background: Dietary intake has been shown to influence the composition and diversity of the gut microbiota in adults, however its impact in childhood and adolescence remains uncertain. Moreover, the impact of other lifestyle behaviors such as physical activity, sedentary behaviors, sleep and fitness on the gut microbiota has rarely been investigated.

Objective: To explore the correlations between intestinal microbiota composition and measures of diversity among 15-17 year-old adolescents with a family history of obesity and

1. lifestyle habits at 15-17 years;
2. lifestyle habits in earlier childhood.

Methods: Data stem from the QUALITY cohort, a prospective cohort study of 630 children with a parental history of obesity. Lifestyle habits were assessed at 8-10 yrs, 10-12 yrs and 15-17 yrs, including: physical activity by 7-day accelerometry, self-reported screen time, dietary intake (at 8-10 and 15-17 yrs only) by 3 non-consecutive 24h dietary recalls, and self-reported sleep duration. Fitness was measured by VO_2peak. 16S-rRNA based microbial profiling of stool samples obtained from 22 participants at 15-17 yrs (14 normal weight, 6 overweight and 2 obese) were performed to determine composition and diversity of the gut microbiota. Measures of diversity include Shannon, Simpson, Chao1 and Observed OTU indices. Pearson's correlations assessed associations between diversity indices and lifestyle habits.

Results: Fitness at 15-17 yrs was positively correlated with measures of diversity (r = 0.33-0.41 across all indices). More importantly, statistically significant positive correlations were noted between fitness at 10-12 yrs and greater microbiotal diversity 5 years later (Shannon r=0.70, p=0.001; Simpson r=0.51, p=0.03; Obs OTU r=0.50, p=0.036). Physical activity and screen time were not associated with microbiota diversity. Both total dietary fat intake and saturated fat intake at 15-17 yrs were negatively correlated with the Simpson index (r=-0.50, p=0.019 and r=-0.43, p=0.046, respectively). Similar, not quite statistically significant, negative correlations between total and saturated fat consumption at 8-10 yrs and measures of diversity at 15-17 yrs were also noted. At both 8-10 yrs and 15-17 yrs, percent carbohydrate intake was

positively correlated with the Simpson index (r= 0.43, p=0.049 and r= 0.49, p=0.021, respectively). Finally, sleep duration at 10-12 yrs tended to positively correlate with indices of diversity at 15-17 yrs, the strongest correlation being with the Shannon index (r= 0.39, p=0.08).

Conclusions: These preliminary findings from a small sample of children followed over 8 years suggest that microbiome diversity in late adolescence may be modulated by lifestyle habits, even in earlier childhood.

P1-P109

Efficiency of Alpha-Lipoic Acid in Metabolic Syndrometreatment in Children

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Aim: To determine the efficiency of α-lipoic acid in metabolic syndrome treatment in children.

Materials and methods: 44 children with metabolic syndrome are observed. The diagnosis of metabolic syndrome is made on the base of obesity, arterial hypertension, disorders of carbohydrate and lipid metabolism according to the ATP III (2001) и IDF (2005) recommendations. All patients are randomized into 2 groups: 22 children (main group), who received diet, physical training and α-lipoic acid. The proposed course of therapy lasts for 2 months and the dose of α-lipoic acid is 300–600 mg daily. Second group (22 children) is received diet and physical training. C-peptide is determined using the immunoferment method and insulin resistance index HOMA-IR is calculated using the formula HOMA-IR=G (serum glucose level (mmol/L) x Ins (serum immune reactive insulin) (mcUnits/mL): 22,5; normal – less than 3,5. The rate of leptin and adiponectin is determined by the IFA method using reactives "Demeditec Adiponectin IFA DEE009". Statistic analysis was made using the program Statistika (ver 2009 for Windows), criteria Mann-Whitney, Wilkinson and χ^2.

Results and discussion: The comparing of insulin resistance indexes is established that after 2 month in children of the main group serum C-peptide decreases from 4,29±1,18 ng/ml to 3,23±0,92 ng/ml (p<0,001), and at 2nd group this index decreases to 4,21±1,15 ng/ml. Insulin resistance index at the 1 group decreased from 4,06±1,14 to 3,41±1,01 (p<0,001), and at the 2nd group to 4,01±1,11.

After 2 months treatment with α-lipoic acid the rate of leptin at the main group became 11,02±2,09 ng/ml (p<0,001), and at the 2nd group this index decreases to 18,12±3,11 ng/ml. The rate of adiponectin at the main group became 6,79±1,51, and in the 2nd group - 6,31±1,49 (p>0,001). It should be noted that there is no side effect of α-lipoic acid in children.

Conclusions: Our data confirmed statistically significant reduction in the level of C-peptide, insulin resistance and leptin under the influence of treatment with α-lipoic acid and. It is well tolerated and can be regarded as a pathogenesis factor in the treatment of metabolic syndrome in children.

P1-P110

Lipid Accumulation Product Is a Predictor of Non-alcoholic Fatty Liver Disease in Childhood Obesity

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Objectives: We aimed to evaluate the performance of lipid accumulation product (LAP) to predict non-alcoholic fatty liver disease (NAFLD) in obese children.

Methods: Eighty obese chidren (39 girl) were included in this study (6-18 years). Height, weight, body mass index (BMI), waist circumference (WC), puberty stage, blood pressure (n=28), fasting glucose, fasting insulin, HOMA-IR, alanine aminotransferase (ALT), aspartate aminotransferase (AST) (n=30), uric asid (n=77), cholesterol, triglyceride, HDL-cholesterol (HDL-C) (n=79), LDL-cholesterol (LDL-C) (n=79) values were obtained from the medical records. SDS and percentiles were calculated. LAP was calculated as [WC(cm)-58)]xtriglyceride concentration(mmol/L) in girls; [WC(cm)-65)]xtriglyceride concentration(mmol/L) in boys. Other two variant LAP values were described according to 3% (minLAP) and 50% (adjLAP) of WC values previously considered for age and gender in childhood. Aterogenic index (AI:Cholesterol/HDL-C) (n=79)was defined. NAFLD was showed by ultrasound. The AUC and appropriate cutoff points for LAP, adjLAP and minLAP were calculated by ROC analysis.

Results: Gender, puberty stage, weight SDS, BMI, BMI SDS, BMI %, WC, fasting insulin, HOMA-IR, ALT, uric acid, LAP, adjLAP and minLAP values were significantly different in chidren with and without NAFLD (p<0.005). LAP showed a positive and moderate correlation with puberty stage (rho=0.409; p<0.001), fasting insulin (rho=0.507; p<0.001), HOMA-IR (rho=0.470; p<0.001), uric acid (rho=0.522; p<0.001), AI (rho=0.494; p<0.001) and a weak negative correlation with HDL-C (rho=-3.833; p<0.001). Similar results were detected for minLAP and adjLAP. It was found that LAP values could be used to diagnose hepatosteatosis (AUC=0.698; p=0.002). Sensitivity and specificity values for LAP ≥ 42.70 cases were found as 53.7% and 84.6%, respectivly. The cut-off points for LAP were AUC=0.704; p=0.033 in males and AUC=0.693; p=0.013 in pubertal. While the cutoff point for adjLAP ≥ 40.05 (AUC=0.691; p=0.003), sensitivity (58.5%) and specificity (74.4%) were calculated. While the cutoff point for minLAP ≥ 53.47 (AUC=0.673; p=0.0083), sensitivity (56.1%) and specificity (76.9%) were found.

Conclusions: LAP is a is a powerfull and easy tool to predict NAFLD in childhood and is correlated with AI and uric acid level. This is the first study assessing the accuracy of LAP in childhood obesity.

P1-P111

Selected Serum Adipokines in Children with Irritable Bowel Syndrome

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Background: Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder. The pathogenesis of this disease has not been clarified so far. It is hypothesized that visceral hypersensitivity observed in IBS is associated with the activation of immune system and development of low-grade inflammation in the intestinal mucosa. Previous studies have shown that hormonal function of adipose tissue in inflammatory bowel disease is disturbed. However, there is only a few reports on serum adipokine concentrations in IBS. Therefore, the aim of this study is: 1) assessment of serum concentrations of leptin, adiponectin, chemerin and omentin-1 in children with IBS and healthy and 2) evaluation of relationships between adipokines and anthropometric as well as metabolic parameters.

Material and methods: The study group comprised 33 IBS patients (11 girls, 22 boys) aged 5-17 years. The control group consisted of 30 healthy children (11 girls, 19 boys) at comparable age. Anthropometric measurements (height, weight, BMI, waist circumference, hip circumference), analysis of body composition using bioimpedance and biochemical tests (C-reactive protein, transaminase levels, fasting glucose, insulin, HOMA-IR, blood lipid profile) were performed in all examined subjects. Adipokines serum concentrations were determined using commercially available ELISA kits.

Results: The values of anthropometric measurements were similar in both groups.

In children with IBS serum triglycerides, HOMA-IR and chemerin concentrations are higher, but HDL cholesterol and omentin-1 – lower than in healthy subjects. Leptin and adiponectin did not differ significantly between the groups. Significant correlations between serum adipokines and the values of anthropometric parameters, some metabolic parameters and serum C-reactive protein concentrations were observed. The analysis of ROC curves showed that serum chemerin is characterized by 30% sensitivity and 87% specificity in differentiating children with IBS from healthy and for omentin-1 these values were 60% and 80%, respectively.

Conclusions: 1) in children with IBS serum chemerin and omentin-1 concentrations show significant differences in comparison to healthy subjects; 2) the observed changes may result from development of low-grade inflammation; 3) serum chemerin and omentin-1 concentrations can be used as IBS biomarkers of good specificity and moderate sensitivity; 4) in children with IBS serum concentrations of the examined adipokines are closely related to their nutritional status, and in the case of chemerin and omentin-1 also with insulin resistance; 5) elevated serum chemerin levels and reduced omentin-1 concentrations may contribute to the development of lipid disorders in children with IBS.

P1-P112

Role of Urinary NGAL and KIM-1 as Early Kidney Injury Biomarkers in Obese Prepubertal Children

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Background: Childhood obesity is one of the most important causes of end-stage renal disease. The onset of obesity-associated renal disease is insidious and asymptomatic. To date available markers do not perfectly mimic kidney injury and may not characterize kidney changes especially in early stages and of renal tubulointerstitium. Tubular changes (KIM-1 and NGAL) are already apparent before the onset of proteinuria or alterations of GFR and thus might represent biomarker that directly reflects kidney injury and which are easily measured from urine, facilitating a direct monitoring of kidney damage early in the course of the disease.

Methods: Therefore we aimed to characterize kidney injury in a group of 40 obese prepubertal children (22Male/18Female; 9.7±1.9 years) compared to 40 healthy prepubertal age- and gender matched peers (18Male/22Female; 9.6±2.2 years). Anthropometric measurements and body composition were determined. Fasting blood samples were collected for measurement of insulin, glucose, lipid profile, ALT, AST, Cystatin C and creatinine (Scr). Urine samples were collected to assess urinary NGAL and KIM-1 and for the evaluation of urinary isoprostanes. Kidney length was measured with Ultrasound evaluation. Differences between the two groups were evaluated by Mann-Whitney U test and Spearman correlation analysis was performed to explore any relationship between variables.

Results: Triglycerides, ALT, glucose, insulin, HOMA-IR and Cystatin C values were significantly higher while HDL cholesterol levels were significantly lower in obese children than normal weight peers. No difference was documented in terms of total cholesterol and LDL cholesterol between the two groups. Scr values were all within normal limits and all patients had normal GFR without significant differences between the two groups. We showed that obese children had larger kidney sizes compared to healthy subjects, indicating organ hypertrophy. NGAL and KIM-1 are increased in obese children with normal kidney function. We documented a significant association between both NGAL and KIM-1 with adiposity indices, insulin status and markers of oxidative stress suggesting a possible obesity effect in inducing kidney abnormalities. In addition, KIM-1 and NGAL are directly related respectively to Cystatin C, isoprostanes and kidney length, supporting the ability of these biomarkers in reflecting early kidney damages in obese subjects.

Conclusions: These findings postulate that obese subjects exhibit a certain degree of renal damage before kidney function

loss and it seems to confirm the hypothesis that the tubular phase of damage precedes the manifestations of classic glomerular lesions.

P1-P113

Maternal Resveratrol Intake During Pregnancy and Lactation Modulates the Long-term Metabolic Effects of Maternal Nutrition on Offspring Depending on the Sex and Diet

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Maternal nutrition can have significant long-term consequences on energy homeostasis in the offspring. However, whether resveratrol, with antioxidant and anti-obesity actions, can improve the impact of poor maternal nutrition on offspring metabolism remains largely unknown. We hypothesized that resveratrol intake by dams would protect the offspring against the harmful effects of a maternal high fat diet (HFD). We also determined if resveratrol's effects are diet and sex dependent. Female Wistar rats received a low-fat diet (LFD; 3.8 Kcal/g, 10.2% fat) or HFD (5.1 Kcal/g, 61.6% fat) during pregnancy and lactation. Half of each group received resveratrol (+R) in their drinking water (50 mg/L; intake 2.0-2.5 mg/Kg/day). Offspring were weaned onto standard chow on postnatal day (PND) 21. Body weight (BW) and energy intake (EI) were measured weekly until PND150. Glycemia, serum insulin and leptin levels, lipid profile, as well as adipose mass and its expression (RT-PCR) of adipokines and enzymes, were determined. On PND150, offspring from HFD mothers weighed more than those from LFD ($p<0.0001$). Maternal resveratrol decreased the BW of females from HFD mothers ($p<0.004$) but increased it in those from LFD dams ($p<0.001$), such that BW of females from LFD+R dams was similar to that of females from HFD mothers. This tendency did not reach statistical significance in males. Offspring from HFD dams had higher accumulated EI than those from LFD dams (males: $p<0.001$; females: $p<0.01$), with maternal resveratrol decreasing EI in males from HFD dams ($p<0.001$) and their weight gain in males ($p<0.05$). Resveratrol increased EI in pups from LFD mothers, reaching statistical significance in females ($p<0.01$). The relative amount of visceral adipose tissue (VAT) and serum leptin levels paralleled the changes in BW. Resveratrol increased leptin levels in female offspring from mothers on LFD ($p<0.0001$) and tended to decrease them in offspring of HFD dams *(NS)*. Changes in proliferator-activated-receptor-gamma expression (PPARγ) paralleled those found in BW and VAT. PAPP-A expression in VAT, involved in adipose metabolism, was lower in females than in males ($p<0.0001$) with a differential effect of resveratrol decreasing its expression in females from HFD dams ($p=0.001$) and increasing it in males from LFD dams ($p=0.01$). **Conclusions: 1)** Maternal resveratrol intake during pregnancy and lactation has long-term effects on metabolism in the offspring. **2)** These effects depend on the type of diet ingested by the mother and the offspring's sex.

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P1-P114

Intrauterine Metformin Exposure and Offspring Metabolic Health at 8-years Follow-up

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Background: Metformin is increasingly used in pregnancy and passes the placenta. Data on long-term effect on the offspring is essentially lacking. We explored possible effects of intrauterine metformin exposure on metabolic health, in 8-years-old children of women with PCOS.

Methods: Follow-up of children from the PregMet-study - an RCT comparing metformin (2000 mg) to placebo during PCOS pregnancies. The primary endpoint was Body Mass Index (BMI). Secondary endpoints included waist circumference, waist-to-height ratio, height, weight, head circumference, bioimpedance-determined muscle-mass and percentage body-fat (%BF), cholesterol, triglyceride, HDL-cholesterol, fasting glucose, HbA1c, blood pressure and heart rate. All anthropometric measurements were converted to, and presented as, standard deviation scores (SDS).

Findings: During April 2014-July 2016 we included 141 (55%) of the 255 invited children. Maternal baseline characteristics were comparable between groups. The BMI SDS was higher in the metformin group than in the placebo group [difference in means (d) =0.41, 95% CI 0.03 to 0.78, p=0.034]. Metformin exposed children had higher waist-to-height ratio SDS [d=0.36, 95% CI 0.06 to 0.67, p=0.021], higher waist circumference SDS [d=0.40, 95% CI 0.08 to 0.71, p=0.014], weighed more [weight SDS d=0.43, 95% CI 0.04 to 0.82, p=0.032], and had a tendency of higher %BF [d=3.04, 95% CI -0.58 to 6.67, p=0.099]. Height, head circumference, muscle-mass (kg), biochemical analyses, blood pressure and heart rate were comparable between groups. A larger proportion of the offspring in the metformin group, n=28 (39.4%) than in the placebo group, n=13 (18.8%), p=0.007 had eczema, while fewer children in the metformin group, 4 (5.6%), than in the placebo group 12 (17.4%), p=0.029 had constipation.

Interpretation: The increased BMI, waist circumference and waist-to-height ratio observed in metformin-exposed offspring indicates central adiposity and a possible risk of inferior metabolic health. However, as biochemical markers were comparable between the groups, the impact of metformin exposure on metabolic health of 8-years-old children might be limited. Implications for adult health are uncertain.

P1-P115

Greater Maternal BMI Early in Pregnancy and Excessive Gestational Weight Gain Are Independently Associated with Adverse Health Outcomes in the Offspring at Age 7 Years

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Background: Maternal overweight/obesity during pregnancy and excessive gestational weight gain (GWtG) have been recognized as important early-life risk factors for childhood obesity. We aimed to examine whether maternal BMI at 20 weeks of gestation and excessive GWtG were associated with alterations in body composition and metabolism in childhood in the offspring of primiparous mothers who participated in a randomised controlled trial of exercise regimen during pregnancy.

Methods: Of the initial 84 women and their offspring who participated in the trial, follow-up data were available on 52 mothers and their children. Children underwent clinical assessments at approximately 7.6 years, including body composition by DXA and fasting blood tests (i.e. glucose, insulin, and lipid profile), while their nutritional intake was estimated from food diaries. Multivariable models were run with maternal BMI (as a continuous variable) and GWtG (excessive or not), while adjusting for other important confounders.

Results: Twenty-five mothers (48%) were overweight/obese early in pregnancy and 35 (67%) had excessive GWtG as per IOM guidelines. Greater maternal BMI at trial recruitment was associated with increased weight SDS (β=0.09; p=0.001), BMI SDS (β=0.08; p=0.005), and percentage body fat (β=0.44; p=0.031) in the offspring in childhood. Maternal BMI early in pregnancy was not associated with any fasting metabolic parameters in their children. Independently of maternal BMI, children born to mothers with excessive GWtG had increased abdominal adiposity (android to gynoid fat ratio 0.64 vs 0.55; p=0.043), as well as a less favourable lipid profile with lower HDL (1.57 vs 1.77 mmol/L; p=0.010), higher triglycerides (0.87 vs 0.63 mmol/L; p=0.003), and higher total cholesterol to HDL ratio (3.13 vs 2.55 mmol/L; p=0.024), even though macronutrient intake was similar in both groups.

Conclusions: Greater maternal BMI early in pregnancy is associated with increased adiposity in the offspring at age 7.6 years. Importantly, irrespective of maternal BMI early in pregnancy, excessive GWtG is also associated with adverse effects in the offspring.

P1-P116

Rapid BMI Gain During Later Infant Accelerates Skeletal Maturation at Prepubertal Obese Children

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Objective: The aim of this study was to reveal the increase of BMI during later infant related to skeletal maturation in prepubertal obese boys.

Subjects and Methods: The subjects were 63 Japanese 10-years old obese boys. Height and weight were measured. Bone age (BA) of left hand-wrist radiographs was assessed using RUS score of the Japanese-standardized Tanner-Whitehouse 2 method. Weight and length or height at birth, 1.5, 3 and 6 years old were obtained from maternal and child health handbook or school health checkup card. We analyzed the relationship between relative BA (bone-chronological age) and BMI at each age, ΔBMI (1.5 to 3 years old), ΔBMI (3 to 6 years old), ΔBMI (6 to 10 years old) using simple linear regression analyses. We analyzed the relation independent variables to relative BA using multiple linear regression analyses. Independent variables were model 1 as BMI at birth, 1.5, 3, 6 and 10 years old, model 2 as ΔBMI (1.5 to 3 years old), ΔBMI (3 to 6 years old), ΔBMI (6 to 10 years old). Odd's ratio of relative bone age ≥2 years old was analyzed using multiple logistics regression analysis.

Results: The mean of height was 141.4±6.2cm, weight was 51.6±6.3kg, body mass index (BMI) was 25.8±2.1 kg/m2, BA and relative BA were, 11.7±1.4 and 1.7±1.3 years old. Simple regression analysis revealed relative BA had positively correlated with BMI at 6 and 10 years old, ΔBMI (1.5 to 3 years old), ΔBMI (3 to 6 years old) significantly. Multiple regression analysis revealed relative BA had significantly positively correlated with BMI at 6 old at model 1, ΔBMI (1.5 to 3 years old), ΔBMI (3 to 6 years old) at model 2. Multiple logistics regression analysis using independent variables as ΔBMI (1.5 to 3 years old)≥0, ΔBMI (3 to 6 years old)≥2 and BMI at 6 years old≥20 revealed odd's ratio of relative bone age ≥2 years old was 1.99 (1.18-3.40) at ΔBMI (3 to 6 years old) ≥2.

Conclusions: Rapid BMI gain and high BMI at later infant period accelerates skeletal maturation in prepubertal obese children. This disorders of bone growth in prepubertal obese children will lead to suboptimal final height and affect their quality of life.

P1-P117

The More Obese – The Less Pubertal Height Gain

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Background: In a population of a community-based setting (BMI_{SDS}range -3.5 to +4.1), there is a negative linear correlation between childhood BMI_{SDS} and pubertal height gain, together with earlier onset of pubertal growth with higher BMI_{SDS} for both sexes[1].

Objective: To investigate the impact of BMI in childhood on the pubertal pattern of growth for obese children in a clinical setting.

Method: Pubertal growth in obese children in a clinical setting (University hospital, Madrid) were analyzed and compared with the longitudinally followed population, the $GrowUp_{1990}$Gothenburg cohort (community-based setting). The obese study-group included 47 children (26 females) with BMI_{SDS} at diagnosis of +2.0 to +7.4. Analyses were done with the QEPS growth model[2]. Individual BMI_{SDS}[3] values were related to individual growth functions from QEPS-model; *Pmax* (specific pubertal gain, cm) and *AgeP5* (age in years at 5% of the specific pubertal growth, representing onset of pubertal growth). The results of the obese children were compared to the population study.

Results: In obese children, as well as in the population study, BMI_{SDS} showed a negative dose-response effect of specific pubertal gain. *Pmax* was 10.19 cm - 0.630 x BMI_{SDS} in females, 15.61 cm - 1.049 x BMI_{SDS} in males, meaning that every increase in BMI_{SDS} by 1 is equal to 0.63 cm less pubertal height gain for females and 1 cm for males. There were significant differences when compared to the population study; however, the patterns were similar (*Pmax* = 13.66-1.35xBMI_{SDS}, in girls, *Pmax* = 18.05-1.61xBMI_{SDS} in boys, population study). There was also a linear correlation of obesity degree (BMI_{SDS}) and onset of pubertal growth (*AgeP5):* 9.60 years - 0.101 x BMI_{SDS} in girls, 11.59 years - 0.1145 x BMI_{SDS} in boys. The regression formula was similar to the results from the population study (with *AgeP5* 9.82 years - 0.137 x BMI_{SDS} in girls, 11.81 years - 0.1267 x BMI_{SDS} in boys, where every increase in BMI_{SDS} by 1 SD-score gave an earlier onset-of-pubertal growth by 1.2-1.6 month.

Conclusion: The higher BMI_{SDS} in childhood, the less the specific pubertal gain in obese boys and girls, and the earlier the onset of pubertal growth. Weight status is an important modifier of pubertal growth in both normal-weight and obese children.

Reference

1. Holmgren A, et al. *Ped. Res* 2017:81,448–454. 2. Nierop A, et al. *J. of Theor. Biol.* 2016;406:143–65. 3. Cole TJ, Lobstein T. *Ped. obesity*. 2012;7(4):284-94.

P1-P118

Longitudinal Changes in Abdominal Fat Distribution in the First Two Years of Life

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Changes in abdominal fat distribution in the first months of life might be critical for adult metabolic health. Type of feeding might influence the abdominal fat distribution in early life. This study aims to determine whether type of feeding is related to abdominal fat distribution and whether changes in early life are associated with abdominal fat distribution at the age of 2 years.

Methods: In the Sophia Pluto Cohort, infants are examined at age 1 and 3 months and 2 years. 301 healthy term born infants (176 boys) completed 2 years. Body composition was measured by Peapod and DXA scan. Abdominal subcutaneous fat (SCF) and visceral fat (VF) were measured by ultrasound, from 3 months. Abdominal subcutaneous/visceral fat ratio (SCF/VF-ratio) was calculated. All data are expressed as medians.

Results: At age 3 months, 118 (39.2%) infants were exclusively breastfed (BF-group) and 78 (25.9%) exclusively formula fed (FF-group) from birth onwards.

At age 3 months, BF-group had a median SCF of 0.42 cm and VF of 2.43 cm, with an SCF/VF-ratio of 0.18, while FF-group had a median SCF of 0.39 cm, VF of 2.50 cm and an SCF/VF-ratio of 0.16. The VF was similar in both groups, but the SCF and SCF/VF-ratio were significantly higher in BF vs FF (p= 0.031 and 0.021, resp.). There was no difference between boys and girls.

Between age 3 months and 2 years, the SCF and VF decreased in BF and FF, not significantly different between both groups.

At age 2 years, BF-group had a median SCF of 0.31 cm, VF of 2.10 cm and an SCF/VF-ratio of 0.16 and FF-group an SCF of 0.32 cm, VF of 2.10 cm and an SCF/VF-ratio of 0.15, not significantly different between groups.

The SCF at 3 months was associated with SCF at 2 years in the FF-group only (r=0.314, p=0.01). The SCF/VF-ratio at age 3 months was borderline associated with the SCF/VF-ratio at 2 years in the FF-group (r=0.239, p=0.048), and significantly in boys (r=0.375, p=0.011).

Conclusion: At age 3 months, infants with exclusive BF had significantly more abdominal subcutaneous fat than infants with exclusive FF and similar visceral fat, but this difference had disappeared at age 2 years. Our data show an association between the abdominal fat distribution in early life and at 2 years in boys with exclusive FF.

P1-P119

Telemedicine Therapy for Overweight Adolescents: First Results of a Novel Smartphone App Intervention Using a Behavioural Health Platform

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Introduction: Despite improved therapy measures since 2014 the prevalence of overweight and obesity in Swiss adolescence stabilized on 19%. Particular challenges are lack of adherence to therapy in youth who are in difficult life situations or live further from specified centres. Therefore it is essential to find simple and novel therapeutic approaches. But although the number of digital based health information systems increases steadily, the effectiveness in reaching long term health goals or life style change mostly remain unproven. The aim is to test a novel design of a health app for overweight adolescents, whether it supports their motivation to participate in a lifestyle intervention including relaxation and activity exercises.

Methods: Based on an open source platform with a text-based healthcare chatbot (THCB), a mobile chat app with a serious game character was designed for Android smartphones. Patients were able to chat with the THCBs Anna or Lukas with the help of predefined answer options. Direct communication between patients and health professionals (HP) was also enabled via a second chat channel. Sensor integration provided measurement of physical activity. In a 12-month randomized controlled study, the THCBs encourage patients to achieve daily challenges during 24 weeks (steps per day, breathing exercises, photos of nutrition and home environment, questions on well-being and eating habits) to earn virtual rewards. Effects on therapy adhesion during the 5.5-month intensive phase of intervention with 4 on-site visits will be compared to a treatment-as-usual group with monthly visits.

Results: At start, in 22 patients (39 % girls) age and BMI-SDS were not significantly different: 14.2 years (11.9–17) and 2.56 SD (1.7–3.5). At 5.5 months (13 THCB; 7 controls), almost 67% of the patients had >4 THCB conversational turns per day and 43% fulfilled daily challenges completely and successfully. Only during the first month, open chat questions, mainly on technical issues, took place in 3.4% of roughly 18.064 conversational turns.

Conclusion: Interim analysis of the THCB intervention group of an ongoing RCT shows a high compliance with the app services over half a year. This may be explained by the rewarding game system, the peer character of the THCBs and the perceived usefulness of the THCBs on the smartphone, a familiar medium for adolescents.

P1-P120

Cardiorespiratory Fitness Effectiveness Is Related to Abdominal Adiposity and Insulin Sensitivity in Overweight Adolescents

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The main pitfall of weight management programs is effective and safe fitness regimen choice. According to HELENA Study (2013) physical activity readiness is negatively correlated with markers of insulin resistance (IR) and central adiposity in adolescent population. Meanwhile, very little is known about cardiorespiratory fitness effectiveness in relation to hepatic, peripheral and whole body insulin sensitivity (IS).

Methods: 64 adolescents aged 13,56 + 2,47 y.o. with different BMI were examined. Waist-to-height-ratio (WHR) used to know the degree of abdominal adiposity. Laboratory assessment of metabolic profile included fasting glucose (mmol/l) and insulin (μIU/ml) followed by standard multistage cycling procedure (Bruce protocol) with subsequent glucose and insulin measurement. Fasting insulin sensitivity assessed by HOMA-IR, peripheral IS – by $ISI_{0,120}$, whole body IS - by Matsuda index.

Cardiorespiratory fitness effectiveness determined by the % of Predicted VO2 max, which used for grouping: Gr.1 - 120-80%, Gr.2 - 50-80%, Gr.3 - less than 50%.

Standard statistical methods were used for the data analysis by SPSS soft.

Results: O2 consumption normalized to the lean body mass reflects progressive reduction of actual parameter (Gr.1–0.069+0,03; Gr.2 - 0.051+0.033; Gr.3 - 0,025+0.049; P_{12}=0.04; P_{23}=0.14; P_{13}=0.002). Energy costs of physical activity (by MET) is greater in effective VO2 uptake (Gr.1–14.59+3.05; Gr.2 - 9.99+3.038; Gr.3–5.66+2.46 kcal/min; $P_{12, 23, 13}$ <0.01).

There was gradual decrease of Predicted VO2 max with growing WHR (Gr.1–0.49+0,149; Gr.2 - 0.502+0.147; Gr.3 - 0,640+0.208; P_{12}=0.825; P_{23}=0.039; P_{13}=0.019), but BMI and height of patients were not different in groups.

There was no significant difference in blood glucose concentration after the exercise boost. Meanwhile insulin level twice as little in subjects, who successfully achieved predicted VO2 (Gr.1–30.139+19.676; Gr.2 - 32.910+24.212; Gr.3–52.260+41.653 μIU/ml; P_{12}=0.651; P_{23}=0.107; P_{13}=0.028).

Group with lowest O2 consumption was characterized by higher insulin resistance for fasting (HOMA-IR = 5.62+3.11 vs. 8.93+5.03, P_{13}<0.02), lower total body insulin sensitivity (Matsuda index = 4.39+1.75 vs. 3.00+1.65, P13=0.03) and deficient glucose metabolic clearance with relevant peripheral insulin sensitivity (ISI 0,120 = Gr.1–55.97+12.91; Gr.2 - 48.81+9.64; Gr.3–39.39+7.16; $P_{12, 23, 13}$<0.01).

Conclusion: Exercise effectiveness in overweight adolescents is related to the abdominal adiposity and highly dependent on peripheral insulin sensitivity. Higher insulin concentration after the exercise boost associated with impaired energy expenditures better than glucose level on its own.

P1-P121

Promoting Healthy Lifestyles in Youth: Preliminary From the CIRCUIT Program

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Introduction: Childhood obesity is an international pandemic which affects 13% of Canadian youth, and is the leading cause of cardiovascular disease (CVD) in children. While the optimal approach to treat pediatric obesity remains elusive, comprehensive and intensive behavioral interventions which leverage the child's living environment in order to promote improvements in healthy lifestyles appear promising. The CIRCUIT program (*Centre Pédiatrique d'Intervention en Prévention et en Réadaptation Cardiovasculaires,* Sainte-Justine Hospital University Center, Montreal, Canada) is an innovative lifestyle intervention program for youth aged 4-18 y at risk of CVD. The program consists of a personalized plan created by a clinical kinesiologist to increase physical activity and reduce sedentary behaviors by considering the specific needs and opportunities of each child within their living environment.

Objective: To assess changes in cardiometabolic health outcomes among 107 participants who completed the 2-year CIRCUIT intervention.

Methods: Children with at least one CVD risk factor were referred to the program by their health care professional. At baseline, 1-year and 2-year follow-up, we measured body mass index z-scores (zBMI), blood pressure z-scores (zBP), adiposity (%body fat and %trunk fat by Tanita), fasting blood glucose and lipid profile (TC, LDL, HDL, triglycerides), aerobic fitness (VO_2max) anaerobic fitness (5m shuttle run test) and physical capacity (flexibility, push-ups, sit-ups, hand grip strength, leg power, balance and hand-eye coordination). Outcomes were analyzed using paired t-tests (for age and sex standardized zBMI and zBP) or multivariable mixed effect models, adjusted for age and sex, for other outcomes.

Results: Among the 107 participants (54 males), mean age was 10.9 years (SD = 3.3). Both zBMI and diastolic zBP improved at years 1 and 2 compared to baseline: zBMI decreased by 0.21SD and 0.29SD, respectively ($p<0.001$); similarly, diastolic zBP decreased by 0.35SD and 0.42SD, respectively ($p<0.001$). No change in systolic zBP was observed. At year 1, participants significantly decreased %trunk fat (β=1.42%, 95%CI: 0.19-2.65) and improved aerobic fitness (β=2.20ml/min.kg, 95%CI: 0.99–3.41), anaerobic fitness (β=0.68 seconds, 95%CI: 0.34-1.02), and physical capacity (push-ups, sit-ups, hand grip strength, leg power). Further improvements, albeit attenuated, were noted at year 2 for these indicators except %trunk fat and sit-ups. Lipid profile and fasting glucose (on average within normal range at baseline) did not significantly change during the intervention period.

Conclusion: CIRCUIT is a promising intervention for children at risk of CVD and is associated with many favorable effects on cardiometabolic health outcomes.

P1-P122

Determinants Of Attrition from a Healthy Lifestyle Intervention: Experience from the CIRCUIT Program

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Introduction: Pediatric obesity is a global public health problem that is associated with severe cardiometabolic consequences. Weight management interventions focusing on lifestyles have shown some promising results, but attrition rates are often high and reasons for dropout are poorly understood.

Objectives: We aimed toestimate the prevalence, and identify the determinants of attrition among pediatric participants in the first year of a 2-year lifestyle intervention program.

Methods: The CIRCUIT (*Centre Pédiatrique d'Intervention en Prévention et en Réadaptation Cardiovasculaires*, Sainte-Justine Hospital University Center, Montreal, Canada) program is an ongoing lifestyle intervention program for youth aged 4-18 y at risk of cardiovascular disease (CVD). It consists of a personalized plan created by a clinical kinesiologist to increase physical activity and reduce sedentary behaviors by considering the specific needs and opportunities of each child and their living environment. Participants are contacted monthly by the kinesiologist and asked to return every 6 months for follow-up evaluations and further plan adjustments. We collected anthropometric and socioeconomic characteristics at baseline. Attrition was defined as having done the baseline visit but ceasing attendance prior to the 1-year follow-up. Differences in baseline characteristics between those who dropped out and those who did not (age, sex, body mass index z-score (zBMI), ethnicity, maternal and paternal education, living with both parents, estimated distance in time and distance in kilometers to the clinic) were analyzed using chi-square-, Fisher's exact-, and t-tests. To determine predictors of drop-out, we used multivariable logistic regression models adjusted for age, sex, baseline zBMI, socio-demographic characteristics, and estimated driving time to the clinic.

Results: From 531 participants who started the program, 263 dropped out before the first year (attrition rate of 49.5%). Youth who dropped out were older (mean age 12.7y vs. 11.3y; $p<0.001$) and less likely to live with both parents (58% vs. 68%, $p=0.03$). They were also less likely to have mothers who had completed high school (79% vs. 90%, $p=0.002$). No group differences were observed for sex, ethnicity, baseline BMI z-score, fathers' education, or driving time/distance to the clinic. In logistic regression models, only older age at initiation of the intervention (OR:1.2, CI: 1.1-1.3) and lower maternal education (OR: 2.3, CI: 1.3-4.3) were significant predictors of attrition.

Conclusion: Our program attrition rate was high, but comparable to other programs. Targeting a younger population and tailoring the program to parental level of education may improve retention to CIRCUIT and other lifestyle intervention programs.

P1-P123

Interleukin-6 Levels Are Associated with High Blood Pressure and Low HDL Cholesterol in Healthy 4-Year-Old Children

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Background: Interleukin-6 (IL-6) is a proinflammatory cytokine associated with obesity, insulin resistance, hypertension, and atherosclerosis in adulthood. Few studies have been conducted in healthy young children. We aimed to investigate whether IL-6 levels are associated with cardiometabolic risk factors in healthy 4-year-old children.

Methods: From a prospective cohort study named Environment and Development of Children (EDC) cohort, a total of 421 singletons aged 4 years (232 boys) born as term and appropriate for gestational age infants were included for this study. We measured IL-6 levels and cardiometabolic risk factors including body mass index (BMI), blood pressure (BP), triglycerides, high density lipoprotein (HDL) cholesterol, fasting plasma glucose (FPG), and insulin resistance (IR) after a 12-hour fast. The homeostatic model assessment (*HOMA*)-IR was calculated according to the formula: fasting insulin (mU/L) x fasting glucose (nmol/L)/22.5.

Results: Mean Z-scores of height, weight, and BMI were 0.36, -0.02 and -0.03, respectively. Mean IL-6 levels were 1.67 pg/mL. Mean systolic and diastolic BP was 96 mmHg and 52 mmHg, respectively. Mean levels of triglycerides and HDL cholesterol were 63 mg/dL and 53 mg/dL, respectively. Mean FPG was 89 mg/dL and mean HOMA-IR was 0.54. On univariate analysis, IL-6 levels were associated with higher systolic BP and lower HDL ($P < 0.05$ for both). Higher systolic BP was significantly associated with higher IL-6 levels ($P < 0.05$), weight gain during the first 4 years of life ($P < 0.05$) and parental hypertension ($P < 0.05$) after adjusting for sex, gestational age (GA), birth weight z-score, height z-score, BMI z-score, dietary sodium intake and physical activity. Additionally, lower HDL cholesterol was significantly associated with higher IL-6 levels ($P < 0.05$), decreased dietary cholesterol ($P < 0.05$) and age ($P < 0.05$) after adjusting for sex, GA, birth weight z-score, weight gain during the first 4 years of life, BMI z-score, dietary fiber intake, physical activity, and parental hyperlipidemia.

Conclusions: IL-6 levels were independently associated with increased systolic BP and decreased HDL cholesterol in even healthy 4-year children, supporting the possible association between inflammation and unhealthy cardiometabolic changes from a young age.

P1-P124

Metabolic Phenotype of Human Adipocytes Overexpressing UCP1

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Background: Functional studies on uncoupling protein 1 (UCP1) are important to identify potential pharmacological targets which interfere with energy metabolism. However, current cell models of human origin are scarce due to limited tissue availability.

In this study, we generated human preadipocytes and adipocytes with an overexpression of UCP1 and studied the metabolic function of these cells.

Methods: Human Simpson-Golabi-Behmel syndrome (SGBS) cells were used as a model system. Cells were transduced in the preadipocyte state with lentivirus encoding human UCP1. Stable cultures were obtained by antibiotic selection. SGBS-UCP1 cells were characterized by qPCR, Western blot, and immunofluorescence. Mitochondrial content was determined by quantification of mitochondrial DNA and citrate synthase activity. Metabolic processes were assessed using an XFe96 Extracellular Flux Analyzer.

Results: UCP1 was not detectable in parental SGBS preadipocytes, but a weak expression on both mRNA and protein level was observed in late adipogenesis. Using lentiviral transduction, we achieved a robust overexpression of UCP1 in preadipocytes. UCP1-overexpressing cells displayed an adipogenic differentiation capacity comparable to control cells. In differentiated adipocytes, we achieved a UCP1 overexpression by ~12-fold on protein level, without affecting the mitochondrial content and the expression of other brown adipose tissue (BAT)-associated genes. Both preadipocytes and adipocytes overexpressing UCP1 showed a significantly increased basal respiration rate (~2-fold and ~1.5-fold, respectively) and a reduced coupling efficiency compared to control cells (30% *vs* 100% and 12% *vs* 70%, respectively). Acute stimulation with dibutyryl-cAMP markedly increased respiration in UCP1-overexpressing adipocytes, which was dependent on hormone sensitive lipase (HSL) activity. UCP1 activity could also be induced by treating SGBS-UCP1 cells with free fatty acids.

Conclusion: Our findings demonstrate that UCP1 overexpressed in a homologous cell system is fully functional and displays the expected uncoupling of the respiratory chain. We introduce these cells as a novel human model system to study UCP1 function and activation.

P1-P125

M2 Macrophage Markers Are Enriched in Human Deep Neck Adipose Tissue and Do Not Correlate with UCP1 Expression

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Background: Secretion of catecholamines by adipose tissue M2 macrophages was recently proposed as a molecular mechanism leading to activation of brown adipose tissue and heat generation in mice. However, published data are conflicting and it is not clear whether this pathway might play a role in humans. To shed light on this, we studied macrophage polarization in human white and brown adipose tissue and related it to thermogenic gene expression.

Methods: Paired samples of subcutaneous (sc), white and deep neck (dn) adipose tissue (AT) samples were collected from n=12 patients undergoing neck surgery for malignancies or nodular goiter. RNA expression of macrophage markers and thermogenic genes was analyzed by qRT-PCR.

Results: The expression of UCP1, PRDM16 and other thermogenic genes was significantly enriched in dn AT, identifying the depot as brown adipose tissue. Expression of the common macrophage marker CD68 as well as the M2 marker genes CD163, CD206/MRC1 and CD301/MGL1 were significantly increased in dn compared to sc adipose tissue (CD68 1.8-fold, CD163 2.1-fold, CD206 4-fold, CD301 2.2-fold). In contrast, CD11c, a marker for M1 macrophage polarization, was not differentially expressed between both depots. There was no correlation between any studied macrophage marker and the expression of UCP1 in both sc and dn adipose tissue.

Conclusion: Our data clearly show an enrichment of alternatively activated M2 macrophages in human deep neck AT. However we could not detect any relationship between the presence of M2 macrophages and UCP1 expression. This suggests that in humans macrophages play no major role for brown AT activation or white AT browning.

P1-P126

Effect of Hormonal Changes on Exocrine Pancreatic Function in Girls with Anorexia Nervosa

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Background: Anorexia nervosa (AN) is a good biological model of chronic malnutrition. Although some reports according to the gastrointestinal disturbances in response to starvation have been published so far, the exocrine function of pancreas in patients with AN has not been studied thoroughly, yet. There is also no data on the effect of hormonal changes in AN on it. Therefore, the aim of this study is: 1) Evaluation of pancreatic exocrine function in patients with anorexia nervosa and control group of healthy girls in the ^{13}C-labeled triglycerides (MTG-BT) breath test; 2) Analysis of the relationships between the results of the breath test and the hormonal parameters in the studied groups of girls.

Material and methods: The study group comprised 31 patients with AN aged 12-17 years. The control group consisted of 38 healthy girls at comparable age. Anthropometric measurements (height, weight, BMI) biochemical (lipid profile, fasting glucose and insulin, alanine and asparagine aminotransferase, bilirubin, GGTP and amylase) and hormonal (serum insulin, leptin, soluble leptin receptor, fT_4, cortisol, FSH, LH, estradiol) assays were performed in all examined subjects. HOMA-IR and total leptin (serum leptin+soluble leptin receptor) values were also calculated. Breath samples were collected before and every 30 minutes after the ingestion of 150 mg of the ^{13}C mixed triglycerides for 360 minutes. The cumulative percentage of ^{13}C recovered in the breath during the 360 minute collection (CP360) as well as time to peak (TTP) of ^{13}C recovery were established using IRIS analyser (Wagner GmBH, Bremen, Germany).

Results: The AN girls had significantly lower weight, BMI, fasting glucose, insulin, HOMA-IR, fT_4, FSH, LH, estradiol, leptin, soluble leptin receptor and total leptin values in comparison to control group. Serum cortisol levels in the AN group was significantly higher than in healthy controls. The mean CP360 was similar in both examined groups, however the time to peak (TTP) was significantly longer in the AN girls. In the control group TTP correlated negatively with serum insulin and HOMA-IR values. In the AN girls significant negative correlations between CP360 and LH, soluble leptin receptor and total leptin were observed.

Conclusions: 1) In girls with AN kinetics of pancreatic secretion of lipase is disturbed; 2) These disorders are dependent on the degree of energy deficit measured by serum total leptin concentration; 3) The abnormalities observed in patients with AN may result from impaired pancreatic endo-exocrine axis.

P1-P127

PCSK9 and Lp(a) Levels of Children Born After Assisted Reproduction Technologies

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Background/Aims: Since the introduction of Assisted Reproduction Technologies (ART), including classic In Vitro Fertilization (IVF) and Intacytoplasmic Sperm Injection (ICSI), in clinical practice, several studies have addressed concerns regarding the long-term health of the offspring, revealing indications of an adverse cardiometabolic outcome. Proprotein convertase subtilisin/kexin type 9 (PCSK9) circulating level is significantly associated with an increased risk of cardiovascular events and may be used as a reliable biomarker. In this study, we aimed at investigating the PCSK9 levels and lipidemic profile of children born ART compared with naturally conceived (NC) controls.

Methods: In this cross-sectional, case-control study, 73 sex- and age-matched children (mean age 98 ± 35 months) of ART (ICSI: n=33, classic IVF: n=40) and 73 NC children were assessed. Blood was drawn for assessment of lipid biomarkers, including PCSK9 and Lp(a) levels, as well as glycemic and inflammatory biomarkers. The role of age in levels of PCSK9 was also evaluated, when age was considered as a categorical variable. For the purpose of this analysis, subjects were classified according to their age in 3 groups (group 1: <8 years, group 2: 8-10 years and group 3: ≥10 years).

Results: In the univariate model of the overall population, circulating PCSK9 levels were related to total cholesterol (r=0.186, P=0.025), LDL (r=0.180, P=0.029) and systolic blood pressure (SBP) (ρ=0.199, P=0.021). Also, in the univariate model of the overall population, circulating Lp(a) levels were related to age (r=0.269, P=0.001), apoB (r=0.214, P=0.01), birth weight (r=−0.183, P=0.037), height (r=0.263, P=0.001), waist to hip ratio (r=−0.350, P<0.001), Homeostasis Model Assessment of insulin resistance (r=0.319, P<0.001), insulin (r=0.316, P<0.001), and high-sensitivity C-reactive protein (ρ=0.241, P=0.018). No significant differences were observed regarding lipid parameters between ART and NC children. However, after adjusting for gender and LDL, a significant interaction was found between age groups and conception method (p for interaction<0.001, Figure), indicating that ART children increase their PCSK9 levels with age in contrary to NC children where levels of PCSK9 decrease with age. Moreover, after adjusting for age, gender and LDL, ART children conceived with IVF showed significantly higher levels of Lp(a) compared to ART children conceived with ICSI (6.5mg/dl vs. 12.0 mg/dl, p=0.022)

Conclusion: This study demonstrates for the first time that PCSK9 levels increase with age in ART children indicating a gradual deterioration of lipidemic profile that could lead to increased cardiovascular risk in the future.

P1-P128

Rate of Accumulation of Abdominal Fat Is Associated with Fasting Glucose Levels in Early Childhood

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Objectives: Abdominal fat has been strongly linked to increased cardiometabolic risk and impaired glucose regulation in adults. Owing to the lack of detailed body composition phenotyping in most previous child cohort studies, the temporal links between abdominal fat accumulation and impaired glucose regulation have not been well established. In this study, we evaluated the associations of abdominal fat assessed by MRI at early infancy (≤21 days after birth) and at 4.5 years, as well as the rate of fat accumulation during this interval with glucose regulation assessed at 6 years.

Methods: The participants were from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study, a prospective mother-offspring cohort comprising 1176 children. Abdominal fat MRI was performed on 331 children within the first 2 weeks after birth, and on 316 children at 4.5y (128 children had MRIs at both ages). Abdominal fat was further segmented into deep subcutaneous adipose tissue (DSAT), superficial subcutaneous adipose tissue (SSAT) and intra-abdominal adipose tissue (IAT). The individual depot volumes at both time points were standardized using z-scores. The relative gain in abdominal fat in each depot was calculated as the difference between the z-scores at 4.5y and at early infancy. Fasting plasma glucose was obtained from 543 children at age 6y, and its associations with abdominal fat z-scores at both time points were analyzed after adjusting for ethnicity, sex, maternal education, maternal BMI at recruitment in the first trimester, maternal antenatal fasting glucose, rate of gestational weight gain, and breastfeeding duration.

Results: Higher DSAT and SSAT volumes at 4.5y were associated with higher fasting glucose concentrations (DSAT: adjusted difference (AD) per SD=0.062 mmol/L, 95%CI: 0.010, 0.114, SSAT: AD=0.07 mmol/L, 95%CI: 0.016, 0.123). Higher gain in all the abdominal fat depots between early infancy and 4.5y also showed as-

sociations with higher fasting glucose (DSAT: AD=0.109 mmol/L, 95%CI: 0.041, 0.178, SSAT: AD=0.103 mmol/L, 95%CI: 0.023, 0.184, IAT: AD=0.072 mmol/L, 95%CI: 0.006, 0.137). No associations were observed between any of the neonatal abdominal fat compartments or IAT at 4.5y and fasting glucose at 6y.

Conclusions: A higher rate of abdominal fat accumulation during early childhood and higher subcutaneous fat levels at 4.5y were associated with higher levels of fasting glucose at 6y in Asian children. Our findings highlight the importance of characterizing the dynamic aspects of abdominal fat accumulation in early life for predicting later metabolic health.

P1-P129

Early Menarche Is Associated with Insulin Resistance and Non-alcoholic Fatty Liver Disease in Obese Adolescents

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Background: Menarche is a significant event in the reproductive life of a woman and represents the late event in puberty indicating that a sexually immature child has become reproductively capable.Even though the timing of puberty onset is approximately conserved in different populations, the puberty starts across a wide range of ages in normal girls.However, in the last decades we are observing that girls are experiencing earlier breast development and earlier menarche, also probably due to raised obesity prevalence in youth. Although early menarche (<12 years) is not considerable as a pathological and then treatable event as precocious puberty, it is associated with increased morbidity (i.e.obesity, diabetes, insulin resistance, metabolic syndrome, cardiovascular disease, stroke) and mortality later in life.In addiction, it has also been found an inverse association between age at menarche and non-alcoholic fatty liver disease (NAFLD) prevalence in a large population of middle-aged women.

Objectives: We aimed to evaluate the impact of early menarche on metabolic parameter and NAFLD in a population of Italian obese pediatric patients.

Methods: Three-hundred eighteen young obese (mean BMI-SDS 2.91±0.81) female patients (mean age early menarche group 11.96±2.89 vs 12.85±2.97 years;mean age menarche 10.30±0.83 vs 12.64±0.80) consecutively attending our Obesity Clinic were enrolled. Anthropometric, biochemical, and metabolic evaluations were conducted in all subjects. To detect the presence of hepatic steatosis, a liver ultrasound was also performed.

Results: Patients with early menarche showed higher fasting glucose levels (p=0.003),Homeostasis model assessment of insulin resistance (HOMA-IR) (p=0.02), higher alanine transaminase (ALT) (p=0.016) values and prevalence of hepatic steatosis(67.6% vs 32.4%, p=0.04) than the other obese patients. The two groups showed no difference in BMI-SDS (p=0.35).Moreover, a higher risk to show hepatic steatosis was found in patient with early menarche (OR 1.80,CI 1.11-2.90, p value 0.016).A general linear model for ALT levels including as covariates, HOMA-IR, BMI-SDS, and menarche age (model R^2 25%; model P < .0001) was performed. It confirmed a direct association of ALT levels with early menarche age (p=0.002).

Conclusion: We demonstrated for the first time that obese girls with early menarche had a higher risk of NAFLD and insulin resistance already in adolescence compared to equally obese patients with regular age at menarche. Given that, early identification of these patients could be useful to carry out an adequate management in order to avoid the progression of NAFLD-related metabolic consequences.

P1-P130

The Frequency of Obstructive Sleep Apnea in Children with Hypothalamic and Exogenous Obesity

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Introduction: Hypothalamus is an important regulator of sleep onset, sleep maintenance and wakefulness as well as appetite control. Thus, hypothalamic damage can lead to both sleep dysregulation and severe morbid obesity. So, sleep apnea may be more prevalent and severe in obesity due to hypothalamic damage in comparison to exogenous obesity.

Aim: We aim to compare frequency and severity of obstructive sleep apnea (OSA) in children with hypothalamic and exogenous obesity in order to test the hypothesis that hypothalamic obese patients would be more prone to OSA than exogenous obese subjects.

Methods: Prospective, cross sectional, case control study consisted of 14 hypothalamic obese (4 males) children in study group (10 craniopharyngiomas, 2 suprasellar non-glial tumors, 1 septo-optic dysplasia and 1 patient with damaged hypothalamus and hydrocephalus due to sequela of meningoencephalitis), and 30 exogenous obese (11 males) children in control group. Informed consent was taken from all patients and families. Mallampati scores and scoring of sleepiness was carried out in all patients, and blood was withdrawn for fasting blood glucose, insulin, lipid profile, orexin-A, hsCRP, TNFα. All patients underwent full-night polysomnography.

Results: Mean age (13.08±3.6 vs 14.58±4.44, cases vs controls) as well as sex distribution were similar between the two groups. All patients with craniopharyngioma were operated at least once and all had multiple pituitary hormone deficiency. Body mass index (BMI) and z-score were higher in exogenous obesity group than hypothalamic obesity group. No difference was detected in frequency of hypertension, dyslipidemia, levels of fasting blood glucose, insulin, ratio of fasting blood glucose to insulin, orexin-A, hsCRP, TNFα, Mallampati scores and scoring of sleepiness between the two groups. Obstructive sleep apnea was not correlated to hypertension, insulin resistance, dyslipidemia, levels of inflammatory markers or orexin-A. The apnea-hypopnea index (AHI) of hypothalamic obesity group was higher than that of exogenous obesity group in full-night polysomnography. After adjusting for

age, sex and BMI z-score; the odds of OSA increased 4.4-fold for hypothalamic obese subjects in multivariant analysis. As a result, risk of OSA is significantly increased in hypothalamic obesity group in comparison to exogenous obesity group.

Conclusion: Our findings show that polysomnography should be a part of routine investigation in hypothalamic obesity, even without any complaint suggesting a sleep disorder.

P1-P131

The Importance of Universal Lipid Profile Screening in Two to Ten Years Old Lebanese Children

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Introduction: Dyslipidemia has been recognized as a risk factor for cardiovascular diseases. Studies showed that the development of atherosclerotic lesions begins in childhood and progresses throughout life. While the prevalence of dyslipidemia in adults has been reported to be 10 times higher in Lebanon, there is no available data on the prevalence of dyslipidemic children in Lebanon.

Objectives: This study was conducted to check if a protocol for universal screening for lipid disorder in Lebanese children aged between two and ten years old is needed.

Materials and Methods: A total of four hundred twenty children aged 2 to 10 years old (51.5% boys) were included in the study. These subjects were recruited from private pediatric clinics after parental consent. Fasting total cholesterol (TC), triglycerides (TG), LDL, HDL levels were measured and non-HDL cholesterol was calculated. The values were categorized according to 2011 Expert on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents.

Results: The overall prevalence of high TC (≥200 mg/dL), high non-HDL-C (≥145 mg/dL), high LDL (≥130 mg/dL), high TG (≥100 mg/dL) and low HDL (240 mg/dL with a P value respectively of 0.006 and 0.0001. Furthermore, high TG is independently associated with a BMI ≥ 95th percentile (P=0.0001).Children with parents having TC >240 mg/dL is significantly correlated with high TC, high non-HDL-C and high LDL (P=0.0001 for all variables). Finally, according to the Pediatric dyslipidemia screening guidelines from the 2011 Expert Panel, 62.3% of dyslipidemic children had at least 1 risk factor that qualified them for screening while 37.7% of them didn't have any risk factor.

Conclusions: We might need to reconsider the latest pediatric dyslipidemia screening guidelines by performing a universal screening program because we are missing 37.7% of our dyslipidemic Lebanese children and a healthier diet should be recommended for all age groups.

Key words: dyslipidemia, screening, Lebanese children.

P1-P132

Non-invasive Measurements of Central Blood Pressure with Arterial Stiffness Indicators as a New Research Tool for Predicting Cardiovascular Risk in Children with Type 1 Diabetes Mellitus and Obesity

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Introduction: The main problem of contemporary diabetology is to prevent chronic complications of carbohydrate metabolism disorders according to DM1 and obesity (pre-disposing for DM2). The task is to find simple tools that allow rapid identification of vascular lesions and early treatment intervention.

Aim of the study: The aim of the study was to evaluate parameters of CBP in patients with DM1 and obesity

Materials and methods: The study conducted 100 children matched for age (mean 13 years), body weight, height and sex. The control group consisted of 35 healthy children (W: 21, M: 14). The study groups: DM1 for <5 years (W: 9(A), M: 12(B)), DM1 > 5 years (W: 12(C), M: 13(D)) and patients with obesity (W: 9(E), M: 10(F)) under the care of the Department of Paediatrics, Endocrinology and Diabetology at UDSK in Bialystok. In Addition, on the basis of the HbA1c level the DM1 patients were divided into 2 groups (HbA1c below(G) or above 7.5% (H)). Three CBP measurements were made using Centron Diagnostic System, and the mean values were calculated. Statistical analysis was performed using Stat12.5 (student's t test).

Results: A clear trend was observed, both in girls and boys with DM1, for unfavourable variability of vascular stiffness indexes (AUG / AMP for WW; A;C resp. 0.58 / 1.75; 0.62 / 1, 64, 0.59 / 1.74; MM; MM: B;D > 5 years resp. 0.58 / 1.78; 0.62 / 1.65, 0.59 / 1.75) without statistical relevance between groups. Patients C and D were characterized by a better AUG and AMP than the groups A and B regardless of gender. Both groups independently of HbA1c showed no statistically significant differences in vessel elasticity. However, in both obese E and F group we observed statistically significantly higher values of CBP and PP (CBP / PP for E vs Ko resp. 99/28 vs 124/36, p = 0.007/0.007; F vs Mo resp. 100/33 vs 114/36 p = 0.004, 0.3).

Conclusions: Indices AUG and AMP showed a more favourable variability in children suffering longer in the majority of those remaining on insulin pumps with better metabolic control. The values of the studied parameters were worse in the group with DM1 <5 years, possibly as a residue of ketoacidosis at the time of diagnosis or treatment with pens. Obesity admittedly predisposes to increase the CBP.

P1-P133

Severe Obesity and Cardiometabolic Comorbidities in Adolescents: Chronology of an Epidemic

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Aims: To assess trend in the prevalence of severe obesity in a national population-based sample of adolescents and to evaluate the association of severe obesity with major cardio-metabolic morbidities.

Methods: Prevalence and severity of obesity was determined among 373,226 Israeli adolescents with abnormal BMI (≥85th percentile for age and sex) examined in an obligatory health assessment at mean age 17.3±0.5 years between 1967 and 2015. Data on abnormal blood pressure measurements and type 2 diabetes (T2DM) were considered in a subgroup of 230,639 adolescents examined from 1997 through 2015. Participants were classified into overweight (≥85th to<95th percentile), class I obesity (≥95th percentile to <120% of the 95th percentile), class II obesity (≥120% to <140% of the 95th percentile), and class III obesity (≥140% of the 95th percentile).

Results: There were 2, 4, 16 and 67 fold increases in the prevalence of overweight and class I, II, and III obesity, respectively, between 1967 and 2015, with an accelerated increase in class II and III obesity during the last two decades. Compared to the overweight adolescents, the odds ratios (OR) for hypertension in the class I, II and III obesity groups respectively were 1.4, 2.1, and 2.9 in males, and 1.8, 2.6 and 3.4 in females. The OR for T2DM increased markedly in class I, II and III obesity compared to the overweight groups, from 5.6 to 38 fold in males and from 4.7 to 25 fold in females.

Conclusion: The increase in the prevalence of obesity is differential and was more pronounced for all classes of severe obesity. This steep increase in ORs for hypertension and particularly T2DM along the obesity classes suggests that the burden of cardiometabolic morbidities is expected to increase.

P1-P134

Evaluation of Intraocular Pressure and Retinal Nerve Fiber Layer, Retinal Ganglion Cell, Central Macular Thickness and Choroidal Thickness Using Optical Coherence Tomography in Obese Children and Healthy Controls

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Objective: Obesity and its complications affecting many organ systems have been documented. Nevertheless, study conducted on the ophthalmological effects of obesity are scarce. The aim of the present study was to evaluate the changes in the ophthalmological parameters in obese children in comparison to their healthy counterparts.

Material and methods: Study included 61 obese and 35 age-sex matched controls. Obesity was defined as body mass index-standard deviation (BMI-SDS) >2 SD. Children with a BMI-SDS between >-1 SD and <+1 SD whilst otherwise healthy was recruited as control group. All clinical and ophthalmological investigations were performed by a pediatric endocrinologist and an experienced ophthalmologist. Ophthalmological examination and intraoculer pressure (IOP) measurement was performed. The average retinal fiber layer (RNFL), retinal ganglion cell (RGC), central macular thickness (CMT), cup-to disc ratio (C/D) and central choroidal thickness (CT) were measured using Spectral domain optical coherence tomography (SD-OCT). Antropometric, biochemical and ophthalmological parameters obese and control subjects were compared.

Results: IOP was higher in obese group compared to the controls (p=0.008), while the average RNFL was lower in obese group (p=0.035). There was a negative correlation between the average RNFL and BMI-SDS (r=-0.203; p=0.044) and waist-hip ratio (WHR) (r=-0.256; p=0.015). There was no statistically significant difference between the RGC, C/D, CMT, CT of obese and control group. IOP was negatively correlated with HOMA-IR, body fat mass, body fat percentage and diastolic blood pressure.

Conclusion: In present study evaluating the obesity and its effects on the ophthalmological parameters, elevated IOP and decreased RNFL thickness detected in obese group may suggest an increased risk of developing glaucoma in younger age in obese children. Therefore, a regular opthalmologic examination of obese children is essential for prompt diagnosis and appropriate management.

Fat, Metabolism and Obesity P2

P2-P123

Allopurinol Ameliorates Non-Alcoholic Fatty Liver Disease in Rats

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Background: Hyperuricemia has been found to be associated with non-alcoholic fatty liver disease (NAFLD).

Aim: The aim of this study was to evaluate whether allopurinol affects the course of experimental NAFLD in rats.

Study Design: Mature, albino Sprague Dawley rats were fed water containing 30% fructose without ethanol for up to 8 weeks. After demonstration of steatosis in the 8th week, either allopurinol or saline was administered daily.

Methods: Liver histopathological score was determined according to steatosis (the percentage of liver cells containing fat): <25% = 1+, 25% - 50% = 2+, 51% - 75% = 3+, >75% = 4+; inflammation and necrosis: 1 focus per low-power field = 1+; and 2 or more foci= 2+. The number of liver IL-1 and IL-2 positive cells was measured by systematically scoring at least 100 hepatocyte cells per field in 10 fields of tissue sections at a magnification of 100.

Results: Allopurinol group presented significant difference in xanthine oxidase (XO) activity and lipid peroxidation compared with saline treatment (XO; 0.098 ± 0.006 mU/mg g vs. 0.162 ± 0.008 mU/mg, $p<0.05$, 0.116 ± 0.040 nmol MDA/mg g vs. 0.246 ± 0.040 nmol MDA/mg, $p<0.05$). Allopurinol group had lower histopathological score, IL-1 and IL-2 immunoexpression in the liver than saline group (2.13 ± 0.35 vs. 5.45 ± 0.24, $p<0.05$, IL-1; 5.76 ± 0.43 vs. 12.85 ± 3.26, $p<0.05$, IL-2; 8.55 ± 1.14 vs. 56.23 ± 7.12, $p<0.05$).

Conclusions: Allopurinol ameliorates non-alcoholic fatty liver disease by reducing xanthine oxidase activity and lipid peroxidation.

P2-P124

Relationships of Dietary Intake and Sugar Rich Products Consumption with Hepatic Fat Content and Insulin Resistance Among Children with Overweight/Obesity: The PREDIKID Study

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Pediatric non-alcoholic fatty liver disease (NAFLD) has increased in parallel with childhood obesity. Dietary habits, particularly products rich in sugars, may influence both hepatic fat content and insulin resistance. Hence, the aim of the current study was to examine the associations of the consumption of dietary foods (cereals, fruits and vegetables, meat and meat products, dairy products, fish and shellfish, total and added sugars) and composition (macronutrients and fiber), as well as the influence of the sugar-sweetened beverages (SSB) and dairy desserts and substitutes (DDS), on hepatic fat and insulin resistance in children with overweight/obesity. For such purpose, dietary intake (two non-consecutive 24h-recalls), hepatic fat content (magnetic resonance imaging) and insulin resistance (HOMA-IR) were assessed in 110 children (10.6±1.1 years old) with overweight/obesity. Linear regression analyses were used to examine the associations of dietary intake with hepatic fat content and HOMA-IR adjusted for potential confounders (sex, age, energy intake, maternal educational level, body fat percent or abdominal adiposity, and sugar intake). The results showed that both SSB consumption and sugar in SSB ($\beta=0.202$ and $\beta=0.204$, adjusted $Ps<0.05$), but not DDS or sugar in DDS or other dietary components, were positively associated with hepatic fat content regardless of potential confounders. In contrast, none of dietary variable was associated with insulin resistance. In conclusion, SSB consumption and its sugar content, but neither DDS nor sugar in DDS, may increase the likelihood of having NAFLD and therefore, nutritional intervention programs should be promoted so as to achieve healthy dietary habits since childhood.

P2-P125

Angiotensin-Converting Enzyme Insertion/Deletion Gene Polymorphism in Egyptian Obese Children and Adolescents: Relation to Hypertension Risk

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Background: Angiotensin converting enzyme (ACE) is a possible candidate gene that may influence both body fatness and blood pressure. Although several genetic studies have been conducted in adults, relatively few studies have examined the contribution of ACE candidate genes for development of the obesity-hypertension phenotype early in life.

Aim: To screen Egyptian obese children and adolescents for insertion/deletion (I/D) polymorphism in the gene encoding ACE and its relation to hypertension and other features of metabolic syndrome.

Methods: Seventy obese children and adolescents were compared to 72 controls. All were subjected to history, blood pressure measurement, anthropometric assessment and assessment of fasting lipid profile and fasting glucose and insulin. In addition, DNA extraction and genotyping for ACE I/D gene polymorphism was done.

Results: Obese children had higher frequency of DD genotype (cases 30% versus 11.1 % in controls, p=0.01) and D alleles (cases: 61.8% versus 48.6% in controls, p=0.01) and lower frequency of II genotype (cases: 27.1% versus 34.7% in controls, p=0.04) and I alleles (38.2% versus 51.4% respectively, p=0.01) than controls. Also, obese children with hypertension and pre-hypertension had higher frequency of DD genotype and D alleles and lower frequency of II genotype and I alleles than those with normal blood pressure. DD genotype and D allele were risk factors for hypertension while dyslipidemia and insulin resistance were not associated with I/D polymorphism in the ACE gene.

Conclusion: DD genotype and D-allele of I/D polymorphism in the ACE gene were associated with a higher risk of hypertension pre-hypertension in Egyptian obese children.

P2-P126

Serum Calprotectin Level in Children: Marker of Obesity and Its Metabolic Complications

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Aim: circulating levels of calprotectin have been reported in obesity-related chronic low-grade inflammation in adults, but has not been evaluated in pediatric population. We investigated serum calprotectin in overweight and obese children and its association with metabolic comorbidities.

Methods: We enrolled 131 children (11.7±4.1 years). According to body mass index (BMI), the subjects were divided into three groups: obese> 95th percentile; overweight BMI 75th–95th percentile and normal weight BMI < 75th percentile. Patients were classified as having Metabolic Syndrome (MetS) if they met three or more of the following criteria for age and sex: BMI>97th percentile, triglycerides >95th percentile, HDL cholesterol <5th percentile, systolic and/or diastolic blood pressure >95th percentile and impaired glucose tolerance. In all patients calprotectin serum levels were also detected.

Results: In obese and overweight children, serum calprotectin level was higher compared to normal weight subjects (p<0.001). No significant difference between patients with obesity and overweight (p=0.07) was observed in calprotectin values. Calprotectin was higher in female than males (p=0.04).

Pathological calprotectin concentration was found in 42/56 children with obesity (75%), in 21/36 overweight children (58.3%) and in 15/39 normal weight ones (38.4%).

Increased calprotectin was related to pathological fasting blood glucose (p<0.001) and insulin resistance (p=0.03). No significant correlation with other pathological clinical or biochemical parameters was noted.

Multiple regression analysis identified BMI (CI 95% 0.53-2.17, p=0.001) and diastolic pressure (CI 95% 0.02-0.11, p=0.001) as independent factor for increased serum calprotectin.

Conclusions: our findings support a role of calprotectin as a marker of obesity-associated chronic low-grade inflammation in children and suggest the potential utility of this biomarker in the monitoring of its metabolic complications.

P2-P127

Pediatric Continuous Metabolic Syndrome Score (PsiMS score): Use in Everyday Clinical Practice

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Introduction: dichotomous nature of current definition of metabolic syndrome (MS) in youth results in loss of information. On the other hand, the complex calculation of continuous MS scores using standardized residuals in linear regression (Z scores) or factor scores of principal component analysis (PCA) is demanding and highly impractical for clinical use. Recently, a novel, easily calculated continuous MS score called Pediatric siMS score (PsiMS score) was developed based on the IDF MS criteria for the pediatric population. Database including data on 153 obese children and adolescents was used for score development. Results showed that PsiMS score calculated using formula: (2xWaist/Height) + (Glucose(mmol/l)/5.6) + (triglycerides(mmol/l)/1.7) + (Systolic BP/130)-(HDL(mmol/l)/1.02) showed high correlation with most of the complex continuous scores calculated using sum of Z scores or factor scores of PCA (0.792-0.901). Complex metabolic syndrome scores require advanced statistical software, limiting their use in everyday clinical practice. The development of PsiMS score overcomes these issues, since it correlates highly with complex scores, while being simple and easy to calculate. Also, PsiMS score is not sample specific, meaning that scores from different studies can be compared, as well as changes in score of a single patient.

Objective: to demonstrate the usefulness of PsiMS score calculation in research and everyday clinical practice.

Method: examples of different clinical scenarios, including significant changes in cardiometabolic risk factors in individual obese subjects with metabolic syndrome will be presented, illustrating the benefits of easily quantifying metabolic syndrome in everyday clinical setting for both patients and physicians.

Conclusion: PsiMS score represents a practical and accurate score for quantification and evaluation of MS in the obese youth.

P2-P128

Leptin and Cytokines Are Not the Best Markers for Metabolic S

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Introduction: Leptin, some cytokines and triglycéride/colesterol -HDL ratio (TG/C-HDL ratio) are markers of insulin-resistance in children and adolescents with overweight/obesity. Due to the high prevalence of this pathology it´s necessary to find and easy and better routinely marker that identify these patients in the outpatient clinic.

Previous results demonstrated that TG/C-HDL ratio >2 was a better predictor of metabolic syndrome (sensitivity 100%; specificity 76.7 %) than HOMA or insulin, without differences between sex and pubertal stage (p<0,0001).).

Objective: Define if leptin and some cytokines are better markers of insulin-resistance than TG/C-HDL ratio in the pediatric population with overweight/obesity

Methods: Patients with overweight/ obesity defined by Orbegozo 2008 were included. Anthropometric variables (body mass index, waist circumference) were measured with standard methods. Sexual maturity was evaluated by Tanner staging. Abdominal ultrasound scan was performed to detect liver steatosis.. Biochemical data: fasting plasma glucose (FPG), 2h OGTT glucose, insulin, HOMA, lipid profile, and C-peptide were analyzed. Cut off point was considered >95th percentile of each variable. Metabolic syndrome was diagnosed according to criteria of Diabetes International Federation. Leptin, adiponectin and osteocalcin were analyzed by enzymoinmunoanalysis. SPSS.19 was used for statistical analysis.

Results: Data from 110 patients (2-17 years of age) were included, 40% boys and 44,6% pubertal.BMI 27,77 (19,4-36,98) kg/m2.

There is a positive correlation between TG/C-HDL ratio and HOMA (p 0.04), leptin (p 0.04) and osteocalcin (p 0.06) and negative with adiponectin (p 0.09).

Those patients (35) with TG/C-HDL ratio >2 have higher levels of leptin (p 0,02).

There were no correlation between leptin y/o cytokines levels with liver steatosisbut interestingly patients with this liver disease have significant higher values of the TG/C-HDLratio (p 0,027).

Conclusions: Due to differences in standard values of leptin and cytokines related to age, sex and pubertal stage, TG/C-HDL ratio>2 could be and effective and simple tool to identify the early stage of potential metabolic syndrome in overweight/obese paediatric population at any age and pubertal stage, avoiding expensive resources.

P2-P129

Early-Life Risk Factors and their Association with Hypertension In Spanish Children and Adolescents

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Introduction: In the last years, the prevalence of high blood pressure (HBP) has increased in children, contributing to raise the risk of future cardiovascular disease. It is known that family history, pregnancy characteristics and type of feeding in the first months of life are of great importance in the prevention of diseases in the offspring. In this study we aimed to investigate the association between early life risk factors and HBP in children and adolescents.

Materials and Methods: A total of 794 children between 5 and 18 years were recruited (53,3% girls, 49,7% prepubertal, 42,9% with overweight/obesity). Blood pressure (BP) was measured and information regarding early life risk factors was collected with a parental questionnaire. HBP was considered when systolic BP≥P90 (Task Force 1996). Associations between HBP and early life risk factors were analyzed with a binary logistic regression adjusted for age, sex and body mass index. All analyses were conducted with SPSS 21.0.

Results: Children whose parents had a history of HBP had an increased risk of HBP themselves (OR=2,031, 95% confidence interval (CI) 1,422-2,900, P<0,001). In addition, children whose mothers had gestational diabetes or pregnancy-induced hypertension showed an increased HBP risk than those born to mothers with healthy pregnancies (OR=2,057, 95% CI 1,214-3,483, P=0,007; OR=3,102, 95% CI 1,911-5,037, P<0,001; respectively). HBP risk also increased in premature children (30-37 weeks) (OR=2,262, 95% CI 1,299-3,938, P=0,004), children born by C-section (OR=2,133, 95% CI 0,766-5,943) or children who had an early start of complementary feeding (<4 months) (OR=2,832, 95% CI 1,526-5,258, P=0,001). No statistically significant associations were observed between birth weight or exclusive breastfeeding and childhood HBP.

Conclusion: Parental history of HBP, pregnancy complications, premature or C-section delivery and an early complementary feeding introduction before 4 months increase the risk of HBP in children and adolescents independently of BMI. Adequate mechanisms should be established in order to avoid modifiable risk factors and to prevent further health alterations in children already at risk.

P2-P130

A Rare Case of Diabetes Mellitus in an Adolescent: Partial Lipodystrophy

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Introduction: Lipodystrophies are heterogeneous group of disorders; characterized by congenital or acquired loss of fat tissue. These disorders can causes severe metabolic complications during childhood.

Case: 10,5 years old girl admitted to our clinic due to pigmented lesions on her body.She was investigated due to sclerotic lesions on her legs when she was 8 years old and was diagnosed as scleroderma and methotrexate was initiated. On physical examination weight was 47 kg (+1,4 SDS) and height was 158.7 cm (+2.6 SDS). Acanthosis nigricans on her neck, prominent musculature, and loss of body fat in lower extremity existed. HOMA-IR was 6. She was treated with life style modifications and medical nutritional therapy. After 4 years follow up, hirsutism, thickening of the voice and menstrual irregularity started. On her physical examination cliteromegaly, increased appearance of acanthosis and increased loss of fat tissue was found. The whole-body MR revealed significant fat tissue loss in lower extremity and fatty liver. Autoimmune disease screening, C3, C4 levels and HIV serology were negative. On her 15th year she was diagnosed as diabetes mellitus (DM) with a serum glucose: 219 mg/dL and HBA1c of 12.4%. Serum leptin value was 4,31 ng/mL. Genetic analysis of familial partial lipodystrophy (LMNA, PPARG, PLIN1, AKT2) was negative.With medical history and severe clinical findings, she was diagnosed as acquired partial lipodystrophy secondary to panniculitis. Her ongoing treatment is multiple daily dose insulin (2.0 unit/kg/day), metformin, life style modifications and medical nutrition therapy. Recombinant leptin (metreleptin) treatment is planned.

Conclusion: Partial lipodystrophies are rare diseases during childhood, but they can lead to insulin resistance, diabetes mellitus and severe metabolic complications. Although high dose insulin treatment is insufficient for controlling DM, metreleptin replacement therapy can be successful.

P2-P131

Visfatin, RBP4 and STRA6 Polymorphisms' in Relation with Childhood Obesity

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Background: Several visfatin, retinol binding protein 4(RBP4) and high affinity receptor for RBP4, STRA6 (stimulated by retinoic acid) single nuclear polymorphisms' (SNP) have been investigated regarding their relationship with obesity with controversial results.

Aim: to analyze the association of two specific SNP for visfatin, RBP4 and STRA6 with anthropometric markers of obesity in children.

Material and method: A case control study was conducted on a sample of obese children and age and sex-matched controls evaluated in the Endocrinology Department of the Mures County Hospital. Variables analyzed: age, sex, environment, body mass index (BMI) standard deviation score (SDS) according to WHO reference, waist circumference SDS, bicipital skinfold SDS, 2 SNP for visfatin - rs4730153 and rs2302559, 2 for RBP 4 - rs3758539 and rs10882280 and two for STRA6 - rs974456 and rs351224. Statistical analysis used SPSS v.17.0 with a level of significance of α=0.05.

Results: 124 obese and 81 age and sex-matched control subjects were assessed with a mean age of 11.5±2.8 years for the cases and 11.7±3.3 years for controls. There is no significant association between the various genotypes analyzed and anthropometric markers. The presence of allele T of the rs2302559 (OR=0.558, 95%CI 0.317-0.984, p=0.046) and allele A for the rs4730153 (OR 0.532, 95%CI 0.297-0.952, p=0.037) have a protective role against obesity defined by BMI SDS.

Conclusions: Visfatin gene SNP might be associated with childhood obesity, but further larger studies in order to confirm the association at population levels is needed.

P2-P132

Characteristics of Blood Lipids in Boys with Hypoandrogenia

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Discussed in literature is primarily the impact of late-onset hypogonadism in men as a factor of development of endothelial dysfunction, insulin resistance and systemic inflammation, while the pathogenic role of hypoandrogenia in development of metabolic disorders in male individuals during puberty currently remains undetermined.

Aim of research: to determine characteristics of lipid profile in adolescent boys with hypoandrogenia.

Materials and methods: There were 25 boys under observation, aged 14–17 years, with signs of androgen deficiency (AD), divided into three groups according to degree of AD (I, II, III). Assessment of puberty stage was performed by Tanner and examination of blood lipids was conducted using kits produced by «CormayMulti» company (Poland), with identification of lipid fractions (triglycerides (TG), total cholesterol (TC), low-density (LDLC) and high-density lipoprotein cholesterol (HDLC)) and subsequent calculation of atherogenic index (AI).

Research results: Analysis of lipid profile indicators in adolescent boys with hypoandrogenia, depending on degree of delay in sexual development, has shown that there are no reliable discrepancies in TC level. We have identified an increase in TG level during the intensification of AD: from 0.76±0.15 mmol/L with I degree to 1.25±0.18 mmol/L with II degree and 1.44±0.19 mmol/L with III degree, p<0.05. HDLC level, on the contrary, was higher with I degree of AD (1.99±0.15 mmol/L) than with II (1.49±0.16 mmol/L) and III degrees of AD (1.42±0.11 mmol/L), p<0.05. Such shifts of lipid indicators have led to respective growth of AI with increase of AD degree: 1.51±0.31 units with I degree, 2.39±0.40 units with II degree and 2.70±0.36 units with III degree of AD (p<0.05).

Conclusion: Therefore, analysis of lipid profile indicators in adolescent boys with hypoandrogenia has shown lipid profile worsening during intensification of AD, due to increase of proatherogenic lipid fractions and decrease of antiatherogenic ones, which may be the evidence to reliable impact of androgen deficiency on early development of atherosclerosis in adolescent boys in the course of puberty.

P2-P133

Tri-Ponderal Mass Index. A Good Anthropometric Index to Evaluate Adiposity in Children and Adolescents

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Background: The adiposity measurement by reliable methods such as dual X-ray absorptiometry (DXA) is not feasible in routine medical care and instead of this, the anthropometric methods are used. However, these methods could be inaccurate to estimate the body fat content. Additionally, in pediatric patients, some anthropometric indexes requires percentiles or Z-scores for their interpretation, like the body mass index (BMI) or the waist circumference (WC). Although anthropometric indexes with a single cut-off point, such as tri-ponderal index (TMI [weight/height^3]) or waist-to-height ratio (WHtR) have been proposed as an alternative to adiposity assessment, it is important to evaluate their accuracy.

Objective: To evaluate different anthropometric methods to estimate body fat percent by DXA (bfDXA) in children and adolescents.

Table 1. Diagnostic performance of anthropometric indexes for the detection of overweight/obesity (for Abstract no P2-P133)

Anthropometric index	Males			Females		
	Sensitivity	Specificity	% Adequate classification	Sensitivity	Specificity	% Adequate classification
BMIZ	73	96	77	71	96	75
WHtR	73	99	76	57	97	63
TMI cut-off previously reported[a]	74	93	91	65	93	89
TMI (≥15.2 kg/m^3)	87	89	88	93	80	82

[a] Males: >16.0 kg/m^3; females: >16.8 kg/m^3.

Methods: We conducted a cross-sectional study. We included 1,513 participants between 5 to 18 years old. We measure weight, height and WC by standardized methods and BMI, TMI and WHtR were calculated. The adiposity was evaluated by whole body less head DXA. A linear regression analysis was performed to estimate bfDXA. We also analyzed ROC curves for the detection of overweight/obesity (≥p85 bfDXA) and we identified the optimal cut-off value for TMI. We compare the diagnostic performance of BMIZ, WC, WHtR and TMI.

Results: We identified a R^2 between 0.28 to 0.76 with the different anthropometric methods in males and 0.51 to 0.66 in females. The WC had the lowest values of R^2 while TMI, BMIZ and WHtR explained a higher variance of bfDXA. The areas under the curve to detect overweight/obesity were found between 0.92 and 0.95 for TMI, BMIZ and WHtR in both genders, without significant differences between them. We identified a TMI≥15.2kg/m^3 in both genders as an optimal cut-off value. Table 1 shows the diagnostic performance to detect overweight/obesity for each anthropometric index.

Conclusion: TMI is an easy and acceptable tool to estimate the body fat in children and adolescents. TMI has a better diagnostic performance for an adequate classification of adiposity in comparison of BMIZ and WHtR.

P2-P134

Serum Spexin Concentrations in Adolescent Females with Metabolic Syndrome, Polycystic Ovary Syndrome and Anorexia Nervosa

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Background: Spexin is a novel hormone that may potentially impact food intake, weight regulation and body adiposity. Circulating spexin has been associated with obesity and insulin resistance indices in women.

Objective: The aim of this study was to determine serum spexin concentrations in adolescent females with metabolic syndrome, with polycystic ovary syndrome (PCOS), with anorexia nervosa as well as in healthy controls, and explore possible relationships between circulating levels of spexin and body mass index (BMI).

Methods: Study participants included adolescent females, aged 12-21years, diagnosed with metabolic syndrome (International Diabetes Federation), PCOS (Rotterdam), anorexia nervosa (DSM-5), as well as healthy controls, who presented to the Centre for Adolescent Medicine and UNESCO Chair on Adolescent Health Care, between January 2015-May 2017. Exclusion criteria included severe comorbidity, chronic medication, contraceptive use and pregnancy. Serum spexin concentrations were measured by ELISA using the Spexin (Human) EIA Kit of Phoenix Pharmaceuticals (USA) with analytical sensitivity of 0.08 ng/ml. Kruskal-Wallis test and Spearman's rho correlation were used for statistical analyses.

Results: A total of 82 adolescent girls aged (mean±SD) 16.2±2.2years; 14 females with metabolic syndrome (mean

age±SD, 14.9±1.9years; mean BMI±SD, 29.1±6.7 kg/m^2), 17 obese females with PCOS (mean age±SD, 15.4±2.0years; mean BMI±SD, 26.7±3.3 kg/m^2), 23 lean females with PCOS (mean age±SD, 16.9±2.1years; mean BMI±SD, 21.1±1.4 kg/m^2), 11 anorexic females (mean age±SD, 15.0±1.5years; mean BMI±SD, 15.9±1.0 kg/m^2) and 17 controls (mean age±SD, 17.7±2.2years; mean BMI±SD, 19.9±1.5 kg/m^2), participated in the study. No significant differences (p=0.260) were observed in serum spexin concentrations among adolescents with metabolic syndrome (median±IQR, 0.27±0.06 ng/mL), obese with PCOS (median±IQR, 0.29±0.09 ng/mL), lean with PCOS (median±IQR, 0.24±0.16 ng/mL), with anorexia nervosa (median±IQR, 0.31±0.12 ng/mL) and controls (median±IQR, 0.20±0.22 ng/mL). Serum spexin levels were not correlated with BMI (r_s=-0.141, p=0.216).

Conclusion: Results suggest that circulating levels of spexin cannot discriminate adolescent females with metabolic syndrome, PCOS or anorexia nervosa and across a wide range of BMI. These findings need to be confirmed in larger adolescent populations.

P2-P135

A Simple Relaxation Exercise Reduces Stress in Obese Youth – A Path to a Healthy Lifestyle?

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Introduction: Lack of impulse control and impaired stress regulation may explain the development of obesity and its challenging therapy, already in youth (Nederkoorn 2007). To improve self-regulation of overweight adolescents and subsequently their weight status, we tested, whether a biofeedback relaxation exercise decreases stress and whether relaxation services implemented in a novel Smartphone App supported intervention have effects on stress and weight outcomes.

Methods: First 6 months' data in 31 adolescents with BMI >P.90 of an ongoing 12-month randomized controlled study are being reported. Patients try to relax over two minutes through a breathing exercise while observing in real time their arousal level measured as skin conductance with NeXus-10. Cortisol in blood as stress marker is measured before and after this exercise, at start, 3, 6 and 12 months. During the intensive phase of 6 months, 18 patients of the intervention group (IG) are equipped with a smartphone and a specially designed chat App with game character, which encourages them through a virtual coach to achieve daily activity or relaxation challenges and earn virtual rewards. While 13 patients of the treatment as-usual group (CG) have monthly visits on site during the intensive phase, IG has only four visits. Beside BMI and BMI Standard Deviation Score (SDS), adjusted for age and sex, clinical parameters and stress questionnaires (TICS) are being assessed at start, 6 and 12 months.

Results: Age (13.7 years, 11-17), mean BMI (30±3.8kg/m^2), mean BMI SDS (2.5±0.5 SD) and cortisol levels (median 217, 48-511mmol/L) were similar in both groups at start. In the IG, cortisol levels decreased after the biofeedback session by 31% (p=0.04) at start, by 24% (p=0.01) after 3 and 32% after 6 months (p=0.002). The CG exhibited a significant cortisol decrease by 34% (p=0.005) at start and by 42% after 3 months (p=0.002), but not after 6 months. No long-term changes of cortisol were observed. BMI SDS was stabilized in the IG (Δ BMI SDS -0.04) while decreased significantly in the CG (Δ BMI SDS -0.4, p=0.01) after 6 months. So far, no consistent correlations between changes in BMI SDS and cortisol during therapy were found.

Conclusion: Electrodermal biofeedback regulates acute stress in obese adolescents, an age group with difficulties managing emotions and can be a valuable tool in obesity therapy. The long-term effects of biofeedback therapy on chronic stress and BMI are currently under investigation.

P2-P136

Dyslipidemia And Its Related Factors in Chinese Children and Adolescents with Turner Syndrome

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Turner syndrome is associated with insulin resistance, increased incidence of type II diabetes, and hypertension, all of which are cardiovascular risk factors. The purpose of this study was to evaluate the lipid profile of Chinese girls with untreated Turner syndrome, (aged 2 to 15 years;50.9% 45,XO) and age-matched, normal girls. A total of 108 girls with Turner syndrome and 99 normal girls had lipid profile measurements, including cholesterol, triglycerides,high-density lipoprotein cholesterol and low-density lipoprotein cholesterol. Older girls with Turner syndrome (>11 years,when the girls with Turner syndrome supposed to receive hormone replacement therapy) had increased triglycerides levels,higher incidence of hypertriglyceridemia, borderline-hypertriglyceridemia and borderline-hypercholesterolemia compared with control subjects. But there were no differences between TS patients who were less than 11 years old and age-matched control girls. TS patients of 45, XO karyotype had decreased triglycerides levels,increased high-density lipoprotein cholesterol levels and lower incidence of borderline-hypertriglyceridemia compared with those of other karyotypes. In the subjects with Turner syndrome but not the normal subjects, serum triglycerides positively related to waist circumference. We conclude that adolescent girls with untreated Turner syndrome have increased triglycerides levels,which may related to estrogen deficiency and chromosome karyotype.

P2-P137

Severity, Duration and Phenotype of Obesity Promote Precocious Cardiovascular Sonographic Alterations in Childhood Obesity

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Introduction: Childhood obesity is known to be associated with an increased risk of cardiovascular and metabolic complications in adulthood.

Objectives: 1) To evaluate precocious cardiovascular sonographic modifications in a cohort of overweight (OW) and obese (OB) children and adolescents brought to Outpatient Clinic of Pediatric Endocrinology for first evaluation, compared with normal weight controls. 2) To investigate the association between clinical and metabolic variables and cardiovascular sonographic parameters; 3) to evaluate their relation with two different phenotypes of obesity: metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUHO).

Material and Methods: Fifty-nine OW and OB children and adolescents (range 6-16 years) and twenty matched lean controls underwent to anthropometric, biochemical, echocardiographic and sonographic evaluation of carotids and ascending aorta (AA) assessment. OW and OB subjects were divided in MHO and MUHO, according to Camhi et al definition (J Obes 2013:984613).

Results: OB and OW children showed significantly higher systolic blood pressure (SBP), left ventricular (LV) dimensions, carotid artery intima-media thickness (CIMT), Beta-index, carotids pulse wave velocity (PWV), and significantly lower peak early diastolic velocity/peak late diastolic velocity-ratio (E/A-ratio), compared to controls.

Among OB and OW children, BMI SD, HOMA-index and SBP were positively related with left atrial (LA) and LV dimension and mass, and with epicardial fat (P-Lax). Moreover, SBP was positively related with PWV. BMI SD was negatively related with E/A-ratio.

BMI SD, SBP, uric acid (UC), triglycerides (Tg) were significant predictors of LA and LV dimension and P-Lax, while SBP and duration of obesity were predictors of AA diameters and stiffness.

Furthermore, BMI SD (p=0.018), waist circumference (WC) (p=0.001), hip circumference (p=0.009), WC/height-ratio (p=0.001), HOMA-index (P=0.004), Tg (p=0.013), UC (p=0.013), SBP (p=0.001), LV dimension and mass (p=0.012), P-Lax (p=0.028), CIMT (p=0.011), PWV (p=0.002), Beta-index (p=0.026), Aortic stiffness (p=0.006) were significantly higher among MUHO compared to MHO children.

Conclusions: Precocious detection of cardiovascular modifications were associated with severity, duration and MUHO phenotype of childhood obesity. MUHO, characterized by higher prevalence of metabolic alterations and early cardiovascular modifications, determines an increased cardiometabolic risk since the pediatric age. Distinction between MHO e MUHO phenotypes is important to plan a personalized approach for the follow-up in obese children.

P2-P138

Physical Activity Determined by Accelerometry Before and After an Integral Treatment Program in Children with Abdominal Obesity

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Introduction: Physical activity (PA) is one of the treatments to promote weight loss in children with obesity. The WHO advices to perform moderate to vigorous (MV) PA during 60-min daily. It is necessary to measure the effect of increasing PA and the adherence to therapy.

Aims: To evaluate PA using accelerometry at the onset and after 8 weeks of treatment with nutritional intervention and increase in PA.

Patients, material and methods: 122 children and adolescents (age 7-16 years) diagnosed with abdominal obesity (waist circumference <p90) were included in a randomized-controlled clinical trial (NCT 03147261). Anthropometrical data: weight, height, BMI, waist (W), hip (H) and fat mass percentage. Patients were randomized in 2 groups: control, treated with the conventional recommendations and intervention group, treated with moderate caloric restriction according to BMI. Both groups were instructed to increase their PA in 200 minutes per week. The PA was determined by 4-day accelerometry including the weekend (Actigraph GT3X accelerometer, Actlife software).

Results: Full accelerometer data were obtained from 106 patients (40 boys), mean age 11.31 (2.47SDS). PA was superior during the week than during the weekend (p<0.001) and the contrary was observed in sedentary time (p<0.001). At the beginning of the study 25% of children fulfilled the WHO recommendations (32% during the week and 16% during the weekend) and 28% after 8 weeks. In the control group sedentary time increased (p=0.007) and light PA (LPA) decreased (p=0.003). The intervention group increased the MVPA (p=0.024) and decrease the LPA (p=0.04). In both groups a decrease (p<0.005) in weight, BMI-SDS, W, W/H index and leptin and glucose serum levels, was observed. In the intervention group serum insulin levels and HOMA also decreased (p<0.05).

Conclusions: Objectively measurement of PA by accelerometry indicates that the intervention group improves the MVPA. The patients included in this study performed more PA during the week than during the weekend.

P2-P139

The Associations Between Neck – and Upper Arm Circumference with Cardiometabolic Risk Over Traditional Risk Factors in Adolescents – Data from Five European Countries (PreSTART-Study)

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Background: Prevalence and severity of obesity and associated comorbidities are increasing in adolescents. Data on neck and upper arm (UA) circumference in addition to established anthropometric measures to define cardiometabolic risk are limited to date.

Methods: Data from Phase I of the EU-funded *PreSTART*-study (trial registration number NCT02545140) was applied. Demographic, clinical, biochemical and lifestyle data were collected in adolescents (12-14 years) from 5 European countries (UK, Portugal, Spain, Germany and Greece). All data were collected with the same standard operating procedures at each site, and fasting blood samples for measurement of HbA1c, glucose, cholesterol (Chol), triglycerides (TG), HDL-C and LDL-C were analysed using the same test kits. Anthropometric measures included weight, height and circumferences for waist, neck and UA. Correlation and linear models were used to establish associations.

Results: 584 adolescents (52% males) were included. Age and sex dependent BMI-z score correlated strongly with neck circumference (0.65 [95% CI 0.61, 0.70], p<0.001) and UA circumference (0.86 [95% CI 0.84, 0.88], p<0.001).

TG was lower in boys (p=0.0011) and showed a strong site dependence (p<0.001) with non-UK centres having lower values. TG was associated with waist to height ratio (WHtR) (1.18-fold [95% CI 1.12 to 1.25] per 0.1 increase in WHtR, p<0.001), neck circumference (1.043-fold [95% CI 1.028 to 1.058 per 1 cm increase], p<0.001) and UA circumference (1.031-fold [95% CI 1.021 to 1.041) per 1 cm increase, p<0.001).

Total Chol (n=539) was lower in boys (p<0.001) and associated with WHtR (0.10 mmol/L [95% CI 0.03 to 0.18] per 0.1 increase, p=0.007) as well as UA circumference (0.017 mmol/L [95% CI 0.004 to 0.031]) per cm increase, p=0.012).

HDL-C (n=536) also showed a site dependence (p=0.032) and was strongly associated with WHtR (-0.11 mmol/L [95% CI -0.15 to -0.07] per 0.1 increase in WHtR, p<0.001), with neck circumference (-0.041 mmol/L [95% CI -0.051 to -0.030] per cm increase, p<0.001) and with UA circumference (-0.024 mmol/L [95% CI -0.032 to -0.016] per cm increase, p<0.001).

HbA1c was not associated with anthropometric or lab parameters.

Discussion: Neck and UA circumference strongly correlate with BMI z-score and WHtR and are associated with cardiometabolic risk in a cohort of 12-14 year old adolescents from 5 European countries. Future studies need to assess to what extent subcutaneous fat depots from the upper body may provide additional predictive power above visceral fat.

P2-P140

Sex-related Differences and Effect of Puberty on Metabolic Syndrome in Obese Children and Adolescents

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Introduction: Metabolic syndrome (MS) is a known complication of obesity. It is still unclear whether gender and puberty influence the prevalence of MS in children and adolescents.

Objective: Aim of the study was to evaluate the effect of gender and puberty on the prevalence of MS and on cardiovascular risk factors (CVRF) in obese children and adolescents.

Patients and Methods: 1437 obese patients (age 9.7 (2.2-17.9) ys; 660 Male) were included in this retrospective analysis. Subjects were stratified according to Tanner pubertal staging (prepubertal (PREP), pubertal stage 2-3 (PS2-3), pubertal stage 4-5 (PS4-5)). Waist circumference (WC), systolic and diastolic blood pressure (SP, DP), fasting plasma glucose (GLU) and insulin (INS), post Oral Glucose Tolerance Test glucose (post-OGTT GLU) and insulin (post-OGTT INS), and lipids were evaluated in all subjects. HOMA index (GLU(mmol/L) x INS(mU/L) / 22.5) was calculated as insulin resistance index. MS was defined according to the IDEF-ICS criteria in 2-10 ys patients (Group 1) and IDF criteria in patients ≥10 ys (10-16 ys=Group 2, ≥16 ys=Group 3).

Results: The overall prevalence of MS was 10.9%. BMI-SDS (PREP, PS4-5), WC (All, PREP, PS4-5), SP (All, PREP, PS2-3, PS4-5), DP (PREP, PS2-3), GLU (All, PREP, PS4-5) and triglycerides (All, PS4-5) were higher in males. Mean INS and post-OGTT INS were higher in All, PREP and PS2-3 females.The CVRF more frequently abnormal in males were WC (All, PREP, PS4-5), SP (All, PS2-3, PS4-5) and GLU (All), while HOMA was more frequently abnormal in All and PS2-3 females.

WC was more frequently abnormal in PREP, while SP was more frequently abnormal in pubertal patients, regardless of sex. PS2-3 males showed more frequent abnormalities of GLU and less frequent abnormalities of HOMA. HDL was more frequently abnormal in PS2-3 female. The prevalence of MS was higher in PREP and PS4-5 males of group 2 and in group 3.

Conclusions: Sex and pubertal status influence the prevalence of MS and the frequency of abnormalities of CVRF in obese children and adolescents. CVRF are already present in prepubertal age, and their prevalence is higher in male. Identifying patients with higher risk of metabolic complications and cardiovascular risk factors is important to design targeted and effective prevention strategies.

P2-P141

Associations Between Total Leptin, Bio-Inactive Leptin, Soluble Leptin Receptor and Anthropometrics in Children with Severe Early-Onset Obesity (SEOO) – The German-Polish Study (EOL-GPS)

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Background: Severe early-onset obesity (SEOO) in children is more frequently observed in subjects with genetic disorders of which those of leptin pathway can be analyzed biochemically and genetically.

Objectives: The aim of the study was to investigate anthropometrics and leptin parameters, specifically searching for bio-inactive leptin, in children with SEOO.

Methods: Study cohort includes children who developed a BMI>25kg/m² before an age of 6years and who were presented at individual study centers (Germany: n=1, Poland: n=4 |German-Polish consortium, EOL-GPS) between July 2015 and Dec 2017. Anthropometric parameters (weight[kg], height[cm], BMI[kg/m²]) were measured and a serum blood sample was taken. If possible, parental anthropometric parameters (weight[kg], height[cm], BMI[kg/m²]) and blood samples were ascertained. Levels of total leptin [totLep,ng/ml[1]], bio-inactive leptin [bioLep[1,2]] and soluble leptin receptor [sLEPR[1]] were measured in serum samples. Quotient of bioLEP/totLep and LEP-SDS[3] were calculated.

Results: Data of n=50 children (female: 56%, Tanner stage 1: 85.7%, age $_{\text{at blood sampling}}$: 7.7±4.5years, BMI: 32.2±9.3kg/m²; BMI-SDS: 3.7±0.9; %BMIP95: 157.3±30.7%), of n=45 mothers and n=43 fathers (n=42 trios) were included in statistical analysis. Based on measured leptin parameter, we identified no child with leptin deficiency or bio-inactive leptin. Measured totLEP concentrations in children ranged between 25.2 and 49.2ng/ml (interquartile range). Within correlation analyses between leptin parameters and anthropometrics in children, we observed that: totLep concentrations were positively correlated with BMI values ($r=0.86$, $p<0.05$) and negatively correlated with sLEPR ($r=-0.39$, $p<0.05$); sLEPR levels were negatively correlated with age ($r=-0.53$, $p<0.05$) and BMI values ($r=-0.44$, $p<0.05$); LEP-SDS values were negatively correlated with BMI values ($r=-0.70$, $p<0.05$). Analysis of trios identified that 80% of parents were overweight/obese.

Conclusions: Disorders of leptin as a cause of obesity are rare. Also in this cohort with SEOO we identified no new cases of children with leptin deficiency or bio-inactive leptin. We confirmed previously published observations of negative associations between sLEPR, age and BMI values in children. The strong negative correlation between LEP-SDS and BMI values could be interpreted as relative leptin deficiency. However further collection and analysis of severely early-onset obese children must prove whether the relationship between BMI and leptin parameters is definitely different from normally weighing children.

References

1 Elisa, Mediagnost, Reutlingen,Germany: www.mediagnost.de.
2 Wabitsch et al. Eur J Endocrinol. 2017;176(3):315-322.
3 Blum et al. JCEM. 1997;82(9):2904-2910.

P2-P142

Children with Obesity Are Taller in Early Childhood with Subsequent Catch-Down Growth Until Adolescence

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Context: Childhood obesity is supposed to affect growth and development in children but there is uncertainty with regard to dynamics and potential causes. We analyzed differences in age-related growth patterns of obese and normal-weight children and their association with circulating endocrine and metabolic factors.

Objective/Design: In a large German childhood cohort from Leipzig including 7986 children (22793 data sets) we compared cross-sectional and longitudinal data between normal-weight and obese individuals from birth to adulthood in a one-year resolution.

Results: Obese children were up to 1.5 SDS taller than normal-weight children in early childhood corresponding to a difference of almost 8 cm in total height. Analyses corrected for parental target height SDS revealed similar patterns, hence excluding familial predisposition as the major cause.

Obese children started off with a significantly higher birth length (Difference: boys 0.33 cm, 0.11 SDS; girls: 0.52 cm, 0.23 SDS; all $p<0.05$) and weight-for-length of around 0.15 SDS and had an increased growth velocity of up to 1.5 cm/y in the first years of life. Subsequently, obese children showed a catch-down of height SDS starting at the age of 6 years. Particularly the pubertal growth spurt was blunted compared to normal-weight peers finally equalizing height SDS between normal-weight and obese

children. When corrected for parental target height the height SDS of obese children remained slightly increased in adolescence, as the parents of obese children were around 1.2 cm smaller than those of normal-weight children. Girls with obesity entered puberty around 6 months earlier than normal-weight girls.

The reduced growth velocity of obese children during puberty coincided with reduced levels of IGF-1 and with a reduction of around 50 % in levels of testosterone in boys and estradiol in girls. There was no difference in IGFBP-3 levels between obese and normal-weight children. Leptin and fasting insulin levels were increased in obese children throughout late childhood and adolescence.

Conclusions: Patterns of linear growth and corresponding circulating hormone levels in obese children are distinct to those from normal-weight peers with a relative taller stature in early childhood followed by a catch-down growth.

P2-P143

The Relationship Between Anthropometric Measurements and Breast Milk Ghrelin and Nesfatin-1 Levels in Infants with Small for Gestational Age

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Introduction: It has been suggested that adipokines found in breast milk and may be effective in early growth of infants.

Purpose: It was aimed to evaluate the relationship between total ghrelin (TGh) and nesfatin-1 levels in breast milk with anthropometric measurements in the first 4 months of life in infants with small for gestation age (SGA) showing fast growth pattern.

Method: A total of 20 SGA and 20 control infants with appropriate for gestational age (AGA) born between February 2017-August 2017 were involved in the study. Anthropometric measurements of infants have been performed at the 0-1st-4th months including head circumference (HC), chest circumference (CC) and mid-upper arm circumference (MAC). TGh and nesfatin-1 levels in the 1st and 4th months in the breast milk were studied with ELIZA method.

Results: The anthropometric measurements of SGA group in the birth and 1st month were determined significantly lower compared to those of AGA group ($p<0,05$). In the 4th month, TGh and nesfatin-1 values in breast milk in SGA infants were significantly lower compared to AGA infants ($p<0,05$). While there was no significant relation between 1st month nesfatin-1 levels in SGA group and 1st month antropometric measurements, it was found moderate negative correlation between birth weight, HC, MAC and 4th month nesfatin-1 levels and birth weight and CC ($p<0,05$).

Conclusion: TGh and nesfatin-1 levels in breast milk were established to show differences in SGA infants compared to AGA infants. In SGA group; determining of low breast milk TGh levels in the 4th month indicates that active Gh can be more effective in growth of these infants. On the other hand, decline in nesfatin-1 levels in the 4th month and negative correlation between nesfatin-1 and antropometric measurements show that nesfatin-1 can be a protective factor from obesity in these babies.

Keywords: Small for gestation age (SGA), appropriate for gestational age (AGA), breast milk, total ghrelin, nesfatin-1

P2-P144

Efficacy, Safety and Tolerability of Liraglutide, GLP-1 Analogue, in Indian Adolescent Population with Obesity

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Introduction: Liraglutide is a long-acting glucagon-like peptide-1 receptor agonist which directly stimulate POMC neurons and inhibit neuropeptide-Y and Agouti-related peptide neurons of the arcuate nucleus resulting in appetite suppression. It has been approved in adult population for obesity.

Aim: To assess the Efficacy and Safety of Liraglutide in Indian Adolescent obese population.

Materials and Methods: 39 Adolescent (age 12-18 years) Obese patients (BMI>95th Percentile or >27 adult equivalent as per age and sex specific IAP growth chart) with Tanner Staging 2-5, not able to loose weight (<5% weight loss) with dietary restrictions and physical exercise (12weeks) and tab. Orlistat and tab. Metformin (12weeks) were included in this study. Patient were started on Inj. Liraglutide single daily dose 0.6 mg with gradual increase of 0.3mg every week till maximum dose of 1.8 mg before dinner and patients were re-evaluated after 12 weeks of treatment.

Results: At baseline, the mean (±SD) age of the patients was 15.4±1.99 years, the mean weight was 94.11±20.19 kg, and the mean BMI was 34.71±4.89 with male to female ratio 0.8:1. At week 12, patients in the liraglutide group had lost a mean of 6.58±4.22 kg of body weight, A total of 23.08% of the patients in the liraglutide group lost at least 10% of their body weight and 51.28 % lost 5-10% of their body weight. The most frequently reported adverse events with liraglutide were mild or moderate nausea, vomiting and diarrhea.

Conclusion: Liraglutide had statistically significant beneficial outcomes in weight loss in adolescent obesity, not responding to conventional weight management interventions. It was well tolerated and none of the patients had deranged amylase or lipase. However longer studies are needed to evaluate the long term effects of this drug in the metabolic profile of the patients.

P2-P145

The Effect of Exclusive Breastfeeding and Formula Feeding on Body Composition During the First Two Years of Life

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Background: Early gain in fat mass (FM) might be influenced by type of feeding. Excessive gain in FM during the first three months of life is associated with an increased risk for adiposity and cardiovascular diseases. This three-month period is also known as the critical window for adiposity programming.

Aims: To investigate differences in body composition between exclusively breastfed (BF) and formula fed (FF) infants from birth to 24 months.

Methods: 106 exclusively BF (i.e. BF for at least 3 months) infants (57 boys) and 67 exclusively FF (i.e. start FF before 1 month) infants (44 boys) were included from the Sophia Pluto Cohort in Rotterdam, The Netherlands.

We measured body composition at 1 and 3 months by PEA-POD (COSMED, Italy) and 24 months by DXA (Lunar Prodigy, GE Healthcare, UK). Abdominal FM was measured by ultrasound at 3 and 24 months.

Results: Median (IQR) FM% at 24 months was 14.7 (13.2-18.0) in breastfed infants and 15.0 (12.9-17.5) in formula fed infants (p=0.968). Changes in weight-for-height$_{1\text{-}24mo}$ (p=0.026) and weight-for-age$_{1\text{-}24mo}$ (p=0.001) were higher in FF infants compared to BF infants. Overall, no significant differences in change in FM%$_{1\text{-}24mo}$ between both groups were found (p=0.159).

However, in boys, change in FM%$_{3\text{-}24mo}$ was significantly higher in FF infants (p=0.017).

Change in FM%$_{1\text{-}3mo}$ correlated positively with FM% at 24 months in the total group (r=0.144, p=0.036) and with subcutaneous FM at 24 months (r=0.167, p=0.007), not with visceral FM (r=0.014, p=0.816).

Conclusions: Infants receiving FF have a significantly higher change in weight-for-height and weight-for-age during the first two years of life compared to BF infants. Change in FM%$_{1\text{-}3mo}$ correlates with FM% at 24 months, which supports the theory of a critical window for FM development after birth.

P2-P146

Body Composition and Cardiovascular Function in Pre-adolescent Children of South Asian and White European Origin: Relationship to Maternal Status in Pregnancy

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South Asian (SA), British-born adults have increased cardiovascular (CV) risk factors compared to White Europeans (WE). Early detection of CV risk may allow intervention. The Manchester HAPO (Hyperglycaemia and Adverse Pregnancy Outcomes) cohort showed babies of SA origin were born significantly shorter, lighter and had a lower mean BMI SDS than those of WE origin. We now report ethnic differences in body composition and CV markers in childhood.

Measurements on 102 children (56 WE, [25F:31M]; 46 SA, [22F:24M], mean age 8.9, range 6-12y) included; height, weight, body fat % (truncal fat for central and arm fat for peripheral adiposity), skinfold thicknesses and Doppler echocardiography. Maternal data in pregnancy on BMI, glucose tolerance and blood pressure were available.

Differences in height, weight and BMI seen at birth were no longer significant. Despite comparable BMIs (19.6 vs 18.7 kg/m^2; p=0.3), SA children had significantly higher mean whole body fat (28.4% vs 23.3%; p=0.001), central fat (6.9% vs 4.6%; p=0.001), peripheral fat (7.2% vs 4.9%; p=0.001) and supra-iliac skinfolds (15.3 vs 10.3 mm; p=0.002) than WE children. Maternal BMI correlated with the child's BMI SDS (0.24; p=0.02), whole body fat (0.30; p=0.01), central fat (0.28; p=0.02), peripheral fat (0.24; p=0.04) and supra-iliac skinfolds (0.32; p=0.002).

Diastolic function also displayed ethnic differences, with late phase LV filling (A wave) being elevated (56.2 vs 48.4 cm/s; p=0.005) and E/A ratio lower (1.74 vs 2.09; p=0.001) in SA versus WE children. Differences were unrelated to maternal BMI, glucose tolerance or blood pressure.

Generalised linear modelling was used to identify the contribution of ethnicity, gender, current height SDS, weight SDS (or BMI SDS), BMI SDS at birth and maternal BMI SDS to the E/A ratio or to central adiposity. Only ethnicity was significantly associated with E/A ratio (p=0.003) whilst ethnicity, height SDS and weight SDS were associated with central adiposity (all p<0.001).

In this cohort: 1) SA children had higher levels of central and peripheral adiposity than their WE counterparts despite comparable BMIs, 2) SA children had lower E/A ratios suggesting poorer diastolic function and 3) maternal BMI in pregnancy correlated with their child's body composition at age 8y.

We conclude that ethnicity influences body composition and cardiovascular function and that maternal BMI in pregnancy has a lasting impact on offspring body composition.

P2-P147

Relation Between Cardiac Function and Anthropometric Parameters in Overweight and Obese School Boys

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Introduction: Approximately 42 million children under the age of five are overweight or obese worldwide. Being overweight or obese at a young age is linked to several health and economic consequences and it is, therefore, important to study causes and risk factors and identify the best prevention and treatment strategies. The result of previous epidemiological study of 277 school boys in Ternopil city demonstrated that the prevalence of overweight and obesity among pupils are 7.6% and 2.7 % respectively. Obesity-related heart disease contributes to premature death. The aim of our current study is to identify the correlation between anthropometrical parameters of a body and echocardiography data in obese school boys.

Methods and results: 45 obese school boys aged 10-16 years were involved in the study. Echocardiography was performed under standard conditions and by standard technique. To assess the physical development of each child, measurements of body weight, height, waist and hip circumferences and body mass index were matched.

Results: The strongest direct correlation was found between waist, hip circumferences and structural parameters (diameter of the ascending aorta, left atrial diameter, left ventricular (LV) dimensions in diastole and systole, LV mass index), r=0,515-0,798, p<0.001), that indicates LV hypertrophy. Similarly, functional values, like LV volumes in systole and diastole directly correlated with waist and hip circumferences (r=0,606-0,688, p<0.001). At the same time, we didn't find direct relation between BMI and any structural or functional parameters of heart, also ejection fraction was not directly related to anthropometric body parameters.

Summary: Obesity has direct effect on heart function, which means that excessive body fat might negatively affect cardiac health during the childhood. However, this fact has not received yet enough attention. Such simple measurements like waist and hip circumferences in school boys may be used as screening tests for further detailed examination of heart structure and function in obese boys.

P2-P148

Evaluation of Hydration Status of Obese Children – A Pilot Study

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Background: Although adequate hydration is recommended for healthy nutrition, the link between less water consumption and obesity is not exactly known. It was demonstrated that less hydrated adults had a higher body mass index (BMI). Data in children are rather limited. Our aim was to compare the hydration status between obese and non-obese children.

Subjects and Methods: Children aged between 7 and 18 years who had a BMI over 2 standard deviation score (SDS) with exogenous obesity were included in the study group (Group 1, n=31), healthy volunteers with a normal weight were included in the control group (Group 2, n=30). The anthropometric measurements were performed and body composition analysis was applied using bioelectrical impedance analysis method (TANITA BC 418). Urine density was tested at the same time of the day after ad libitum water consumption and lunch. The fluid intake diary was recorded over two consecutive days using two different methods. Total fluid intake was compared with European Food Safety Authority (EFSA) recommendations. The intake of water and sugar sweetened beverages (SSBs) were compared between groups.

Results: There was no differences regarding age and gender between groups (p>0.005 for both). The median BMI-SDS was 2.57 (0.52) kg/m^2 in Group 1 and 0.01 (1.48) kg/m^2 in Group 2 (p < 0.001). Subjects in Group 1 had a higher percentage of body fat (p <0.001), and lower percentages of total body water (TBW) and fat free mass (p=0.007 and <0.001 respectively). The fluid intake per body surface of Group 1 was found significantly less than Group 2 both in the first and in the second day (p<0.001). The urine density was found significantly higher in Group 1 (1020 (10) and 1015(10), p<0.001). Urine density correlated positively with BMI-SDS (r=0.508, p=<0.001), negatively with TBW (r=-0.412, p=0.001) and fluid intake per body surface (first day: r=-0.477, p<0.001, second day: r=-0.519, p<0.001). While 55% of subjects (n=17) in Group 1 satisfied the recommended daily fluid intake, this was 80% (n=24) in Group 2 (p=0.036). The consumption of SSBs was 71% in Group 1 and 20% in Group 2, with higher amount in Group 1 (median 200 ml vs 0 ml, p<0.001).

Conclusions: We found that obese children had less fluid intake, lower TBW percentages and higher urine density. The results of this cross-sectional preliminary study showed that obese children were less hydrated than normal weighted children.

P2-P149

Galanin is Positively Correlated with Insulin Resistance and Triglyceride Levels in Obese Children

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Introduction: Galanin is a neuropeptide involved in the regulation of food intake and glucose homeostasis. The objective of this study was to assess the relation of serum galanin levels with anthropometric and metabolic parameters in obese and healthy children.

Material and methods: This cross-sectional study consisted of 38 obese children (mean age, 11.9 ± 3.0 years) and 30 healthy children (mean age, 11.4 ± 2.0 years). Clinical and biochemical [glucose, insulin, homeostasis model assessment-insulin resistance (HOMA-IR) lipids, galanin, and leptin levels] parameters were analyzed.

Results: Serum galanin and leptin levels were significantly higher in obese children. In obese children, galanin levels were positively correlated with fasting glucose (r = 0.398, p = 0.013), insulin (r = 0.383, p = 0.018), HOMA-IR (r = 0.375, p = 0.020), and triglyceride levels (r = 0.391, p=0.015). Multivariate backward regression analysis revealed that galanin levels were significantly associated with fasting glucose, insulin, HOMA-IR, and triglyceride, which explained 42.0 % of the variance ($r^2 = 0.483$, $p < 0.001$).

Conclusions: In obese children, serum galanin levels were significantly higher and were positively correlated with insulin resistance and triglycerides. Galanin may have a negative effect on glucose homeostasis and lipid metabolism in childhood obesity.

P2-P150

Brown Adipose Tissue in Prepubertal Children: Associations with Sex and with the Sequence of Prenatal Growth Restraint and Postnatal Catch-up

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Background/Objectives: Individuals born small-for-gestational age (SGA), especially those who experience postnatal catch-up growth, are at increased risk for developing endocrine-metabolic abnormalities before puberty. In adults, brown adipose tissue (BAT) has been associated with protection against metabolic disorders, such as obesity, type 2 diabetes and dyslipidaemia. Here, we assessed for the first time whether BAT activation differs between prepubertal children born SGA or appropriate-for-gestational age (AGA).

Subjects/Methods: The study population consisted of 86 prepubertal children [41 AGA and 45 SGA; age (mean ± SEM), 8.5 ± 0.1 yr], recruited into two prospective longitudinal studies assessing endocrine-metabolic status and body composition in infancy and childhood. The temperature at the supraclavicular region (SCR) before and after a cold stimulus was measured by infrared thermal imaging, and the area of thermally active SCR (increase after cold challenge, $\Delta Area_{SCR}$) was calculated as a surrogate index of BAT activation. The results were correlated with clinical, endocrine-metabolic and inflammation variables, and with visceral and hepatic adiposity (assessed by Magnetic Resonance Imaging).

Results: No differences in BAT activation index, as judged by $\Delta Area_{SCR}$, were found between AGA and SGA children. However, girls showed higher baseline and post-cold induction $Area_{SCR}$ than boys (both $p \leq 0.01$). An interaction between gender and birthweight subgroup was observed for BAT activation so that AGA girls increased significantly the thermally active SCR after cold challenge as compared to AGA boys; this increase did not occur in SGA girls *vs* SGA boys. Cold-induced $\Delta Area_{SCR}$ negatively correlated with HOMA-IR, us-CRP, liver volume and liver fat.

Conclusions: As compared to SGA girls, prepubertal girls born AGA appear to have a surplus of BAT *vs* their gender counterparts, that is negatively related to central (ectopic) adiposity. Long-term follow–up of these cohorts will disclose whether those differences are maintained through puberty and relate to pubertal timing, to subsequent changes in liver volume and hepatic fat, and to the development of obesity and metabolic and cardiovascular disorders.

P2-P151

The Age of Pubertal Onset Correlates with Pubertal Growth Pattern and Body Weight Change in Girls

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Background: Precocious puberty in girls may result in loss of FAH, and particularly may relates to obesity when entering adulthood. However,The influence of the timing of pubertal onset on the FAH and the change of body weight during pubertal stages is still controversial.

Objective: The research is to investigate the pubertal growth pattern and the change of BMI levels in girls with ICPP and those who have normal onset of puberty but at different ages.

Method: 23 girls with ICPP without interventions (entered puberty at age from 6 to 8yrs) and 250 normal Cantonese schoolgirls (recruited at 7.24±0.38 yrs of age) were followed up annually until they reached FAH. ICPP girls defined as Group 1, and normal girls were subdivided into 4 groups according to the ages at the onset of puberty: group 2=8-9 yrs(N=69), group 3= 9 -10 yrs(N=82), group 4= 10-11 yrs(N=52), group 5=>11 yrs(N=47).

Results

- From Group 1 to 5, girls reached menarche at 10.59±1.36yrs, 11.55±1.12yrs, 12.19±1.17yrs, 13.00±1.13yrs,13.58±0.83yrs, respectively (p<0.001).
- Girls with early pubertal onset had longer duration from the onset of B2 to FAH (5.76±0.89yrs, 4.31±0.74yrs, 4.02±0.84yrs, 3.69±0.60yrs, 3.06±0.78yrs in each group respectively, p<0.001), and had increased PHV (9.03±0.95cm, 8.48±0.79cm, 8.21±1.20cm, 8.16±0.92cm, 7.79±1.08cm, p<0.001) as well as more total pubertal height gain (33.29±4.43cm, 28.45±3.99cm ,25.22±4.32cm, 24.38±4.29cm, 23.06±3.93cm, p<0.001).
- No significant differences of FAH (158.61±7.40 cm, 157.60±6.25 cm, 158.13±5.28 cm, 159.58±5.74 cm, 159.95±6.11 cm, p=0.478) and FAHSDS (0.06±1.34, -0.17±1.35, -0.04±0.96, 0.26±1.04, 0.15±1.13, p=0.325) were found between groups.
- However, girls who enter puberty earlier had increased BMISDS levels both at age of onset of puberty (0.59±1.09, 0.55±1.26, 0.21±1.26,0.14±1.11, -0.28±1.09,p=0.014) and at time when they reached FAH (0.30±1.11, 0.33±1.07, 0.09±1.21,-0.20±1.07, -0.29±1.19,p=0.001).

Conclusions: Pubertal growth pattern depends on the timing of the onset of puberty in girls. Girls who mature at early age but exhibit the compensatory pubertal development can achieve normal FAH, however, may exhibit increased body weight gain during puberty.

P2-P152

Does Late Sleeping Time Results Increased Bedtime Snack? What Is the Risk of This in Childhood Obesity?

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Objective: Several studies have shown that sleep plays an important role as a modulator of metabolic homeostasis. Indeed, hundreds of studies have been published to examine the relationship between insufficient sleep, late bedtime and obesity. We have studied bedtime snack as another parameter. We suggested that ıt may be a risk factor for obesity. When we looked at the literature, we could not find any study about bedtime snack in childhood, but there are a few studies in adults. In this study, we aimed to determine the relationship between obesity and late sleeping time and increased bedtime snack due to that.

Methods: Our study was prospectively conducted between July 2017-November 2017 by enrollment of children, aged 6-18 years, who admitted to the pediatric primary care clinic of Ankara University School of Medicine. Children with any chronic disease or a history of drug use which increases the risk of obesity were excluded. Anthropometric values were recorded. Approximate bedtime and bedtime snack habits of each child were questioned. Data were evaluated by appropriate statistical methods.

Results: The mean age of 1949 cases in our study was 11.1 ± 3.8 years. Of the cases, 57.6% were female, 42.4% were male. We found that 12.5% of our cases were overweight and 17.9% were obese. We found that 32.5% of the cases were have bedtime snack. The obesity rate was 16.2% in those who did not eat before going to bed, whereas the obesity rate was 21.5% in those who had eaten before going to sleep. We found a significant relationship between bedtime snack and obesity (p <0.001). In our study, it was observed that 70.8% of cases were sleeping after 22:00 at night. Obesity was found to be 14.9% in those who slept before 22:00, while it was 19.2% in late sleepers with bed time snack. There was no significant difference in obesity between late sleepers and the other group(p:0,82). Obesity frequency were higher among late sleepers who had bedtime snack.

Conclusion: Our study represents as the first study to evaluate the relation between childhood obesity and bedtime snack habit. We observed higher risk of obesity in children who slept late in addition to having bedtime snack. This should be accepted as a dramatic consequence of irregular eating habits of today's life. We believe that increasing number of well-designed preventive studies on this issue should be conducted in the future.

P2-P153

Early BMI Trajectory Classes Are Linked to Distinct Body Fat Partitioning Later in Childhood

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Background: Growth patterns in infancy and early childhood have been linked to risks of obesity and cardiometabolic disorders in adulthood. Body fat partitioning, particularly increased fat accumulation at ectopic sites, has been strongly associated with cardiometabolic disorders. However, the lack of precise body composition measures in prior longitudinal birth-cohort studies has made it difficult to ascertain if early growth patterns could result in consolidation of distinct body fat partitioning phenotypes later in childhood, which could in turn track to adulthood.

Objective: In this study, we evaluated differences in body fat depots in 4.5-year-old children who had grown along different BMI trajectories in their first 2 years of life.

Method: Study participants were from the Growing Up in Singapore Towards Healthy Outcomes (GUSTO) mother-child birth cohort (n=1170). Using latent class growth mixture modeling of BMI-for-age z-scores in the first two years of life, we previously identified 4 distinct trajectories: stable low, normal, stable high and rapid gain after 3 months. In a subset of 335 children (244 normal, 45 stable low, 29 stable high and 17 rapid gain), MR imaging and spectroscopy at 4.5 years was used to quantify subcutaneous adipose tissue (SAT), intra-abdominal adipose tissue (IAT), liver fat and intramyocellular lipids (IMCL). Differences in fat depots across the 4 infant BMI trajectory classes were adjusted for ethnicity, sex, maternal education, maternal BMI at booking in the first trimester, maternal age, parity, gestational fasting glucose, rate of gestational weight gain, gestational age, and breastfeeding duration.

Results: Compared to the normal trajectory, IMCL levels were significantly higher among children in the rapid gain trajectory [adjusted difference (AD)=0.23% of water signal; 95%CI: 0.05, 0.41]. SAT volumes were significantly higher in the rapid gain (AD=679.8 ml, 95%CI: 443.9, 915.8) and stable high (AD=172.9 ml, 95%CI: 17.4, 328.4), and lower in the stable low (AD=-256.8 ml, 95%CI: -398.1, -115.5) trajectories. IAT volumes were significantly elevated in the rapid gain (AD=125.8 ml, 95%CI: 76.9, 174.7) and lower in the stable low (AD=-34.5 ml, 95%CI: -63.8, -5.2) trajectories. No statistically significant ADs were observed in liver fat among the trajectory classes.

Conclusion: Characterizing the dynamic aspects of early growth patterns using BMI trajectories revealed distinct body fat partitioning phenotypes even in early childhood, with a significant elevation in the pathogenic IAT and IMCL depots in the rapid gain group. These pathogenic depots could mediate future cardiometabolic risk.

P2-P154

Hair Cortisol Concentrations in Overweight and Obese Children and Adolescents

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Background: Obesity in childhood and adolescence represents a major health problem of our century that has reached epidemic proportions globally during the last decades. In obese subjects, a relatively high cortisol output in urine has been observed compared to nonobese individuals. However, cortisol concentrations in blood, saliva, and urine in association with obesity have not been consistent across studies. Hair cortisol concentrations (HCC) determined in scalp hair provide a marker for long-term cortisol exposure, and have been associated with cardiovascular disease.

Objektive and Hypotheses: The aim of this cross-sectional study was to examine the association of cortisol concentration both in serum and hair with BMI in childhood and adolescence and to assess its relation with clinical and endocrinologic parameters.

Methods: Three hundred (n=300) children and adolescents aged 4-18 years [mean age ± SEM: 10.49 ± 2.57 years; 140 (46.7%) obese, 94 (31.3%) overweight, 66 (22%) normal-weight; 76 males, 224 females] were studied prospectively. The study was approved by the local Committee on the Ethics of Human Research. Written informed consent was obtained in all cases by a parent of all participants, and assent was given by children older than 7 years. All participants underwent clinical examination, including pubertal assessment and standard anthropometric measurements were obtained by a single trained observer. A blood sample for baseline hematological, biochemical and endocrinologic investigations was drawn at 08:00h following a 12-hour fast. Scalp hair samples were collected from the posterior vertex and HCC was measured from the proximal 3cm hair segment using Electrochemiluminescense immunoassay.

Results: Obese subjects had significantly higher systolic blood pressure (SBP), diastolic blood pressure (DBP), waist and hip circumferences, waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) than overweight and normal-weight subjects. Obese subjects had significantly higher concentrations of ALT, γ-GT, LDL, triglycerides, ApoB, Insulin, HbA1C and HOMA-IR index, and lower HDL, ApoA1, 25-OH-Vitamin D and QUICKI than overweight and normal-BMI subjects. Interestingly, plasma ACTH and serum cortisol did not differ between the groups. No significant difference was found in HCC among groups. Multivariate linear regression analysis demonstrated no significant relations between hair cortisol and ApoA1, after adjustment for potential confounders such as age, gender and puberty

Conclusions: The findings of our study indicate that obesity is not associated with elevated HCC, however, further studies are necessary to delineate this association.

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Associations Between Body Fat Mass and Internalizing and Externalizing Behaviors and Anxiety in Children and Adolescents

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Introduction: Body composition analysis is a painless, bloodless and highly informative method of assessing health indicators that can be used extensively in the pediatric population. This is particularly important granted that the prevalence of childhood obesity has been increasing at a fast pace worldwide. Increased

adiposity in children and adolescents is an important issue for children's growth and psychologic development. Assessing the psychosocial status of children and adolescents with excess body fat and providing appropriate cognitive and behavioral therapy may help with the treatment and amelioration of the negative consequences of obesity.

Hypothesis: This study investigates the interrelations between body composition parameters and metabolic and inflammatory biomarkers and the prevalence of internalizing (depression/anxiety, somatic complains and withdrawal) and externalizing (delinquent and aggressive) behaviors reported by parents in a clinical population of obese and overweight children (OC) compared to normal-weight lean children.

Methods: One hundred twenty-one children and adolescents (78 girls and 43 boys) were studied: 40 normal weight (BMI z-scores - 0.1923 ± 0.6), 22 overweight (BMI z-scores 0.922 ± 0.4) and 59 obese (BMI z-score 2.669 ± 1.39) aged 5-15 years old (mean age 8.93 ± 2.23). Physical examination and medical history were obtained by a certified pediatrician. The Anthropometrics were obtained, and body composition analyses were done using an advanced bioimpedance apparatus (BIA-ACC, Biotekna, Venice, Italy). The Child Behavior Checklist questionnaire was completed by parents, whereas the State-Trait Anxiety Inventory for children was completed by the children themselves.

Results: Percent body fat mass (PBFM) correlated positively with externalizing behaviors, such us rule breaking (p=0.027) and aggressiveness (p=0.047).There was a negative correlation between PBFM and social competence (p=0.014) and a positive one between PBFM and thought problems (p=0.011), and conduct (p=0.001), sluggish (p=0.01), and affective behaviors (p=0.017). Moreover, PBFM correlated positively with STAIC scoring (p=0.002). All the above statistical analyses are adjusted for sex and Tanner pubertal stages.

Conclusion: Body fat accumulation in children and adolescents is associated with behavioural, emotional and cognitive problems. Whether the psychosocial state of children is the cause or the consequence of elevated body fat accumulation remains to be answered. This information is important for the design of prevention and intervention strategies for childhood obesity.

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Pharmacotherapy and the Effects on LDL Levels and Growth in 2 Children with Severe Familial Hypercholesterolemia

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Background: Familial Hypercholesterolemia (FH) is an autosomal dominant disorder causing increased levels of total and LDL cholesterol (LDL-C). When onset is in early childhood, it is associated with higher risk of coronary heart disease and hence the emphasis on early identification and strict management to improve the life expectancy. Of the two types of FH, the homozygous variant is the most severe form associated with extremely high levels of LDL.

Aim: To present the sequential changes in LDL-C levels, anthopometry and pharmacotherapy in 2 children with severe prepubertal onset FH treated with a single drug and/or a combination during a period of 8 years with regular monitoring of cholesterol levels.

Methods: 2 pre-pubertal children, diagnosed in 2009 and 2010 with severe FH, high LDL-C levels at presentation (> 15.6mmol/L = 600 mg/dl), good compliance to diet and medications prescribed were chosen. Data was retrospectively collected to look at the growth, medications used and doses at which they were used. LDL-C levels were charted over 8 years and percent reduction from peak LDL-C was determined.

Results: Child A and B presented with xanthomas following which a lipid panel confirmed FH. Child A (5y 7m) and B (2y 6m) had LDL levels suggestive of homozygous FH at 17.4mmol/L and 16.0mmol/L respectively. Both of them were initiated on colestyramine resulting in LDL-C reductions from peak to 43.2% (9.9mmol/L) and 34.4% (10.5mmol/L) with colestyramine monotherapy alone. Since colestyramine monotherapy was unable to achieve further improvement, a statin was added. On a combination of statin and colestyramine, the LDL-C levels fell further to 60.4% and 47.5% from peak corresponding to 6.9mmol/L and 8.4mmol/L respectively. When ezetimibe was combined with statin, LDL-C levels continued to fall further to 71.9% and 60.7% from peak, corresponding to 4.9mmol/L and 6.3mmol/L which were their lowest attained levels, respectively. Growth data plotted over the 8 years of follow up showed that growth was not affected.

Conclusions: Combination therapy was able to achieve 60–72% reduction of LDL-C levels from peak. Ezetimibe/Statin combination was more effective than colestyramine/statin in lowering LDL-C. Although statins are not yet recommended as initial pharmacotherapy in very young children with FH, colestyramine monotherapy is unable to achieve 50% reduction in our patients.

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Brown Tumors in Children on Hemodialysis

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Introduction: Secondary hyperparathyroidism is a serious and expected complication in almost every patient with chronic kidney disease (CKD). Nevertheless brown tumors formed by osteoclasts are rarely found in this subtype of patients and are extremely rare in children with CKD. The most common localizations of brown tumors are the jaw and long bones. We aimed to present three clinical cases of brown tumors in children with CKD on hemodialysis observed in a single dialysis center for a period of 30 years.

Material and methods: Three children with CKD on hemodialysis were diagnosed as having brown tumors using clinical, laboratory and instrumental methods of investigations.

Results: 4 years after the initiation of the hemodialysis treatment the first child presented with pain in the bones with valgus deformation in the knee joints. After 1 and a half year two brown tumors were found in the lower and upper jaw which grew up to 6

and extended to the facial bones with cyst-like bone lesions. Their size ranged between 1 and 8 cm. The laboratory results showed relative hypercalcemia, hyperphosphatemia, elevated alkaline phosphatase, serum parathyroid hormone (PTH) levels elevated 25 times more than the reference range. On ultrasound examination there was a hyperplasia of the right inferior parathyroid gland. In the second child 4 years after the initiation of the hemodialysis treatment there was pain in the bones with valgus deformation in the knee joints. After 1 year two brown tumors were found in the lower jaw which size was around 1 cm. The laboratory and radiographic results were similar to that in the first child and on ultrasound examination there was a hyperplasia of the two inferior parathyroid glands. The third child presented with pain and tumor formation in the upper part of the right femur 4 years after the initiation of the hemodialysis and soon after a lesion in the upper left femur appeared. The MRI results confirmed the diagnosis of brown tumors.

Conclusion: Brown tumors are a very rare complication in children with CKD on hemodialysis and should be taken in mind in cases of bone pain and deformities. Laboratory and imaging methods of investigations should be used when suspecting the diagnosis and histological examination could be used to confirm their presence in the bones.

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The Role of Fibroblast Growth Factor 21 and Irisin in the Pathogenesis of Obesity in Childhood and Adolescence

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Background: Obesity in childhood and adolescence represents a major health problem that reached epidemic proportions in the last decades. Obesity is characterized by an increase in the adipose tissue, which leads to chronic inflammation and release of adipokines, like Fibroblast Growth Factor 21 (FGF21). On the other hand, intense exercise results in decreased adipose tissue, which leads to the release of proteins, the myokines, like irisin. In obesity a resistance in FGF21 and irisin is noted, as an adaptation mechanism.

Objective and Hypothesis: The aim of our study was to determine the role of FGF21 and Irisin in the pathogenesis of obesity in childhood and adolescence.

Methods: Two hundred children and adolescents [106 males (53%), 94 females (47%); 96 prepubertal (48%), 104 pubertal (52%)] aged [mean ± standard deviation (SD)] 10.7 ± 3 years were studied prospectively for one year. Subjects were classified as obese (141,70.4%), overweight (46,23.1%) and of normal BMI (13,6.5%) according to the International Obesity Task Force cut-off points. All subjects were evaluated by a multi-disciplinary team at frequent intervals and received personalized advice on diet and exercise. Psychologic assessment and management was included when required. Endocrinologic and biochemical investigations were performed at the beginning and at the end of the study. The study was approved by the Committee on the Ethics of Human Research, and written informed consent was obtained by all parents.

Results: A significant decrease in Body Mass Index (-2.7kg/m^2, p<0.001), Waist/Hip ratio (-0.1, p=0.001), cholesterol (-4.2mg/dL, p=0.002), Low Density Lipoprotein (-7.3mg/dL, p<0.001), insulin (-2.5μUI/mL, p<0.001), irisin (-146.4ng/ml, p<0.001), leptin (-4.6ng/ml, p=0.001) and resistin (-719 pg/ml, p<0.001) were documented over the study period. Also, a significant increase was observed in high-density lipoprotein (5.1mg/dL, p<0.001). No significant differences in glucose, triglycerides, FGF21 and adiponectin concentrations were noted.

Conclusion: Our findings demonstrate that a personalized multi-disciplinary management plan is effective at reducing the BMI and improving risk factors of cardiovascular disease. There was a significant decrease in irisin concentrations following the reduction of BMI, which supports the hypothesis of irisin resistance during obesity. However, there was no significant difference in FGF21 concentrations following the decrease in BMI, which might be due to a moderate weight loss.

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Serum NAMPT levels Are Not Associated with Parameters of Liver Function in Children and Adolescents

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Background/Aim: Serum NAMPT (nicotinamide phosphoribosyltransferase) levels are altered in adult patients with non-alcoholic fatty liver disease (NAFLD). However, less is known about NAMPT serum levels children and adolescents and their association with parameters of liver function.

Methods: Blood and anthropometric data of 416 children and adolescents who participated in the LIFE Child Study Leipzig were collected. Serum NAMPT (Adipogen) and cytokeratin-18 (PEVIVA®, TECOmedical) levels were measured by ELISA Kit. Vibration-Controlled Transient Elastography (VCTE) and Controlled Attenuation Parameter (CAP) (FibroScan®, M Probe, 10 successful measurements) were used to define the liver fibrosis and steatosis, respectively. Association between NAMPT serum levels with liver parameters (alanine aminotransferase (ALAT), γ-glutamyltransferase (GGT), aspartate aminotransferase (ASAT), VCTE, CAP, cytokeratin-18 (CK18), pediatric NAFLD score) as well as metabolic and inflammatory markers were calculated by

Spearman's correlation or multiple regression analysis. Differences between groups were calculated by Mann–Whitney U test.

Results: We found no differences in serum NAMPT levels between girls and boys. A positive correlation of NAMPT with anthropometric data such as BMI [kg/m^2] (r=0.141, p=0.005) and hip circumference [cm] (r=0.132, p=0.01) was detected in all children and adolescents. Alanine aminotransferase level (ALAT) [U/l] were positively correlated with serum NAMPT, especially in children with obesity (r=0.211, p=0.02). In this subgroup, γ-glutamyltransferase (GGT) [U/l] (r=0.333, p=0.021) and CK18 (r=0.205, p=0.015) showed a positive correlation with NAMPT in serum However, no correlation could be found with liver steatosis and fibrosis as measured by FibroScan® as well as the calculated pediatric NAFLD score. Further, circulating NAMPT was correlated with inflammatory markers such as C-reactive protein [mg/l] (r=0.252, p=0.000), leucocyte count [10^9/l] (r=0.350, p=0.000) and neutrophil count [10^9/l] (r=0.298, p=0.000), in particular in children with overweight (C-reactive protein: r=0.361, p=0.014; leucocyte count: r=0.467, p=0.007; neutrophil count: r=0.375, p=0.007) and obesity (C-reactive protein: r=0.326, p=0.000, leucocyte count: r=0.336, p=0.000). After multiple regression analysis and adjustment on BMI-SDS, age and sex, association between NAMPT and inflammatory markers but not liver parameters remained, especially leucocyte count, in all children and adolescents (R^2= 0.126, p=0.000) as well as in children and adolescents with overweight (R^2 =0.289, p= 0.002).

Discussion: Our data show that serum NAMPT levels in children and adolescents are not associated parameters of liver dysfunction. We could confirm previous studies that showed a positive association with NAMPT serum levels and inflammatory markers in children and adolescents.

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Obesogenic Environment and their Influence on Adiposity on Mexican Children and Adolescents

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Introduction: Obesity is the main public health problem in Mexico. Several factors have been described as explanations, mainly: increased sedentarism and caloric intake. Such environment has been described as "obesogenic".

The aim of this study was to describe the relationship between the components of such obesogenic environment and the adiposity of Mexican children and adolescents.

Methods: We carried a population-based cross-sectional study of Mexican children/adolescents (5-20 years old). We recruited subjects from public and private schools of Mexico City and performed full paediatric and nutritional assessment to them. We assessed diet habits by a 24-hour food intake survey on *The Food Processor Nutrition Software*, registered time dedicated to activities of interest (i.e. time dedicated to screen, sleep, exercise). We measured body composition by dual-energy X-ray absorptiometry Lunar-iDXA. Adiposity measured as total body fat (kg), relative to weight body fat (%).

We analysed the differences in adiposity (mean differences by total fat mass and fat mass percentage) between BMI-groups: underweight, normal weight, overweight and obesity.

To assess the relationship between such obesogenic environment and the adiposity results, we performed a multiple lineal regression analysis considering daily screen-hours, hours of exercise and food intake adequacy as explicative variables and age, sex and pubertal status as cofounding variables.

Results: We assessed 1600 children/adolescents, whose BMI-group distribution corresponded to 14.4% of scholars and 18.4% of adolescents with overweight, and 17.7% of scholars and 12,3% of adolescents with obesity.

The mean differences in total fat mass and fat mass percentage was statistical significance in all groups, with and increasing in the mean value of each group: underweight, normal weight, overweight and obesity, respectively.

The three obesogenic environment components were significantly associated with increased adiposity: ≤60 minutes/day of physical activity, ≥2 hours/day of screen time and those who we classified as "short sleepers" (i.e. children with <9 hours/day and adolescents with <8 hours/day of sleep), with beta values of 5.5, 0.81 and 0.57 respectively.

Conclusions: The Mexican children/adolescents have a poor attachment to recommendations for healthy habits. Being the physical activity and an adequate dietary intake those that less attention receive.

We have shown that habits such as exercise, screen time and lipid intake have a direct impact on the adiposity of Mexican children, so we must work on educating families.

P2-P161

Metabolic Alterations and Weight Status in Children at 8 Years: A Prospective Cohort Study

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Background: Prevalence of childhood obesity (OB) represents a major public health concern, given the tracking of body weight from childhood to adult age and obesity-related morbidity.

Objective: To describe prevalence of overweight (OW) and OB in children at 8 years and investigate relationship with metabolic alterations (lipid profile and insulin resistance).

Methods: 485 pregnant mothers recruited between 2004-2007 and 409 children from a population-based cohort study. Research

Table 1. (for Abstract no P2-P161)

	Boys N (%)	Girls N (%)	Total N (%)
BMI			
Normal	138 (71.9)	110 (64.7)	248 (68.5)
Overweight	39 (20.3)	42 (24.7)	81 (22.4)
Obesity	15 (7.8)	18 (10.6)	33 (9.1)
Waist circumference			
<P90	153 (79.7)	107 (62.9)	260 (71.8)
≥P90	39 (20.3)	63 (37.1)	102 (28.2)
Waist circumference / Height			
Normal	54 (28.1)	32 (18.8)	86 (23.8)
Overweight	85 (44.3)	64 (37.6)	149 (41.2)
Obesity	53 (27.8)	74 (43.5)	127 (35.1)
% Body fat			
<25%	124 (73.4)	102 (65.8)	226 (69.8)
≥25%	45 (26.6)	53 (34.2)	98 (30.2)

protocol was approved by the Ethics Committee. We analysed BMI, waist circumference (WC) and body composition (by electrical bioimpedance) at 8 years. Prevalence of OW and OB was calculated according to IOTF criteria. Plasma total cholesterol, triglycerides, HDL and LDL, glycaemia and insulin were determined in children. Lipid ratios and HOMA index were calculated. A proatherogenic lipid profile was defined as having the three lipid ratios in the third tertile.

Results: 362 (170 girls) were studied when aged 8.33 years (0.36). Table 1 shows their anthropometric characteristic total and by sex. 31.5% children had OW or OB at 8 years. There is positive relation between BMI and HOMA at 8 years: normoweight 2.12; OW 2.78; OB 5.62. (p-trend <0.000). 45 children (17.9%) had a proatherogenic lipid profile. The risk of a proatherogenic lipid profile was increased 5.51-fold (95% CI 2.77-10.96) if they were OW/obese, 4.63-fold (95% CI 2.36-9.09) if the WC was higher P90 and 5.32-fold (95% CI 2.56-11.07) if fat percentage higher than 25%.

Conclusions: High prevalence of OW and OB at 8 years were found. There is positive correlation among weight status, central obesity or body fat and HOMA index or lipid profile. Being OW or obese in childhood may have an unfavourable cardio metabolic profile who need early intervention to promote healthier lifestyles and to prevent cardiovascular disease in adulthood.

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Correlation of Dietary Habits with Systolic Blood Pressure in Healthy Children

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Background: Pediatric hypertension is a risk factor for adult hypertension and cardiovascular disease which entails the necessity of early detection.

Aim: To investigate how nutrition habits are correlated with systolic blood pressure (SBP) in health children and adolescent population.

Methods: 1395 children and adolescents from Greece were enrolled to participate in the research. A specially designed questionnaire regarding to eating habits -on a weekly basis- was used. Blood pressure was measured twice for each child with a 10-minute interval between the measurements. The mean value was taken into consideration as the final. The percentile for blood pressure was calculated according to children's age and height. Children had studied in 3 groups: group A were children< 9 years old (36.77%), group B were children ≥9 and ≤14 years old (36.06%) and group C were children children>14 and <17 years old (27.17%).

Results: The percentage of children with SBP%>95 was: 29.4% in group A, 35.9% in group B and 34% in group C. The majority of children consume breakfast every morning (85.9%). Children of group C consume less fruits, vegetables, cereals, olive oil and milk products and more fast food while they are not used to consume their meals at the same time every day. The logistic regression analysis showed that children of the group A who consume meat more than 3 times per week have 123.6% greater relative probability for increased SBP (p= 0.038). Additionally it was found that children of the group B who consume cereals more than 3 times per week have 83.2%% greater relative probability for increased SBP (p= 0.032). Regarding children of the group C, it was found that those who consume meat and fast food more than 3 times per week have respectively 226.4% (p= 0.045) and 70.2% (p= 0.037) greater relative probability for increased SBP. On the contrary, children who consume fish more than 3 times per week have 61.5% lower relative probability for increased SBP (p= 0.003). Children who consume olive oil products more than 3 times per week have 71.1% lower relative probability for increased SBP (p= 0.043).

Children who breastfed have a 44.8% lower chance of an increase in SBP% (≥90%) versus others (p = 0.031).

Conclusions: Diet plays a crucial role in blood pressure regulation. The adjustment of dietary structure may be helpful in both prevention and treatment of hypertension.

P2-P163

Evaluation of Voiding Dysfunction in Obese Children

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Obesity is a common public health problem. Secondary complications are increasing with the increase in the prevalence of obesity. Studies on the effect of obesity on the urinary system in children continue and are limited. In this study, it was aimed to evaluate the relationship between childhood obesity and lower urinary tract dysfunction (LUTD) with metabolic and anthropometric measures. 400 obese children between 6 and 18 years of age who had a body mass index ≥95 percentile were included in the study. Dysfunctional Voiding and Incontinence Scoring System (DVISS) questionnaire was administered. The children with a score of ≥9 were accepted as having lower urinary tract dysfunction (LUTD). Patients with and without LUTD were compared in age, gender, anthropometric measurements, puberty, acanthosis nigricans, blood pressure, fasting blood glucose, fasting insulin and blood lipids, HOMA-IR, family history of LUTD, parents' age and educational status, number of siblings. LUTD was detected in 19% of obese children. The mean age of the group with LUTD was significantly smaller ($p < 0.05$). There was no significant difference in terms of gender. It was seen that the risk of LUTD was 2.1 times higher in those with mothers' voiding dysfunction and 3.1 times higher in those with a history of voiding dysfunction in children. There was no significant difference between mother and father educational status, sibling numbers. Weight SDS, BMI SDS, waist circumference, HOMA-IR values were higher in patients with LUTD. Acanthosis nigricans were detected more frequently in patients with LUTD ($P < 0.05$). The presence of acanthosis nigricans was found to increase risk of LUTD 1.75 times. LUTD is a problem that should be assessed in obese children. Acanthosis nigricans is an important physical examination finding for LUTD.

P2-P164

Comparison of Antropometric and Biochemical Parameters in Obese Children with or Without Primary Headache

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Aim: The objective of our study was to investigate the physical examination and laboratory findings in obese children with or without primary headaches.

Methods: A total of 161 children, aged 8-18, with obesity (90 female and 71 male) and primary headache, admitted to pediatric endocrinology and pediatric neurology department between 2013 and 2018 were evaluated retrospectively. Participants were divided into subgroups as with tension headache and migraine headache. Obese children without primary headache were included in the control group. Laboratory and *oxologic data were compared between the groups.*

Results: 29 obese children had migraine and 35 had tension type headache. There was no statistically significant difference between the groups with respect to gender, age, body mass index (BMI), BMI standard deviation score (BMI SDS), waist circumference and hip circumference. LDL-cholesterol (LDL-C) and total cholesterol (TC) levels were significantly higher in obese children with migraine headache compared to group without primary headache. There was no difference between the groups in terms of other biochemical parameters.

Conclusion: There is a probable relationship between cholesterol elevation and migraine headache in obese children. Fot that reason, blood lipids should be followed carefully in obese children with migraine headache.

P2-P165

The Protective Effect of Exclusive Breastfeeding for Overweight / Obesity in Children with High Birth Weight

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Background and Objectives: A positive association between birth weight and body mass index (BMI) among children and adolescents has been shown in many populations. Several studies have indicated that breastfed children have lower risk of childhood obesity. Therefore, the aim of this study was to investigate the BMI trajectory according to birth weight status and protective effect of breastfeeding on overweight/obesity prevalence in children 6 years of age.

Methods: A retrospective cohort study was conducted between January 1, 2008 and December 31, 2016 utilizing data from the National Health Information Database (NHID) of Korea. The total number of 38,039 participants was followed until the end of 2016, provided that participants were completely eligible for all health check-ups from birth to 6 years of age. At each check-up period, multiple logistic regressions was used to investigate the association between three birth weight (BW) status (low BW [LBW], normal BW [NBW], high BW [HBW]) and growth development categorized into three groups, overweight/obese, normal and underweight.

Results: HBW infants are highly likely to be overweight/obesity compared to NBW infants (OR 1.70~2.35) and LBW infants are highly likely to be underweight (OR 1.69~2.20) through 6 years of age. The risk of overweight/obesity decreases significantly if HBW infant get exclusively breast-feeding for 6 months (OR 0.54~0.79).

Conclusions: High birth weight status is associated with overweight/obesity during early childhood. Exclusively breastfeeding is a significant protective factor against overweight/obese in children with HBW.

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Determinants and Consequences of Exaggerated Adrenarche in Simple Obesity

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Obese children are at risk for increased DHEAS production, which is assumed to arise from hyperinsulinemia, hyperleptinemia, increased IGF-1 production or chronic low grade inflammation. Exaggerated adrenarche is suspected to be a forerunner of polycystic ovary syndrome in girls, but its consequences in obese boys are less well studied.

In this study we evaluated the presence of exaggerated adrenarche in a cohort of obese boys and girls and investigated whether obese children with an exaggerated adrenarche are at higher risk for a more advanced pubertal maturation, dyslipidemia or a more central obesity.

Fasting serum insulin, IGF-1, leptin and DHEAS (by automated immuno-assays), fibrinogen and lipid levels (by standard laboratory methods) were measured in 234 (99 male) overweight (BMI SDS > 1.3) children, aged between 4 and 17.5 years (median 9.9 years), before the start of a weight loss program. Skinfolds thickness at 4 sites and waist circumference were measured, as well as Tanner stage and body fat percentage (by bio-electrical impedance analysis) were assessed. Data on birth history and familial history of obesity were collected. Logarithms of all hormones were standardised for age using residuals of a simple regression analysis (res). Spearman Rank and Pearson correlations tests and Mann-Whitney U tests were performed.

DHEAS concentration increased significantly (< 0.005) with age (r=0.706), insulin (r= 0.501), IGF-1 (r = 0.442), leptin (0.403) and fibrinogen (0.181). The log DHEAS res correlated significantly with log insulin res (r=0.216, p< 0.001) and log leptin res (r= 0.160, p< 0.05), as well as with birth weight SDS (r= -0.241, p < 0.001) and waist SDS (r=0.221, p< 0.001). The 23 (14 male) children with a DHEAS conc. above 2.4 mg/L, compared to the obese children with levels below this upper reference limit in adolescence, were older (p< 0.005) and had higher median serum insulin (p<0.005) and IGF1 (p< 0.005) concentrations, but a comparable median waist SDS, BMI SDS and body fat percentage. Significantly (p < 0.05) lower HDL cholesterol concentrations and a more advanced genital development were observed in the adolescent (age > 10 years) boys with an exaggerated adrenarche.

In conclusion, exaggerated adrenarche is observed in 10 % of obese children, appears to be driven by compensatory hyperinsulinemia and is associated with lower HDL cholesterol levels and a more advanced genital development in adolescent boys.

P2-P167

Metabolic Alteration in Patients Affected by PseudoHypoParathyroidismo 1a (PHP1a): A Preliminary Data

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Pseudohypoparathyroidism (PHP) is a rare disease characterized by hormone resistance due to defect of the α subunit of the stimulatory G protein (Gsα). Hypocalcemia due to parathyroid hormone (PTH) resistance is common. PHP1a determined by maternal LoF mutations in *GNAS,* presents severe obesity as early feature with increased risk of developing metabolic derangement during life. The aim of the study was to evaluate the metabolic alteration in a population of PHP1a from our center. To our Knowledge very few studies have addressed this topic. All subjects affected by genetically confirmed PHP1a were included. Auxological parameters (BMI; BMI SD), metabolic and hormonal parameters and HOMA-IR, ISI were also calculated. Data were analyzed to find correlation also with ongoing therapies (vitamin D and hormonal replacement). To date 21 patients (6 pts> 18 years) were included (mean age: 15.3±11.6 years; range: 1-41 years; 13 males). Out of 21, 16 were on Calcitriol and 15 on Levothyroxine. None were on sex steroid or GH therapy, hypolipidic or antihypertensive drugs. Mean BMI was 25.6±6.3 (+2.1±0.9 SD); biochemical parameters showed: calcium 9.3±0.9 mg/dl; P 5.3±1.5 mg/dl; uric acid 4.8±1.6 mg/dl; Total cholesterol 172±25 mg/dl; HDL 46.2±14 mg/dl; GPT 28.1±25.6 U/ml; HbA1c 33.7±1.9 mmol/mol; HOMAIR 3.6±3.4 ; ISI 8.6±8.5; TSH 2.3±1.5 mUi/l; PTH 292±276 U/ml ; 25OHvitD 43.2±40.9 U/ml IGF1 150±40.2 ng/ml. None is affected by Metabolic Syndrome according to international criteria for children and adults. Although with limit of sample size, we compared all the parameters between pts on (n.16) vs without (n.5) vitamin D and only age was statistically significant (6.3 yrs vs 18.1 yrs). Univariate analysis among all variables did not show any significant correlation, also considered according to sex or age (<18 yrs vs >18 yrs). Our preliminary data confirm the increasing of obesity (BMI>2SD) among patients affected by PHP1a and altered insulin resistance measured as HOMA-IR (>2.4). None of the patients showed metabolic syndrome. Either Vitamin D or levothyroxine therapy did not seem to influence metabolic parameters. At the moment recruitment of patients is ongoing in order to confirm these data on larger population stratified for gender, BMI and age.

P2-P168

Weight Loss Outcomes in Two-Year Multidisciplinary Lifestyle Intervention Program Involving Obese Children and their Parents

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Background: Increasing prevalence of obesity requires improvement in current therapeutic approaches. Multidisciplinary lifestyle intervention programs involving both children and their parents are showing promising results.

Aim: To compare the efficacy of family-based multidisciplinary program with standard weight loss counseling program in obese children.

Methods: The intervention group consisted of 119 obese children with body mass index (BMI) 85kg/m2, recruited from the outpatient pediatric endocrinology clinic who were introduced to structured educational courses delivered by pediatric endocrinologist, registered nurse, psychologist, nutritionist and social pedagogue. Total of 79 of them (45 girls, 34 boys, age 6-18 yrs) have finished the two year educational-interventional program during which both children and their parents learned about metabolic complications of obesity, healthy eating habits and importance of physical activity. Improvement in self-confidence, motivation and lifestyle changes were encouraged. Participants were divided in small age-homogenous groups (6-10 participants). Intense one-week course was followed by regular follow-up visits each month during the first 6 months, and every two months thereafter. Multidisciplinary team participated in all follow-up visits.

The control group consisted of 81 obese children (39 girls, 42 boys, age 6-17 yrs), followed for two years through regular outpatient visits with individual physician counseling.

Main outcome was weight reduction measured through change in BMI z-score (zBMI).

Results: Weight loss was achieved in 90% of participants in intervention group and 60% of controls. Significantly reduced zBMI was found in both groups 1yr and 2 yrs after the baseline (1^{st} year: $\Delta zBMI_{int}$=0.5, t=9.26, p<0,001; $\Delta zBMI_{contr}$=0.2, t=3.23, p<0.01, 2^{nd} year: $\Delta zBMI_{int}$=0.6, t=6.43, p<0.001; $\Delta zBMI_{contr}$=0.2, t=4.2, p<0.001). Drop-out rate in intervention group was 33.6%. Children younger than 12 yrs had better success (t=2.15, p=0.035; t_{interv}=2.6, p=0.015; t_{contr}=2.2, p=0.034). There was no significant difference in weight reduction rate between girls and boys in both groups. Children who were more regular during follow up had better success rate in both groups (r=0.433, p<0,001). At 2-yrs-follow up 86% of participants in intervention group and 70% of controls maintained weight loss. Intervention group achieved higher zBMI reduction than control group both 1yr (t=4.266, p<0,001) and 2 yrs after the baseline (t=3.268, p=0.002).

Conclusion: Multidisciplinary approach, structured education and family-oriented program for weight loss have favorable outcome. Dedication to program measured through regularity of participation and better parental control of younger children lead to better results. Nevertheless, improvement in weight reduction is modest, and new intervention modalities for both children and their parents are necessary.

P2-P169

Relationship Between Glucose and Lipid Metabolism, Inflammatory Factors and Adipokines in Children with Obesity

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Objective: To investigate the co-relationship among glucolipid metabolism and inflammation, adipokines in obese and normal weight children.

Methods: Children aged 5 to 15 year-old were collected. Fasting venous blood samples were collected to test liver function, triglyceride (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), fasting plasma glucose (FPG) and insulin. The inflammatory markers interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), and adipokines including leptin and glucagon-like peptide 2 (GLP-2) levels were detected by ELISA.

Results: A total of 40 obese children (22 males, 18 females, 9.81±1.83 year-old) and 29 gender- and age-matched normal weight children as controls (13 males, 16 females, 8.98±1.98 year-old) were enrolled. The ALT, TG, LDL, homeostasis model insulin resistance index (HOMA-IR), IL-6, TNFα, leptin and GLP-2 were significantly higher in obese group, and HDL levels were significantly lower compared with the control group (p<0.05). There were no significant differences in TC, AST and FPG levels between the two groups (p>0.05). The IL-6 level was positively correlated with WHR (p<0.05); the TNFα level was positively correlated with WHR, BMI, TG, FBG and HOMA-IR. Both IL-6 and TNFα levels were negatively correlated with HDL (p<0.05). The GLP2 level was positively correlated with WHR and BMI (p<0.05), but had no significant correlation with glycolipid index (p>0.05); Leptin was positively correlated with BMI, TG, LDL and HOMA-IR, and negatively correlated with HDL (p<0.05). TNFα was positively correlated with leptin (p<0.05); GLP-2 level was positively correlated with leptin (p<0. 05).

Conclusion: Obese children are in a state of chronic low-grade inflammation. TNFα level were increased with BMI, and may participate in the course of insulin resistance; IL-6 may be associated with abdominal obesity and involved in lipid metabolism. GLP-2 was associated with leptin, and the interaction mechanism between the two adipokines are still needed further studies.

P2-P170

Development of Resistance to Sorafenib®, a Multikinase Inhibitor, in Hepatocellular Carcinoma Is Mediated by SIRT

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Background/Aim: Sorafenib® is a multi-kinase inhibitor and one of the few systemic treatment options for patients with advanced hepatocellular carcinomas (HCCs). Resistance to Sorafenib® develops frequently and could be mediated by the NAD dependent deacetylase sirtuin (SIRT) 1, a master regulator of cellular energy metabolism and stress responses. We aimed to find out if Sorafenib® treatment depends on changes in cellular NAD levels, SIRT1 activity and the cellular energy sensor adenosine monophosphate kinase (AMPK).

Methods: Hepatocarcinoma cells (HCC) (HepG2, Hep3B und Huh7) were stimulated with different concentrations of Sorafenib® (0 to 5 μM) and/or NMN (0.2 mM). Apoptosis was measured by AnnexinV-FITC/PI staining. NAD levels were determined by reversed phase HPLC. ATP levels were measured by CellTiter-Glo® Luminescent Cell Viability Assay. Protein and mRNA levels were analysed by Western blotting and qPCR, respectively. Mitochondrial activity was measured by high resolution respirometry.

Results: We could show that Sorafenib® treatment of HCC cell lines induced apoptosis after stimulation with 5 μM Sorafenib® (HUH7: 6.0 ±1.5-fold; Hep3B: 2.4±0.4 fold; HepG2 1.9 ±0.3 fold). Sirt1 protein was downregulated to 60.7 ±5.4%. Cellular NAD concentrations were significantly decreased from 6.8±0.7 to 2.3±0.5 nmol/mg protein in Huh7 cells after exposure to Sorafenib® for 24h. ATP levels were decreased to 32.4±12.6%. Concomitant to increasing phosphorylation of AMP kinase (3.4±0.5 fold), activity of its downstream target mammalian target of rapamycin (mTOR) was decreased to 83.4 ±7.2% after Sorafenib® treatment, which could indicate energy deprivation. Oxygen flow in permeabilised cells was lower and citrate synthase activity was inhibited by 28.4 ± 7.8% after Sorafenib® treatment (1μM, 24h). While pharmacologically inhibiting NAMPT by FK866 or knockdown of SIRT1 by siRNA did not sensitise HCC to Sorafenib® treatment, transient overexpression of SIRT1 decreased Sorafenib®-induced apoptosis via normalisation of p53 acetylation. Both number of apoptotic cells and effects on AMPK/mTOR phosphorylation were reversed by supplementation of nicotinamide mononucleotide (NMN), the enzyme product of NAMPT. However, mitochondrial activity could not be rescued by NMN supplementation.

Conclusion: We can therefore conclude that Sorafenib® influences SIRT1 and that overexpression of SIRT1 could be an underlying mechanism of resistance to Sorafenib® treatment in HCC.

P2-P171

Gender and Pubertal Tendencies of Plasma Leptin and Dopamine Levels Depending on TaqIA DRD2 Gene Polymorphism in the Different Pediatric Obesity Classes

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Study aim was to evaluate the contribution of DRD2 gene TaqIA polymorphism, plasma leptin and dopamine concentrations to obesity development in children with different adiposity classes, depending on gender and pubertal stage.

Materials and methods: 223 children aged from 11 to 17.9 years were involved in the retrospective one-stage analysis, 179 of them were randomly genotyped in the TaqIA of DRD2 gene and blood dopamine (BD) concentrations were detected. Children were split up in terms of BMI SDS into three groups: the first — normal weight (NW) (±1, n=30), the second — alimentary obesity (AO) (BMI≥+2, <+4, n=86), the third — extreme obesity (EO) (≥+4, n=107). These groups were split off by gender (f/m, n=112/111) and pubertal periods (preprubertal – the 1st Tanner stage; early pubertal – the 2nd + 3rd Tanner stage; late pubertal – the 4th+5th Tanner stage) Statistical analysis were performed by means of SPSS 21.0 ($p < 0.05$) with data shown as a median and quartile range (25–75).

Results: Children with EO had increased D levels 31.88 (7.82–99.38) in comparison with NW kids – 6.28 (4.57–26.54) (p=0.002), and AO patients with 10.44 (4.80–46.88) pg/ml BD ($p = 0.008$). The same pattern had EO boys with BD 31.88 (9.69–93.75) compared to NW kids – 6.46 (3.73–26.54) (p=0.002), and AO patients with 7.83 (4.47–13.04) pg/ml BD ($p = 0.008$). Early pubertal male: AO patients had the lowest plasma D 4.84 (3.54–9.32), that were significantly differ than NW children (8.20 (5.96–56.25) pg/ml; p=0.046) and EO ones (5.78 (4.62–19.38) pg/ml; p=0.002). NW late pubertal boys had minimal D levels (5.96 (3.73–14.16)) pg/ml with gradual D raising in AO (14.53 (6.55–65.63) pg/ml; p=0.01) and EO groups (48.75 (11.68–114.25) pg/ml; p=0.0001). Children with AO and EO had raised A1 TaqI DRD2 allele frequencies: in 50% and 40% equally in contrast with NW patients (10%) (p=0.015). AO boys had more frequent TaqI A1 polymorphism of DRD2-gene (66.7%) compared to EO (23.8%) and NW boys (14.3%), p=0.05.

Conclusions: Patients with AO and EO had enlarged prevalence of the high L and D concentrations in comparison with NW children, who had decreased and low these neuropeptides levels. TaqI A1 polymorphism of DRD2-gene was more prevalent in AO and EO patients as opposed to NW children ($p = 0.015$).

P2-P172

Iron Metabolism Disorders in Prepubertal Obese Children with and Without NAFLD

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Background: Childhood obesity is associated with non-alcoholic fatty liver disease (NAFLD). Previous studies in obese adult and pubertal children with NAFLD have shown that chronic inflammation/oxidative stress and insulin resistance might induce iron metabolism disorders, characterized by increased Hepcidin and Ferritin levels and decreased serum Iron levels. However, data evaluating these findings in a well selected population of obese prepubertal children are still missing.

Methods: Therefore we aimed to characterize iron metabolism in a group of 40 obese prepubertal children with (11Male/9Female) and without (12Male/8Female) NAFLD defined by ultrasonography, compared to 40 healthy prepubertal age- and gender matched peers (22Male/18Female). We also investigated correlations between iron metabolism and both oxidative stress and metabolic markers. Anthropometric measurements were determined. Fasting blood samples were collected for measurement of insulin, glucose, lipid profile, ALT, AST and iron profile including iron concentration, ferritin and hepcidin. Lag-phase and MDA were evaluated as markers of oxidative stress. Differences across the three groups were evaluated by One-way Anova test and post-hoc assessment was calculated by Bonferroni test. In obese subjects a Pearson's correlation was used for searching correlations between Hepcidin and other parameters.

Results: A significant increase of total cholesterol, triglycerides, Insulin, HOMA-IR and ALT values were higher in obese prepubertal children with and without NAFLD compared to controls, while only ALT were significantly higher in those with NAFLD compared to those without NAFLD. A significant increase of Ferritin and hepcidin values were documented across the three groups (all $p<0.05$). In particular, significant higher values were shown between obese prepubertal children with NAFLD compared to those without NAFLD and controls, while only ferritin but not hepcidin was significantly different in those without NAFLD compared to controls. Similarly, compared to controls MDA and Lag-phase were increased and decreased respectively in the two groups of obese without and with NAFLD, showing the last one significant differences compared to those without NAFLD. In addition, Iron values were lower in obese with NAFLD compared to controls, while no differences were found between those without NAFLD and the other two groups. In obese prepubertal children Hepcidin levels inversely correlated with oxidative stress activity (lag-phase).

Conclusions: Obese prepubertal children show impaired iron metabolism disorders, especially in those subjects with NAFLD. The correlation between Hepcidin levels and increased oxidative stress activity in obese prepubertal children suggest a role of these components in the early pathogenesis of NAFLD in prepubertal children.

P2-P173

Familial Hypercholesterolemia Due to Homozygous Ldlrap1 Mutation: Variability of Phenotype and Response to Medical Therapy

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Background: Familial hypercholesterolemia (FH) leads to markedly elevated circulating levels of low-density lipoprotein cholesterol (LDL-C) and is associated with a significantly increased cardiovascular mortality already in childhood and adolescence. FH is caused by dominant mutations in the genes encoding LDL-receptor (LDLR), ApoB-100 and protein convertase subtilin/kexin9 (PCSK9), whereas rarely recessive forms due to mutations in LDL receptor adaptor protein 1 (*LDLRAP1*) have been reported. Treatment strategies include lipid apheresis, plasmapheresis, pharmacological therapy with statins, PCSK9 inhibitors and bile acid sequestrants, and in few cases liver transplantation.

Objective: To describe the clinical course and response to pharmacotherapy in two patients with homozygous FH due to a homozygous *LDLRAP1* gene mutation.

Methods / Results: We report on two siblings of consanguinous Syrian parents with a late diagnosis of FH. The older sibling, a 10.5-year-old girl presented in our outpatient clinic for treatment of „molluscum contagiosum" after a five-year-long history of exanthema on the extensor surfaces of her extremities. Based on the morphological appearance we suspected eruptive xanthomas. Subsequent biochemical analysis revealed drastically elevated levels of total cholesterol (18.4 mmol/l) and LDL-C (14.3 mmol/l). In addition, ultrasound of the carotid arteries demonstrated abnormal carotid intima-media thickness with small atherosclerotic plaque lesions. A 9-year-old brother did not yet present xanthomas. However, his laboratory tests also demonstrated significantly elevated levels of total cholesterol (9.8 mmol/l) and LDL-C (7.2 mmol/l). All remaining family members did neither exhibit hyperlipidaemia nor any history of cardiovascular diseases.

Based on the biochemical findings and clinical picture, we suspected FH and started atorvastatin and ezetimibe treatment in both subjects, with a final daily dosage of atorvastatin 40 and 20 mg, respectively, and ezetimibe 10mg in both. Combination therapy led to a decrease of total cholesterol to 5.5 mmol/l (girl) and 4.8 mmol/l (boy), respectively, and LDL-C of 3.2 mmol/l and 3.3 mmol/l, respectively after 3 months. So far combination pharmacotherapy was efficient and safe for 12 months, with no relevant adverse events.

Genetic analysis of the *LDLRAP1* gene revealed a previously described homozygous mutation in the *LDLRAP1* gene (c.406C>T; p.Gln136*) in both siblings, probably leading to an extremely shortened, non-functional protein.

Conclusion: Pharmacological combination therapy with statin/ezetimibe can effectively decrease cholesterol concentrations into the target range in homozygous FH. Still, to avoid accelerated atheromatous disease, an earlier diagnosis of FH through a general screening program would be warranted.

P2-P174

Can Triponderal Mass Index Be a New Indicator in the Predicting Cardiometabolic Risk in Obese Adolescents?

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Introduction: Body mass index (BMI) is claimed to be unreliable in the determination of body fat rate and cardiometabolic risk. Troublesome and reproducibility low measurements like waist circumference, waist circumference/height rate are used in the evaluation of cardiometabolic risk. Triponderal mass index (TMI; weight/height^3), however, is suggested to be superior BMI in determining body fat rate and obesity.

Purpose: In this study TMI's relationship with body mass rate and metabolic parameters and its superiority to other indexes in the determination of cardiometabolic risk were examined.

Method: Obese adolescents over BMI>95% according to the data of Turkish children were involved in the study. Anthropometric parameters, blood pressures, fasting glucose, lipid levels of cases were measured. Body fat rate was evaluated with bioelectric impedance. Metabolic syndrome (MS) was described according to International Diabetes Federation (IDF) criteria.

Results: Of 247 obese adolescents (14,8±1,5 years, 158 female, 105 MS) involved in the study, BMI 34,1±4,7kg/m^2; BMI SDS 3,03±0,6; TMI 20,8±2,9kg/m^3, waist circumference/height rate 0,63±0,06 and body fat rate was established as 40,1±7,4%. BMI, BMI-SDS, TMI, waist circumference/height rates in cases diagnosed with MS (n=105) were determined significantly high (Table 1). BMI, BMI SDS, waist circumference/height rate and TMI's connection with anthropometric and metabolic parameters were summarized in Table 2. It was identified that BMI showed a potent relationship with BMI SDS and TMI and moderate positive relationship with waist circumference/height rate and BMI.

It was displayed that TMI had only low connection with HDL-K, fasting insulin and HOMA-IR out of metabolic parameters. In the prediction of MS diagnosis, when diagnostic susceptibility and authenticity of TMI, BMI, BMI SDS, waist circumference/height rate were evaluated with ROC analysis, those below the curve were determined as similar and significantly high.

Conclusion: While TMI shows body fat rate more accurately compared to BMI and waist circumference/height rate, it has no superiority to BMI SDS. Nevertheless, since TMI can be calculated more practically compared to BMI SDS, it has made us think that it can be used in determining body fat rate. In addition, it cannot be shown that TMI has superiority to BMI, BMI SDS, waist circumference/height rate in displaying cardiometabolic risk.

P2-P175

Social Networks, Social Support and Weight-Related Outcomes among Adolescents

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Introduction: People's weight-related behaviors may be influenced by their personal social network (SN), notably via family and friends' behavioral modelling and motivational social support (SS).

Objective: We examined the cross-sectional relation between social network-based social support (SS) and weight-related outcomes among adolescents ina pilot study within the QUALITY cohort, a longitudinal study investigating the natural history of obesity in youth.

Methods: Participants (egos) completed a social network questionnaire, in which they nominated up to 10 people (alters) with whom they discussed important matters in the past year. Participants reported their own and each alters' age, sex, body shape, lifestyle behaviors (frequency being active, web surfing, eating healthfully), relationship (family, friend), frequency alter exercises with ego, and frequency alter encourages ego to exercise. We created a motivational SS score based on these two latter items, and a role-modeling SS score based on alters' body shape and lifestyle behaviors. Scores above the overall median were categorized as supportive. Outcomes were body mass index z-score (zBMI) and accelerometer-measured minutes of moderate-to-vigorous physical activity (MVPA). Multiple linear regressions adjusted for age and stratified by sex were conducted.

Results: 45 participants were included (29 boys); mean age was 16.4 years, zBMI ranged from -1.2 to 3.9, mean MVPA was 22.4 minutes/day. Participants nominated a mean of 6.6 alters (38% family and 62% friends). The motivational SS score was significantly associated with zBMI, positively in girls (+0.19 zBMI for a 10% increase in the proportion of supportive alters) and negatively in boys (-0.14 zBMI for a 10% increase in the proportion of supportive alters). Motivational SS was not associated with MVPA. Role-modelling SS was not associated with either outcome.

Conclusion: Our study suggests that the relation between perceived motivational SS and weight status differs between adolescent boys and girls. These preliminary findings suggest that leveraging social support to enhance lifestyle interventions nee

P2-P176

Identification of A Novel Homozygous Mutation in BBS10 in Five Children With Bardet-Biedl Syndrome

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Bardet-Biedl syndrome (BBS) is a rare and multisystemic disorder characterized by rod-cone dystrophy, post-axial polydactyly, learning difficulties, renal abnormalities, obesity and hypogonadism. The disorder is genetically heterogeneous. To date, 21 genes present on different chromosomes have been mapped. The most common genes are BBS1 (locus 11q13) and BBS10 (locus 12q21.2). We aimed to report two family with five affected children with typical clinical features of Bardet-Biedl Syndrome. The first family was Turkish, and the second family was Syrian. There were a consanguineous marriage in both family. There were two affected girls in the turkish family, and they were 14 and 17 years old, respectively. Two of the three affected children in the syrian family were boys and one was girls. their ages were 4, 7 and 10. All of the children had obesity, polydactyly and cognitive impairment. Rode-cone dystrophy and hepatic steatosis were more severe in Syrian families. they had no kidney disease. whereas both children had pelvicalyceal ectasia in the first family. In addition, there was pulmonary hypertension at the girl who is seventeen. Cognitive impairment was mild in all. Screening analysis was performed for BBS1, BBS2 and BBS10 genes. There were no changes that could be pathogenic in the BBS1 and BB2 genes.BBS10 gene 1-2. exons were amplified by PCR method and then DNA sequence analysis were done. We identified a novel homozygous mutation in exon 2 in BSS10 gene. The change in pThr516Asnfs * 8 (c.1547 delC) detected in patients was not defined in HGMD. However, the mutation taster bioinformatics program predicts that change is the cause of the disease. This change also constitutes an early stop codon. It is thought to be pathogenic for this reason. Due to the rare and heterogeneous nature of BBS, the detection of specific and non-specific clinical findings, including ocular findings, obesity, cognitive impairment, should be considered BBS. Genetic testing is necessary to confirm the diagnosis.

P2-P177

The Effects of the Birth Weight on the Fat Distribution and Fatness Parameters of the Body

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The weight of birth affects the weight status and fat distribution in the later period of life. It is suggested that both low and high birth weight pose a risk for cardiometabolic diseases. In this study, the effects of birth weight on body fat mass and body fat distribution parameters during childhood and adolescence period were evaluated.

Method: In this cross-sectional study, 4581 children ages between 6-17 years at primary and secondary schools were determined by the stratified sampling system. Anthropometric parameters such as height, weight, waist circumference, neck circumference, triceps skin fold thickness were measured by appropriate methods. BMI values were calculated, and amount of total body fat was assessed by bioelectrical impedance. Week and weight of birth information noted by the questionnaire sent to the parents. 755 children were excluded from the study due to missing data, history of premature or late-born.

Results: 46% of children were male. Birth weight was below 2500 gr in 11.6% and over 4500 gr in 4.1% of patients. The 10th, 50th and 90th percentile values of the anthropometric measurements were evaluated separately according to age and gender. Birth weight was found low in all age and gender groups. Those who are above the 90th percentile are more common than the normal weighted ones in almost all parameters and the 10th percentile values are at the lowest level compared to the other groups. Likewise, those who had more birth weight had the 10th percentile value at the top of all anthropometric measurements from the age of six. However, this group could not be evaluated because it is not suitable number for the 90th percentile. While all anthropometric measurements showed an increase with age, body fat percentage decreased in boys from pubertal ages, while it showed little increase in girls with age.

Comment: It is known that children with low or high birth weight are at higher risk for obesity and cardiovascular diseases in older ages. In this study, the effect of birth weight on anthropometric parameters showing fat deposition such as body fat percentage, body fat percentage and upper body fattening and central fattening from 6 years of age was evaluated according to age and sex and it shows the effect of birth weight at older ages.

P2-P178

Oxidative Homeostasis Dysregulation May Promote Pathogenesis of Cardio-Metabolic Complications in Childhood Obesity

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Introduction: Advanced glycation end-products (AGEs) are heterogeneous groups of irreversible adducts resulting from non-enzymatic glycation and glyoxidation of proteins, lipids, and nucleic acid. AGEs and its cell receptor RAGE have been involved in the pathophysiology of cardiovascular and metabolic diseases. Interaction of AGEs with RAGE results in an increased generation of oxygen radicals and increased expressions of pro-inflammatory cytokines. Circulating soluble AGE receptor (sRAGE) competes with RAGE for AGEs, to counterbalance the negative effects of their interaction. AGE/sRAGE-ratio have been suggested to be expression of the oxidative state, as well as advanced oxidation protein products (AOPPs).

Objective: To investigate the changes in oxidative balance and to define factors influencing AGEs, sRAGE, AGEs/sRAGE-ratio and AOPPs levels in a cohort of obese children compared to controls.

Material and methods: Forty-one overweight and obese children and adolescents (range 5–16 years) and thirty-six healthy, lean, age and sex-matched controls were recruited. Inclusion criteria: BMI SD>1 corrected for age and sex, born as healthy full-term infant. Exclusion criteria were: genetic and endocrinological causes of obesity, arterial hypertension, chronic diseases and therapies, smoking. Lipid and glucose profiles, liver, renal and thyroid functionality, uric acid, C-reactive protein (CRP), AGEs, sRAGE and AOPPs serum concentrations, were evaluated in both groups.

Results: HOMA, triglycerides, cholesterol/HDL-ratio, atherogenic-index of plasma (AIP), CRP, AOPPs, AGEs/sRAGE-ratio were significantly higher whereas HDL and sRAGE were significantly lower in overweight/obese patients compared to controls.

AGE/sRAGE-ratio and AOPPs positively correlate with BMI SD ($p<0.005$), cholesterol/HDL-ratio($p=0.000$), AIP ($p=0.02$ and $p=0.000$,respectively), CRP ($p=0.000$), and negatively correlate with HDL($p=0.004$ and $p=0.000$,respectively). AOPPs positively correlate with HOMA ($p=0.002$) and AGEs ($p=0.003$), and negatively with sRAGE ($p=0.003$).

BMI SD was a significant predictor of AGEs/sRAGE-ratio ($B=0.06$; $p=0.000$),AOPPs ($B=0.202$; $p=0.000$) and sRAGE ($B=-67.1$;$p=0.000$). CRP was significant predictor of AGEs/sRAGE-ratio ($B=0.21$; $p=0.000$),AOPPs ($B=0.55$; $p=0.01$) and AGEs ($B=34.1$; $p=0.04$). Cholesterol/HDL-ratio was a significant predictor of AGEs/sRAGE-ratio ($B=0.06$; $p=0.008$), AOPPs ($B=0.23$; $p=0.000$), AGEs ($B=14.1$; $p=0.02$), and sRAGE ($B=-56.3$; $p=0.01$). HOMA was a significant predictor of AOPPs ($B=0.12$; $p=0.03$).

Conclusions: Our findings demonstrate a relative shift in stressors from anti-stressors in overweight/obese children, suggesting the presence of oxidative homeostasis dysregulation and an enhanced susceptibility to oxidative/inflammatory tissues damage, that may contribute to the pathogenesis of long-term cardiovascular and metabolic complications. Moreover, we confirmed the role of AGEs/sRAGE-ratio as biomarkers for oxidative state.

P2-P179

Body Composition Parameters, Systemic Inflammation and Metabolic Syndrome Manifestations in Children and Adolescents

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Introduction: Increased adiposity has been associated with smoldering systemic inflammation and metabolic syndrome manifestations, leading to further morbidity by increasing the risk for type 2 diabetes mellitus and cardiovascular disease in adults. Similar analyses have not been performed systematically in children and adolescents.

Hypothesis: This study investigates the interrelations between body composition parameters and indices of inflammation and metabolic syndrome.

Methods: One hundred twenty-one normal weight (40), overweight (22) and obese (59) children and adolescents (43 boys and 78 girls) were studied: Normal weight BMI z-score -0.1923 ± 0.6, Overweight BMI z-score 0.922 ± 0.4 and obese BMI z-score 2.669 ± 1.3 children aged 5-15 years. Medical history, physical examination and anthropometry were obtained by a certified pediatrician. Body composition analysis was performed using an advanced bioimpedance apparatus (BIA-ACC, Biotekna Co, Venice, Italy) and fasting blood samples were withdrawn for measuring serum inflammatory and metabolic markers.

Results: Body fat mass (BFM) both as an absolute value in Kg and as a percentage of body mass was positively associated with morning fasting insulin ($p=0.000$ and $p=0.000$ respectively), hsCRP ($p=0.000$ and $p=0.000$, respectively), ferritin ($p=0.014$ and $p=0.002$, respectively), uric acid ($p=0.000$ and $p=0.000$ respectively), triglycerides ($p=0.000$ and $p=0.000$, respectively), SGPT ($p=0.042$ and $p=0.006$, respectively) and γGT($p=0.000$ and $p=0.000$, respectively) concentrations. BFM as an absolute value in Kg and as a percentage was negatively associated with high density lipoprotein ($p=0.002$ and $p=0.000$, respectively) and iron ($p=0.002$ and $p=0.000$, respectively) concentrations. Extracellular water percentage was positively associated with insulin ($p=0.000$) and hsCRP ($p=0.011$), while skeletal muscle mass both as an absolute value in Kg and as a percentage (%) of body mass were also respectively associated with insulin ($p=0.000$ and $p=0.000$) and hsCRP ($p=0.05$ and $p=0.009$) concentrations. Moreover, insulin levels correlated positively with glucose levels estimated by the

BIA-ACC apparatus (p=0.000). All the above statistical analyses are adjusted for sex and Tanner pubertal stages.

Conclusion: Body fat accumulation in children is associated with elevated inflammatory and metabolic syndrome markers. Bioelectric impedance can be a direct screening and monitoring tool for the assessment of metabolic disorders in children and adolescents. Further studies are needed to evaluate the pathophysiologic mechanisms mediating these effects in children.

P2-P180

Relationships Between Obesity Parameters and Urinary Concentrations of Phthalates and Phenols in Korean Girls

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Background: Humans are exposed to a variety of endocrine disruptors (EDs), including phthalates and phenol substitutes, in daily life. Previous studies have suggested the association between individual EDs and the risk of obesity, however, studies on the effects of multiple EDs have been extremely limited. We investigated the associations of urinary 12 phthalates, 3 polycyclic aromatic hydrocarbons, and 26 phenol substitutes with adiposity measures in Korean girls.

Methods: A total of 75 girls, aged 7 to 8 years old (28 obese and 47 controls), were recruited. Anthropometric indices, such as body mass index (BMI) and waist circumferences (WC), were also determined. The urinary concentrations of phthalates and phenol substitutes were measured using column switching coupled to liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Results: Obese girls had higher urinary concentrations of nonylphenol (0.42 vs. 0.26 ng/mL), 2,5-dichlorophenol (0.69 vs. 0.41 ng/mL), and benzophenone-3 (1.93 vs. 0.95 ng/mL) after adjusting for log-transformed urinary creatinine ($P < 0.05$), while other EDs monitored were not significantly different by obesity. After adjusting for all the covariates, girls in the highest quartile of nonylphenol and 2,5-dichlorophenol had significantly higher weight (mean difference-6.35kg), BMI (3.24 kg/m2), and WC (8.23 cm), compared with those in the lowest quartile. After adjusting for covariates, the girls in a higher nonylphenol quartile showed a significantly higher odds ratio (OR) for general obesity (OR: 7.1 for quartile 3; 10.1 for quartile 4). and central obesity (OR: 9.2 for quartile 3; 10.7 for quartile 4) than those in the lowest quartile (P-for-trend <0.01). No statistical significance was observed in adjusted OR for obesity by quartiles of urinary 2,5-dichlorophenol levels.

Conclusion: We demonstrated a positive association between urinary nonylphenol and obesity in girls. Longitudinal studies with larger sample sizes are needed to confirm and elucidate our results.

Fat, Metabolism and Obesity P3

P3-P125

NKX2-2 Human Mutation Causes Neonatal Diabetes Followed by Severe Infantile Obesity Associated with Paradoxical Upregulated Ghrelin Levels – Do Beta-cells Secrete Ghrelin?

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Background: *NKX2-2* gene mutation (reported in 3 cases worldwide) cause severe IUGR and neonatal diabetes. Beta-cells of the mice *Nkx2-2* $^{(-/-)}$ model were recently shown to convert into cells producing the appetite-promoting peptide ghrelin.

Classically, ghrelin secretion is stimulated during fast and suppressed by nutrients or glucose ingestion in all age groups.

In obese children this ghrelin suppression reaches a minimum of 60% of baseline at the 60 minutes time point following glucose ingestion.

Objective: To examine the ghrelin secretion in response to OGTT in a severely obese hyperphagic child with neonatal diabetes due to *NKX2-2* mutation in order to test the hypothesis that beta to ghrelin producing cell conversion is responsible to her rapid weight gain.

Methods: A 3.5 years old girl with neonatal diabetes due to *NKX2-2* mutation (c.356delG, p.P119fs64*64*) and severe obesity performed OGGT (1.75 gr/kg).

Glucose, insulin and total ghrelin levels were measured at 0,30,60 minutes time points.

The ghrelin levels were assessed in comparison to reported data of age matched healthy obese and non- obese children.

Results: Our patients gained weight dramatically since one year of age and her weigh at the age of 3.5 years old weights 19.5 Kg (BMI SDS +4.32).

During the OGTT-while glucose increased from 19.4 mmol/l at baseline to 30.8 mmol /l after 60 minutes insulin levels dropped from 101.36 pmol/l to 31.11 pmol/l with constantly undetectable C- peptide levels.

Interestingly, total ghrelin levels paradoxically increased from 1011 pg/ml at baseline (similar to baseline values in obese children) to 1349 pg/ml after glucose ingestion.

Conclusion: *NKX2-2* mutation phenotype includes severe early childhood obesity in addition to neonatal diabetes. During OGTT, our obese (neonatal diabetic) patient showed paradoxical increase in ghrelin levels concomitantly with decrease in insulin levels. This results suggest that in patients with *NKX2-2* mutation- human beta cell mimic *Nkx2-2* $^{(-/-)}$ mice's beta cells conversion to ghrelin producing cells and elevated ghrelin levels are the pathophysiologic mechanism for hyperphagia and obesity.

P3-P126

Tracing the Effect of the Melanocortin-4 Receptor Pathway in Obesity: Study Design and Methodology of the TEMPO Registry

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Introduction: The hypothalamic melanocortin-4 receptor (MC4R) pathway plays a vital role in energy balance. Genetic defects in the MC4R pathway may result in severe early onset obesity.

Objective: The TEMPO registry (NCT03479437) aims to identify and enroll approximately 1000 participants with rare genetic forms of obesity that are potentially related to key genes, upstream or downstream, of the MC4R. In addition, the TEMPO registry will evaluate the burden of disease on participants, caregivers, health care providers and the health care system.

Study Design and Population: The TEMPO registry is a voluntary, prospective, open-ended, registry. Participants must meet both phenotypic and genotypic entry criteria. Participants aged ≥2 years with severe obesity, defined as BMI >40 mg/kg^2 (for participants ≥18 years) or BMI that is >1.4 x the corresponding age/sex 95th percentile (in children 2-17 years) are eligible for inclusion. Participants must possess at least one of the following genotypes: 1) Bi-allelic (homozygous or compound heterozygous) *POMC, PCSK1 or LEPR* pathogenic or likely pathogenic variants, or encoding a subset of variants of unknown significance, leading to either clinical POMC or LEPR deficiency obesity; 2) Presence of pathogenic, likely pathogenic or a subset of variants of unknown significance in at least 2 genes in the pathway (a composite genotype); 3) Presence of other high-confidence, high-impact genetic variations in the *MC4R* gene or other MC4R pathway genes carried by non-syndromic participants with severe obesity. Participants with recognized syndromic forms of obesity will be excluded.

Methodology: Data sources will include electronic surveys completed by adult and minor (aged 13-17) participants, caregivers for all minors and healthcare providers. Surveys will be completed at study entry (baseline) and annually thereafter. Surveys will collect demographics, results of genetic testing, medical/family history, disease characteristics, resource utilization, eating habits/hunger episodes, quality of life, and burden of disease on participants, caregivers, healthcare providers and the healthcare system.

Conclusions: The TEMPO registry will enable the identification of patients with rare forms of severe early-onset obesity resulting from rare genetic variants in the MC4R pathway. This registry will provide insights into the overall course and disease burden of genetic disorders presenting with these extreme obesity features.

P3-P127

BigO: Big Data Against Childhood Obesity

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Background: Childhood obesity is a major global and European public health problem. The need for community-targeted actions has long been recognized, however it has been prevented by the lack of monitoring and evaluation framework, and the methodological inability to objectively quantify the local community characteristics in a reasonable timeframe. Recent technological achievements in mobile and wearable electronics and Big Data infrastructures allow the engagement of European citizens in the data collection process.

Objective: BigO (bigoprogram.eu) is an EU-funded project that collects objective evidence on the causes of obesity in local communities and enables public health authorities to design effective interventions to prevent or combat obesity. BigO aims to redefine the way those strategies are designed and deployed.

Method: A novel technological platform will be built relying on big data analytics and visualization. The BigO platform will use sensor technologies to record children's daily eating and physical activity behavior and correlate it with environment data from on-line sources. Widely spread sensors in smartphones or activity bracelets will be used, in combination with Mandometer®, a clinically validated device monitoring the rate of food intake. Data as a whole will include what and how children eat, how they move and sleep, along with characteristics of their urban, socioeconomic, commercial and school environment. Data driven analytics will then be employed to extract relationships between environment, personal behavior, obesity risk factors and obesity prevalence, and determine which particular local conditions are associated with the development of obesity in children

of a specific region. BigO will engage children and adolescents aged 9-18 years from Greece, Sweden and Ireland, to share their data as citizen scientists. Moreover, age-matched obese children will be recruited from obesity clinics in these countries. The BigO consortium brings together 13 European partners from Greece, Sweden, Ireland, Spain and the Netherlands. The project started in December 2016 and aims to reach out to more than 25,000 children in its 4-year duration targeting the active participation of 9,000 volunteers.

Results: Comprehensive models of the obesity prevalence dependence matrix will be created, allowing, for the first time the data-driven effectiveness predictions about specific policies on a community and the real-time monitoring of the population response, supported by powerful real-time data visualizations.

Conclusion: BigO will provide an innovative suite, allowing the Public Health Authorities to evaluate their communities based on their obesity prevalence risk and to take local action, based on objective evidence.

P3-P128

Exposure to Bisphenol-A and Phtalates in Obese Girls

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Background: The increasing incidence of obesity is a global public health challenge. Although energy imbalance is the major cause of obesity, evidence suggests that other risk factors such as exposure to endocrine-disrupting chemicals (EDCs) may contribute to the development of obesity. Early life exposure to obesogens may result in a higher risk of developing obesity. Among the chemicals suspected to have obesogenic effects, bisphenol A (BPA) and phthalates are under worldwide investigation.

Objective: The aim of our study was to investigate the association between the exposure to BPA and phthalate metabolites in idiopathic obese (IO) girls.

Methods: A case-control study was conducted on 62 girls, subdivided into 2 groups: 31 girls with IO (mean age 8.07±1.54) and 31 controls (mean age 6.67± 2.3). Urine BPA and phthalate metabolites were evaluated by high-performance liquid chromatography coupled with mass spectrometer (LC–MS/MS). Individual exposure was evaluated through "ad hoc" questionnaires providing data on life styles, diet and other potential determinants of exposure.

Results: Both BPA and phthalate metabolites were measurable in all tested samples, including those from control group. Obese girls showed significantly higher BPA urinary levels than controls: median BPA 8.7 μg/g creatinine (range 0.88-150.69) vs 4.61 μg/g creatinine (range 0.4-10.80), respectively ($p<0.001$).

No significant difference in phthalate metabolites was found. In the obese group, no significant correlation between EDC levels and metabolic parameters was observed.

Conclusions: Our findings show the widespread exposure to BPA and phthalates and suggest that the exposure to BPA is significantly higher in obese girls. Further experimental and clinical investigations are necessary to unveil the potential cause-effect relationship.

P3-P129

Obesity of Childhood and Ambulatory Glucose Monitorization

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Introduction: Childhood obesity (CO) is an important risk factor for the development of many chronic metabolic diseases of the adult age, and one of the most important ones is glucose homeostasis. However, the parameters used to diagnose carbohydrate metabolism disorders in obese children are not always guiding early in detecting pathologies, and may be inadequate to predict the pathologies. *For this reason new diagnostic methods are needed.* For this purpose, in this study it was deemed suitable to investigate the importance of ambulatory glucose monitoring (AGM) in obese children to evaluate metabolic complications of the glucose homeostasis system in early stages.

Material and Methods: After detailed history, anthropometric evaluation and physical examination in seven obese children(according to BMI and BMIpercentile for age and sex) who applied to our pediatric endocrine polyclinic, biochemical and hormonal panels were searched. First of all, ambulatory glucose monitoring (AGM) was applied to all cases and measurements were taken seven times a day for 14 days.Diet and exercise treatment were not performed during these measurements. Especially we wanted them to go on their daily life and habits during this period.Other conventional diagnostic methods (basal and postprandial blood glucose level, HOMA-IR, OGTT, HbAlc) were used to determine glucose homeostasis after 14 days of measurement. Measurements were determined as morning hunger, first and second hours after breakfast, before lunch and dinner, after 1 and 2 hours after meals, and at 03:00 in the morning. Measurements of blood glucose level below 70 mg / dl were assessed as hypoglycemia, values above 180 mg / dl were assessed as hyperglycemia.

Results: Although conventional parameters of glucose homeostasis were normal levels of all cases, AGM records showed that fasting glucose intolerance in 4 cases and postprandial glucose intolerance in one case. In the other hand 29 hypoglycemic attacs were recorded during AGM data.

Discussion: As a result; basal and OGTT glucose levels, insulin, HbA1c and HOMA IR index in obese children may not always provide healthy information. Particularly, hypoglycemia will affect all basal values, especially HbA1c. *AGM is highly valuable in this group of patients in terms of ensuring a long follow-up of fourteen*

days in obese cases with this study protocol, assessment of blood glucose fluctuations (hypo-hyperglycaemia) and individual regulation of feeding through demonstration of relationships with nutrition. Another important point, this study may guide physicians to determine if medical treatment is necessary for the cases.

P3-P130

Familial Partial Lipodystrophy, Importance of Family History - A Case Report

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TN was seen in India aged 7 years by her GP, with concerns about tall stature and increase in belly fat. She had a family history of diabetes, high cholesterol and early deaths. Her mother has diabetes, a round face and prominent limb musculature with very little subcutaneous fat.

TN was investigated by a paediatric endocrinologist in India. Tests showed high triglycerides and insulin levels at the upper level of normal for her age. She was put on a strict diet and exercise programme.

TN and family then moved to UK. On examination TN was noted to have accumulation of fat around her face and neck with acanthosis of the neck, axillae and groin, (photographs available). Her abdomen was protuberant but there was no organomegaly. TN did not appear lipodystrophic but, given her family history, she had a OGTT and baseline blood tests. OGTT was normal with Insulin at the upper level of normal, raised triglycerides & Total/HDL ratio, raised ALT, LDH, ALP & low Vit D, Non alcoholic Fatty liver on Ultrasound. In the family history, TN's 10 maternal relatives spanning 5 generations are all reported to have had a round face and slender limbs, lipodystrophic body build, (Family tree available). 5 relatives had early cardiac deaths, 6 were confirmed diabetes, 4 had dyslipidaemia. Grandfather, and great grandmother were never investigated for diabetes or dyslipidaemia, but died early aged about 50 from cardiac arrest.

TN's mother has well-defined musculature in the upper and lower limbs and accumulation of fat around face, neck and central adiposity, typical partial lipodystrophic build, (photographs available). She has hypothyroidism, diabetes, PCOS, elevated cholesterol and triglycerides.

A diagnosis of autosomal dominant LMNA-related Familial Partial Lipodystrophy was suspected. Gene testing identified a pathogenic mutation in exon 8 of the LMNA gene, c.1444C>T, p.Arg482Trp, in TNs mother, confirming the diagnosis. Subsequent testing of TN showed that she had inherited the LMNA mutation from her mother.

The diagnosis of a form of lipodystrophy had not been recognised in this family previously and will allow appropriate management in TN and the wider family. This case illustrates the importance of taking a detailed family history and doing appropriate genetic testing on an affected relative if a specific diagnosis is suspected.

Trials of metroleptin have been done in paediatric cases with improvement. We wait to see if TN will be suitable in future.

P3-P131

Development of Severe Obesity in a Children with a Brainstem Tumor

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The homeostatic control of energy balance is tightly regulated. Appetite and energy expenditure regulation involves neurons in the hypothalamus as well as other brain regions, including the limbic system, amygdala and the brainstem. Hypothalamic obesity is a well-recognized consequence of lesions such as craniopharyngiomas and other tumors in the hypothalamic region. Less known is obesity related to tumors in other brain regions.

The child presented at 14 years of age with fainting episodes associated with severe obstructive sleep apnea and hypophonia. He was found to have a heterogeneous mass in the medulla extending inferiorly past the foramen of magnum into the cervical spinal cord, measuring 3.3 x 3.3 x 5.6 cm; lateral, third and fourth ventricles were diffusely enlarged.

Surgical resection ensued and this was found to be a ganglioglioma, positive for a BRAF mutation. He was started on a tyrosine kinase inhibitor, vemurafenib. In monitoring for adverse effects of vemurafenib, he was found to have glucosuria. He had a HbA1Cof 6.6%, and was referred for endocrine evaluation.

Medical history was significant for early onset morbid obesity, with normal birth weight of 3.6 kg but obese by 2 years of age. While he did not have true hyperphagia except for the brief period that he was on dexamethasone just after tumor diagnosis, he described long-standing issues of obsession with food and nighttime food cravings. He maintained a high level of physical activity, 1 hour per day at least 5 days/week. He denied polyuria or nocturia but did have polydipsia.

On examination, his BMI was 44 kg/m2, blood pressure 136/73. General appearance was that of a severely obese young man. Pertinent findings include severe acanthosis nigricans, mid-puberty.

Diabetes autoantibodies were negative; random insulin level was 195 mcIU/ml.

Brain imaging revealed the site of the tumor and subsequent resection bed involved the area encompassing the nucleus tractus solitarius (NTS).

He was started on metformin, with improvement in his HbA1C but no change in weight or appetite. He was then started on once-weekly long-acting exenatide; HbA1C became normal at 5.0%, BMI z-score decreased by 0.12 within 3 months, and food preoccupation has resolved.

This case represents obesity and diabetes in a child with a brainstem lesion involving the region of the NTS, a site known to be involved in body weight regulation. Treatment with a GLP-1 agonist was effective for diabetes as well as eating behaviors, and weight stabilized.

P3-P132

Correlation Between Obesity, Body Mass Index and Insulin Resistance in Bulgarian Children

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Background and aims: The spread of obesity among children and adolescents is increasing significantly in the last decades. The World Health Organisation defined the disease as a global epidemic and the need of complex interventions worldwide is well recognised. Obesity is major risk factor for many chronic diseases, including diabetes, cardiovascular and lung diseases, orthopaedic and skin problems, and cancer. There are strong predictors that 50% of pre-pubertal and 50-70% of post-pubertal obese children will continue to have obesity in the adulthood.

Insulin resistance and glucose intolerance are frequent in obese children and adolescents. Homeostasis model assessment for insulin resistance (HOMA-IR) was found to be very reliable in determining insulin resistance in obese children. The purpose of our study was to find a correlation between the obesity defined as body mass index (BMI) and HOMA-IR.

Methods: Thirty children with obesity (12 girls, 18 boys) aged between 4 and 17 years were included in the study. All children had BMI > 97th centile. They all had oral glucose tolerance test performed and HOMA-IR calculated.

Results: In 18 children (10 girls, 8 boys) we found high insulin resistance – HOMA-IR>2,5, and the correlation analysis showed significant association between BMI and HOMA-IR. We also looked at the vitamin D levels in all patients, no association was found in those with high HOMA-IR.

Conclusions: Our findings suggest that the increased BMI is associated with high insulin resistance. Weight reduction in children with obesity will improve insulin sensitivity and therefore reduce the risk of developing diabetes type 2, cardiovascular diseases and other complications.

P3-P133

Nonclassical Manifestation of PWS

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Background: Prader-Willi syndrome (PWS) is a complex, multisystem disorder and is the most frequent cause of syndromic obesity that arises from lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13. Its major clinical features include neonatal hypotonia, short stature, developmental delay, behavioral abnormalities, hyperphagia, childhood onset obesity, hypothalamic hypogonadism, and characteristic appearance.

Case history: We report on 16 years old girl, who was referred to an endocrinologist due to amenorrhea, overweight and a short stature. Physical examination revealed: height 145,8 cm (SDS=-2,73), weight 59 kg, BMI=27,75 kg/м2 (SDS=+1,92), acromicria (short hands and feet) without facial dysmorphic features, Tanner stage 3, primary amenorrhea. When she was born, she presented neonatal muscle hypotonia, feeding problems. Her development progress was slightly delayed during the childhood and she had learning difficulties at school. The girl didn't have the excessive appetite and her weight parameters were normal until 15 years. Growth retardation appeared at 14 years and at 15 - exessive weight gain. Laboratory data showed low IGF-1 level of 165,8 ng/ml (-5,8 SD), LG level of 0,4 IU/l, FSG 3,23 IU/l, estradiol level was 86,7 pmol/l. Gonadotrophin releasing hormone stimulation test revealed hypogonadotropic hypogonadism (LH peak 4,4 IU/l, FSH peak 11,8 IU/l). During GH provocative testing with the insulin tolerance test GH deficiency was excluded. Dual-energy x-ray absorptiometry revealed osteopenia. Diagnosis of Prader-Willi syndrome was suspected and genetically confirmed by methylation analysis of SNRPN. The girl was placed on sex hormone replacement therapy and the diet, providing 10 kcal/cm with a carbohydrate content as low as 45% of total calories and healthy balance of macronutrients, was recommended.

Discussion: Hyperphagia is the most salient and constant feature of the syndrome. Patients typically display abnormal eating behaviors including obsessive food seeking, food storage, foraging and hoarding that represent a lifelong source of distress for them and their family. However «nonclassical forms» of this syndrome exist, whose genetics are similar to PWS, but clinical symptomatology is not exactly typical.

P3-P134

Metabolic Parameters in Children with Syndromic Obesity

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Background: Obesity is a complex disease that have an impact of many organs and systems. Syndromic obesity, although rare separately, encompasses around 70 entities with different phenotypic expression, gene involvement and associated anomalies. There are many genes that can influence obesity, either monogenic or polygenic in basis. Children with syndromic obesity need additional testing in order to indentify a specific disorder. Metabolic set up and endocrinological disturbances are variable in comparison with simple obesity.

Objective and hypotheses: evaluation of metabolic parameters in children with syndromic obesity

Method: We present a group of 14 patients with various syndromes that have obesity in their clinical presentation, including patients with Prader-Willi syndrome(PW), Laurence-Moon syndrome(LM), Beckwith-Wiedemann (BW) syndrome, Albright (AlS) and Alstrom syndrome(AS). General methods in dysmorphology were used, detecting non-random combinations of major and minor anomalies. Antropometric measurements were taken in all and were compared to the age and gender matched simple

obese (SO) subjects. Fasting and postprandial glycaemia and insulinemia were evaluated from each subject, as well as IGF1, high sensitive CRP, hepatic enzymes, lipid profile and thyroid function screening. HOMA/IR has been performed in all.

Results: Median body mass index BMI was 26.3 kg/m^2, being the highest in PW group, followed by subjects with BW. Hypogonadism and/or impaired menstrual cycle was most prevalent in PW patients. From all, dyslipidaemia was present in simple obesity group and was correlated with BMI. Lower levels of IGF1 were noticed in PW patients, followed by AlS patient. Among all, insulin concentrations and HOMA index were higher in simple obese patients, followed by BW and AS patients.

Conclusion: Syndromic obesity has metabolic and hormonal differences from simple obesity and should be recognized as a distinct category. Team approach is required for diagnosis and training of the guardians to help the patient apart from standard treatment recommended in simple obesity.

P3-P135

Cut-off for the Follow-up of Obese Children: Cynicism or Realism?

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The majority of treated obese children fail the goals set in the medium-long term or do not show themselves up at the short term follow up. These results, which do not improve even with the proliferation of facilities aimed to the treatment of obesity and of its complications, pose serious questions on how to make the best use of scarce resources available by the National health system.

We have visited, between 2013 and 2015, 378 seriously obese children (> 2 DS from national BMI curves of the Italian Society of Pediatric Endocrinology and Diabetology) -215 males and 163 females, aged 6-14 years, in the years 2013-2015. We calculated the BMI of their parents and we split the patients into two groups: group A, in which we included those whose parents' sum of BMI-SDS overcame 4; group B, the remaining patients. We evaluated how many in each group were still in follow-up at six and twelve months, and those who had achieved and maintained a reduction of at least 1 BMI-SDS twenty-four months after the first logon.

In Group A 90.2% were lost to follow up in 6 months, and the remaining 80.1 was absent at 12 months; whereas in Group B this percentage was respectively 78.4 ($p < 0.05$) and 43.7 ($p < 0.05$). At 24 months, 29.5% of children still followed in group A had achieved the result of reducing and maintaining at least 1 DS their own BMI vs 38.3 in Group B ($p < 0.05$).

These results have suggested us that parental obesity may influence the adherence to lifestyle modification proposals (slightly hypocaloric diet, increased physical activity, practical advice on how to eat and how to do physical activity). On the basis of these findings, despite being surely influenced by the limited means our Center could dispose of, and also because of this, we decided to send to the follow up, after the first visit, only those whose parents, according to the history and the sum of its BMI-SDS, were likely to become less „obesogenic" (cut-off 4 BMI-SDS), and to send everyone else again to the family doctor. With this selection, we believe we can provide a more adequate support to those who could most potentially promise better results; in this way we believe we employ at best the human and economic resources the Local Health Authority makes available for the treatment of childhood obesity.

P3-P136

Proximal Microdelection 16p11.2 Syndrome

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Clinical History and Symptoms: XX, 9.37 years, was referred to our Clinic for obesity and psycho-motor delay. Family history: Fibromyalgic mother, two maternal cousins with psycho-motor delay, paternal uncle with epilepsy and intellectual disability. Born at term from caesarean section for placental detachment after physiological pregnancy (birth weight g 1900, SGA). In the first years of life she had psychomotor retardation, episodes of affective spasms, nocturnal enuresis, aggression in case of food containment, allergic asthma in steroid therapy, DSA and language disorder (followed by territorial NPI and scholastic support), headache (negative brain MRI, no EEG anomalies, on therapy with Oxcarbazepina), mild right transmission hearing loss. XX was previously submitted to several investigations: Rx rachis (left-convex scoliotic attitude, bilateral cervical rib sketch, antiversion of the physiological lordosis), echocardiography (normal), basic hormonal blood-based were substantially normal. At physical exam height and BMI were at the upper percentiles (83 ° perc, SDS 0.95, TH-SDS 2.13 and 29.7 kg / m2, respectively). She showed initial signs of pubertal activation (P1-2, S2, A +/-) and several dysmorphic features: synophry, reduced intercantal distance, small mouth, acanthosis at the base of the neck, hump, lower limb valgus, fifth finger clinodactyly of right hand, relevant abdominal adipose panniculus.

Diagnostic Hypothesis and I and Ii Level Investigations: We measured TSH (2,49 mcUI/ml) and FT4 (13,9 pg/ml), cortisolemia at the lower limits (2,3 mcg/dl) with normal adrenal function, prepubertal hormonal structure and initial insulin resistance (blood sugar / insulin 4.06, HOMA index 4.10); abdomen ultrasound (steatosis); fibroscan (modest fibrosis); karyotype (normal female).

Diagnosis and Eventual Therapy: On the basis of dysmorphic signs microarray analysis was performed that detect a deletion of approximately 813kb in 16p11.2 arr [hg19] 16p11.2 (29.427.215-30.240.227) x1, including the deletion of 593kb responsible for Proximal Microdelection 16p11.2 syndrome. This syndrome, from contiguous genes, is characterized by delayed development and language, mild cognitive impairment, social disability (autism spectrum disorders), mild variable dysmorphism, EEG abnormalities, predisposition to obesity, vertebral anomalies. Microdeletion 16p11.2 (Group 1) explains all the clinical features presented by our patient. The presence of obesity, in absence of involvement of

the gene recognized as causative of the same, suggests that the deletion in question affects a gene region involved in the predisposition to obesity, not yet described in the literature.

P3-P137

The Level of the Vitamin D and Metabolic Status in Children with Obesity

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Objective: determination of changes in metabolic status and vitamin D concentrations in obese children.

Methods: We examined 212 children in the University Hospital (Minsk) from 2016 to 2018 yrs. Their anthropometric parameters (height, weight, body mass index (BMI)) were determined. Blood levels of vitamin D, insulin, uric acid were determined.

All children were divided into 2 groups: group 1 children with morbid obesity - 140 patients (90 boys(B)/50 girls(G)) (BMI 33.04±4.67 kg/m2, age 14.17±2.42 years); group 2 - 72 patients (B/G=34/38) with alimentary obesity (BMI 27.60±2.06 kg/m2, age 14.43±2.27 years). The control group consisted of 83 patients (B/G=43/40) with normal body weight (BMI 19.86±2.24 kg/m2, age 14.32±2.30 years).

Results: In the subgroups of boys with obesity, there were significant differences in the concentration of uric acid in comparison with the control (alimentary obesity 424.10±65.25 mmol/l vs 242.58±49.90 mmol/l (p=0.01)), morbid 324.10±59.33 mmol/l vs 242.58±49.90 mmol/l (p=0.01)). Girls with obesity have a significant increase in uric acid level in comparison with the control group (alimentary 324.10±59.33 mmol/l vs 213.0±39.64 mmol/l (p=0.0001), morbid 409.04±84.23 mmol/l vs 213.0±39.64 mmol/l (p=0.0001)).

In the obese boys, the level of vitamin D is significantly lower than in the control group (alimentary obesity 29.56±6.01 ng/ml vs 33.02±4.10 ng/ml (p=0.05), morbid obesity 27.56±5.75 ng/ml vs 33.02±4.10 ng/ml (p=0.05)). Obese girls showed a significant decrease in vitamin D relative to the control group (alimentary obesity 24.21±10.75 ng/ml vs 31.34±7.35 ng/ml (p=0.05), morbid obesity 23.52±4,18 ng/ml vs 31.34±7.35 ng/ml (p=0.04)).

In boys with obesity higher concentrations of insulin were detected relative to the control group (alimentary obesity 18.9±12.7 μU/ml vs 9.1±4.2 μU/ml (p=0.0001), morbid 28.71±7.36 μU/ml vs 9.1±4.2 μU/ml (p=0.001)). In girls with obesity (alimentary obesity 20.28±6.25 μU/ml vs 14.10±6.80 μU/ml (p=0.001)), morbid 23.32±9.65 μE/ml vs 14.10±6.80 μU/ml (p=0.001)).

Conclusion: Children with obesity have a significant decrease in the concentration of vitamin D. There is an increase in insulin rates.

P3-P138

A Compound Heterozygote Mutation in a Chinese Patient Affected with Methylmalonic Acidemia

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Objective: The aim of this study was to detect potential gene mutation of Methylmalonic acidemia (MAA) in a Chinese patient.

Methods: Patient with clinical diagnosis and parents were analyzed in this study. The analysis included medical histories, clinical analysis, and genetic tests. A NGS panel include MUT, MMAA, MMAB, MMADHC and MCEE genes was identify the pathogenic mutation responsible for the MAA and verified by Sanger.

Results: A compound heterozygote mutation c.571C>T (p.R191W) and c.539C>G (p.S180W) of the MMAB gene was found in the patient, and inherit from his father and mother. The same mutations were not found among 100 healthy controls. **Conclusion** A compound heterozygote mutation c.571C>T (p.R191W) and c.539C>G (p.S180W) of the MMAB gene mutation can be a cause of Cb1b MAA in Chinese. We think that genetic studies to may assist in making Cb1b MAA diagnosis and providing the consultant for their families.

P3-P139

Lymposomal Acid Lipase Deficit in Patients with Hypercholesterolemia

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The deficit of lysosomal acid lipase (LAL) is an infrequent (1: 40,000-300,000 prevalence), autosomal recessive, monogenic pathology. It can aggressively (Wolman's disease): malabsorption and severe dyslipidemia with survival less than one year of life. The cholesterol ester storage disease (CESD) presents with dyslipidemia, liver disease and early cardiovascular disease.

Goals: Descriptive study of the prevalence of LAL deficiency and carriers in a subsample of patients with hypercholesterolemia. Comparison with data already published

Materials and methods: Of 42 patients monitored in the clinic for suspected familial hypercholesterolemia but a genetic study for negative HFC, 12 patients with persistent dyslipidemia were selected despite strict dietary measures. A sample of dried blood was collected in which the enzyme activity was analyzed, with prior informed consent. Reference values were considered for LAL 0.61 -2.79 nmol / punch / h. For LAL activity values with values close to the minimum of the range in the reference population, the genetic variant c.894G> A (p.delS275_Q298) [„Exon 8 Splice Junction Mutation", E8SJM] was studied,

We analyzed: age, sex, time since diagnosis, BMI, nutritional status, total cholesterol, HDL-cholesterol, LDL-cholesterol, tri-

glycerides, treatment with statins / resins; family history of obesity, dyslipidemia and cardiovascular disease early. Data processing with SPSS-19.0

Results: We studied 10 patients, 60% males, average age at diagnosis 8 ± 2.5 years, mean time from diagnosis 4.5 ± 1.2 years. Mean BMI 20.2 ± 3.1Kg / m2, overweight 20%, obesity 10%. Average values of: total cholesterol 225 ± 29mg / dl, HDL-cholesterol 50 ± 18 mg / dl, LDL-cholesterol 161 ± 27mg / dl, triglycerides 101 ± 72 mg / dl. Hepatic echo 2/10 mild steatosis

Statin treatment: 20%, 30% ezetrol, 50% resins. Family history of: obesity 2/10, dyslipidemia 7/10 and early cardiovascular disease in the father of 1 patient Mean values of: LAL 1.32 ± 0.58 nmol / punch / h and enzymatic activity 98.1 ± 52%. Values close to the minimum range in 2 patients, both with normal E8SJM and 1 below with genetic heterozygosis mutation

Conclusions: LAL deficiency is an infrequent entity, detecting a carrier (10%) LAL deficit screening may be beneficial in patients with diliphemia not affiliated. The data coincide with other nearby CCAA (Navarra)

P3-P140

Hepatic Steatosis and Its Relationship with the Metabolic Syndrome

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Introduction: Hepatic steatosis(HS) is a frequent finding in obese children.Insulin resistance, hypertriglyceridemia and abdominal circumference(AC)are known risk factors, similar to Metabolic Syndrome(MS),but the precise pathophysyology remains unexplained.

Objectives: To analyze the prevalence of HS as identified by ultrasound as well as acanthosis Nigricans(AN) in two groups of obese patients;with or without presence of MS;by studying anthropometric, analytical characteristics and waist-length-ratio (WLR).

Material and methods: In this descriptive cross-sectional study, 190children aged 5-14 with BMI>2SD where evaluated. Those patients with secondary causes of obesity have been excluded as HS due to other causes.We analyze somatometry, biochemical parameters (glucose,insulin, lipid profile, hepatic transaminases,HOMA,uric acid), as well as the presence or absence of acanthosis nigricans (AN) in both groups.Liver ultrasound was performed to define the presence or absence of steatosis and we have followed the classification IDF, to define the presence of MS in patients older than 11 years of age.All patients underwent an oral glucose tolerance test (OGTT).The statistical analysis was performed in SPSS 17.

Results: The cohort of 190 patients was equally weighted with respect to sex.The prevalence of HS was 36.8% (60% males vs 40% women).Metabolic criteria of MS are presented in the 36% (n = 25) of patients with HS vs 11% without HS(n = 13).There is positive correlation (R = 0.78) between patients with metabolic syndrome and hepatic steatosis($p < 0.05$).

Conclusions: The prevalence of HS in our population is higher than previously published.Our results show that HS is related to BMI,AC,hypertriglyceridemia and HOMA index.We observed higher waist-length ratio in the population with HS and a higher incidence of MS.AN is also more prevalent in those patients with HS.

Table 1. (for Abstract no P3-P140)

	HS	Without HS	
N	70	120	
Age	13±1.7	10.4±1.5	P<0.05
BMI	31.7±2.2	26.7±1.3	P<0.005
SD OF BMI	4.6	3.1	P<0.05
AC	100±8	90±15	P<0.005
Insulin	18.5±3.5	14±5.5	P<0.05
Homa	3.8±1.5	2.8±1.1	P=0.003
Cholesterol	160±20	157±17	Non significant
HDL	39±4	48.8±3.8	P=0.003
Triglicerides	153±6.4	74±5.3	P<0.005
Uric Acid	5.9±0.2 4	4±0.1	P=0.005
GOT	40±4.7	26±2	P<0.005
GPT	39±3.8	37±1.5	P<0.05
Acanthosis nigricans	80%	20%	P<0.001
Waist Length ratio	0.78±0.1	0.55±0.2	P<0.05

P3-P141

Serum Hepcidin and Ferritin in Prepubertal Obese Children

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Introduction: Obesity is the direct cause of a number of immediate problems during childhood. Recently, fat mass was described as a significant negative predictor of serum iron. Hepcidin is a hormone stimulated by an increase in plasma iron levels and iron deposits in tissues, and decreases iron release from macrophages and duodenal enterocytes into the plasma. This protein prevents excessive iron absorption and iron accumulation in tissues. Ferritin is the most commonly deployed indicator for determining iron deficiency. Several studied showed an association between obesity and iron deficiency in children, but the pathophysiological mechanisms linking these nutritional disorders are not well understood.

The aim of this study was to investigate serum hepcidin, ferritin and iron concentrations in obese and non-obese children during prepubertal period.

Methods: We determined serum concentrations of hepcidin, ferritin, and iron in 30 obese children (z-score BMI≥2SD) aged 5-10 years. Exclusion criteria were: (a) presence of endocrine disorders or genetic syndromes, including syndromic obesity; (b) other chronic medical conditions; (c) intake of medications that could affect growth, pubertal development, nutritional or dietary status; (d) patients who did not sign the informed consent. The control group consisted of 30 non-obese children (z-score BMI

<-1+1>). We assessed the average daily energy intake and the percentage of energy intake from protein, fat and carbohydrates in the diets of obese and non-obese children. Average daily food rations and their nutritional value were calculated using nutritional analysis software (Dieta 5®).

Results: Serum hepcidin concentration was higher by about 40% in obese than non-obese children ($p<0.05$). Similar values of ferritin and iron in both studied groups were found. Ferritin/hepcidin ($p<0.05$) ratio was almost 2-fold lower in obese children than controls. In obese children, hepcidin concentrations correlated negatively with BMI values ($p<0.05$), and positively with ferritin concentrations ($p<0.01$). Daily energy intake in children with obesity were higher ($p<0.001$) compared with the controls, but proportions of proteins, carbohydrates and fats in daily energy intake were similar in both groups. The diet of obese children had higher intake of iron ($p<0.01$) and vitamin C ($p<0.001$) than the diet of normal-weight children.

Conclusions: Our preliminary study suggests that higher hepcidin concentrations may not affect the serum level of iron in prepubertal obese children with sufficient iron consumption.

P3-P142

Osse Registry for Patients with Lipodystrophy Run by the European Consortium of Lipodystrophy (ECLip)

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Introduction: The term lipodystrophy describes a rare disease subdivided into a heterogenous group of even rarer subforms. The rarity of this disease makes research in this area extremely difficult and international co-operation is mandatory to accumulate data sets of sufficient size. The European Consortium of Lipodystrophy (ECLip) consisting of an association of European experts in the field of lipodystrophy has therefore decided to set up a registry for patients with lipodystrophy using OSSE (Open Source Registry System for Rare Diseases in the EU) – an open source software and toolbox (www.osse-register.de).

Methods: The Open Source Software OSSE provides an easily accessible IT framework and organizational processes to set up a Rare Diseases Registry. The platform is web based; data is entered locally at each center and transferred via the internet to a server. In this process, each patient is pseudonymized and identifying data (IDAT) and medical data (MDAT) are stored on different servers to comply data protection requirements.

Results: Medical data collected within the registry encompasses diagnosis including genetic analysis, onset and symptoms of disease and natural progression of disease, family history, anthropometry, comorbidities, metabolic changes and treatment. The information is divided into basic forms and longitudinal forms.

The Registry has been registered at ClinicialTrials.gov and positive ethic vote at 6 institutions has been achieved, all of which are already entering patient data. Ten additional institutions are currently in the process of applying for ethic committee approval.

Discussion: The establishment and implementation of interinstitutional clinical care and research for rare diseases is difficult due to small patient numbers and heterogeneous IT infrastructure. By providing a networking-platform for experts for lipodystrophy from different countries and medical disciplines, this OSSE-based registry offers a new possibility to compare diagnosis of and care for affected patients across Europe. Apart from new insights into the pathophysiology of lipodystrophy this will help to develop improved therapeutic options for the patients. Furthermore, this registry strives to compile information material for patients and care-givers.

Every center within and also without Europe interested in entering patient data is invited to participate in this registry.

P3-P143

Acanthosis Nigricans in Obese Children and Adolescents in Relation to Severity of Obesity and Insulin Resistance

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Acnathosis nigricans (AN) is known to be common dermatologic manifestation in obese children and adolescents. The aim of this study is to examine the association of AN and insulin resistance in obese children and adolescents.

One hundred seventy-nine obese subjects aged 6-17 years who participated in the intervention study, Childhood and Adolescents Obesity *via* Activity and Nutrition (ICAAN) study, were enrolled in 2017-2017. AN was diagnosed by physician. Anthropometric measurements and blood sampling including fasting glucose, insulin, aspartate transaminase(AST), alanine transaminase (ALT), and leptin levels were assessed. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated from FPG and insulin using the equation.

One hundred ten of subjects were male (61.5%). Eighty-four subjects (48.3%) had AN. The rate of severe obesity was significantly higher in AN group than non-AN group (24.2% vs. 48.8%, $p=0.001$). Mean BMI, ALT, rGT, HOMA-IR, and leptin levels were significantly higher in AN group. The rate of severe obesity and HOMA-IR increased with the severity of AN.

Early identification of AN in obese children and adolescent can be recommended for screening of insulin resistance.

P3-P144

Serum Uric Acid and Its Correlation with Metabolic Syndrome Factors in Simple Obesity Children

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Objective: To study the relationship between serum uric acid (SUA) and metabolic syndrome (MS) factors in simple obesity children.

Methods: Data of 70 simple obesity children (50 boys and 20 girls, ages 10.50±3.44) and 30 age-and sex-matched children (17 boys and 13 girls, ages 9.96±2.48) with normal body mass index (BMI) were studied. Anthropometrics, SUA, lipid profiles, glucose and insulin concentration were determined. The differences of parameters between these two groups and the correlations of SUA with other parameters were analyzed. Multiple stepwise regression analysis was done to study the parameters affecting SUA.

Results 1. Compared with 30 normal controls, the waist circumference(WC) (81.58±14.90, p=0.00), waist and height ratio (0.58±0.12, p=0.00), systolic blood pressure (SBP) (115.46±14.73, p=0.00), diastolic blood pressure (DBP) (74.96±10.00, p=0.01), serum triglyceride (TG) (1.59±1.20, p=0.02), SUA (412.00±114.72, p=0.00) were higher while high density lipoprotein(HDL-C) (1.21±0.27, p=0.00) was lower in simple obesity children, and total cholesterol(CHOL), fasting blood-glucose(IFG) was no difference. 2. The detection rate of hyperuricemia(HUA) (<416umol/L) in obese children(37.50%) was significantly higher than that in normal controls(10.00%), and the detection rate of HUA in MS(55.00%) was higher than without MS(32.00%) in obese children. 3. The SUA concentration was positively correlated with weight(0.54, p=0.00), height(0.51, p=0.00), BMI(0.41, p=0.01), waist and height ratio (0.27, p=0.01), SBP(0.44, p=0.00), DBP(0.38, p=0.00), homeostasis model of insulin resistance (HOMA-IR)(0.25, p=0.02), and negatively correlated with HDL-C(-0.264, p=0.027), homeostasis model of insulin sensitivity (HOMA-IS)(-0.34,p=0.00) in obese children.

Conclusions: Expect for changes of BP, serum lipids and glucose, purine metabolic disorders were also found in children with MS. HUA was associated with BMI, BP, HDL-C, HOMA-IR. HUA could be one of the risks in the development of MS.

P3-P145

Thyroid Function, Lipid Profile and Carbohydrate Metabolism Parameters in Patients with Alstrom Syndrome

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Introduction: Alstrom syndrome is an autosomal recessive genetic disorder with mutation in the ALMS 2p12-13 gene and its characteristic features are: pigmented retinopathy, deafness, growth deficiency, obesity, metabolic syndrome, diabetes, thyroid dysfunction, nephropathy and cardiomyopathy.

Aim of the study: Evaluation of anthropometric parameters, thyroid function, carbohydrate metabolism and lipid profile in five patients with diagnosed Alstrom syndrome.

Material and methods: Data of five patients (4 male and 1 female) with genetic confirmation of the Alstrom syndrome hospitalized in the Department of Pediatrics, Diabetology and Endocrinology in Gdańsk, Poland were analyzed. The height, body weight, waist circumference, body mass index (BMI), blood pressure, puberty stage in Tanner scale and laboratory tests such as TSH, fT4, thyroid antibodies, lipid profile, diabetes antibodies, oral glucose tolerance test (OGTT) and thyroid and abdominal ultrasound were performed.

Results: The age of patients at the time of the study was between 4 years 9 months and 17 years. Body height in patients over 10 years was between 3rd-10th centile, in 4 year 9 months old patient it was between 90th-97th centile and in 7 years old patient it was over 97th centile. Body weight and BMI were between 90th and 97th centile in 3 patinets and in one it was over 97th centile. Waist circumference above the normal range was reported in 3 patients. Blood pressure was within the normal range in all patients. Laboratory euthyreosis was found in 3 patients, hypothyroidism requiring treatment in 2 patients. Dyslipidemia was diagnosed in 3 patients with low HDL cholesterol level. All patients had HbA1c levels within the normal range (5.2-5.6%). In OGTT, there was reported imparied glucose tolerance (IGT) in one patient and insulin resitance in 2 patients. In patient with IGT, positive anti-GAD antibodies were found. Thyroid ultrasound in all patients has showed normal thyroid images. In the abdominal ultrasound enlarged and fatty liver in 2 patients was found.

Conclusions: In patients with Alstrom syndrome obesity is very common and it may lead to complications such as IGT, lipid disorders and fatty liver disease. Patients with Alstrom syndrome could also aquire hypothyroidism and it is important to monitor their thyroid function as well.

P3-P146

Does the Level of Studies of Parents Influence the Follow-up of the Recommendations of the Nutritional Pyramid?

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Introduction: Several studies show the negative impact of low level of studies of parents on the dietary patterns and the degree of adiposity of their children. The objective of this study is to evaluate the relationship between the level of studies and compliance with the recommendations of healthy eating pyramid.

Material and method: An anthropometric study was conducted in 895 Spanish children and adolescents (53% women), between 3 and 18 years old (10.25 ± 2.67), which are classified according to the body mass index according to the International Standards of Cole and Bellizi. Data are collected regarding the level of studies of the parents, stratifying into 3 groups (high, medium and low). Likewise, a validated questionnaire on frequency and habit of food consumption (CFCA) is completed. 3 clusters of dietary patterns are established according to compliance with daily healthy eating recommendations (consumption of dairy products, fruit and vegetables, cereals and olive oil), weekly (meat, egg, fish and vegetables) and sporadic (sugars, snacks, beverages sugary, processed foods and fats). The conglomerate 1 does not meet, by excess or default, any of the daily, weekly or sporadic recommendations, the number 2 does not meet the weekly and the 3 meets the daily and weekly but not the sporadic. Average K analysis is performed with the statistical package SPSS19.

Results: A lower prevalence of obesity was observed when the level of studies of the parents increased (under 50.1% vs 39.5% and high 10.4%, p <0.000). 35.8% of the children of parents with low educational level are in cluster 2 (34.5% in the 1 and 29.6% in the 3). The highest percentage of children of parents with medium or high level education are located in the number 1 cluster, which is the most separated from the healthy recommendations (47.5% in the middle studies and 42.7% in the high ones). There are statistically significant differences (p = 0.015).

Conclusions: The level of studies of the parents is inversely related to the prevalence of obesity in the children and directly with a lower adherence to the healthy recommendations of the healthy eating pyramid.

P3-P147

Bariatric Surgery as Treatment of Primary *Pseudotumor Cerebri* in a Male Adolescent: Case Report

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Introduction: Primary Pseudotumor cerebri (PPTC), also known as idiopathic intracranial hypertension, is clinically characterized by increased intracranial pressure in an alert and oriented patient, with no evidence of deformity or obstruction of the ventricular system on neuroimaging. Cerebrospinal fluid analysis is normal except for increased intracranial pressure at lumbar puncture, greater than the 90th percentile (28 cm of H2O) in the pediatric population. Papilledema may or may not be present. Headache is the most common presenting symptom of PPTC (84%) and is often described as daily, bilateral, frontal or retroocular. Obesity is a consistent risk factor for the development of PPTC. Association between body mass index (BMI) and risk of PPTC has been demonstrated.

Patient Presentation: A 16-year-old morbidly obese African Brazilian boy [weight: 133.6kg; BMI: 44.1 kg/m2 (+3.83 standard deviations (SD)], stage Tanner 5, presented with bi-parietal, high intensity and pulsatile headaches. The headaches had progressively worsened over the last three months. They were occurring five times per week and were associated with nocturnal awakenings. There was partial improvement with common analgesics. He was not able to stand still or walk straight without falling during the headache episodes. Cranial computed tomography revealed no mass or anatomic abnormalities. Lumbar puncture showed an elevated opening intracranial pressure of 40 cm of H2O with normal contents. Ophthalmologic evaluation confirmed bilateral papilledema, normal visual acuity and absence of abducens nerve palsy. PPTC was diagnosed. The patient was started on acetazolamide (*Diamox*) q12h with partial improvement of his symptoms. However, after 3 months, he was still symptomatic. As he had already failed to lose weight after been enrolled in a medically supervised weight-loss program (composed of a multi-disciplinary team including nutritionist, physical therapist, psychologist and pediatric surgeon specialized in bariatric surgery), bariatric surgery was indicated. The patient underwent an uncomplicated laparoscopic sleeve gastrectomy. Ophthalmologic evaluation, performed 5 months after surgery, revealed normal visual acuity in both eyes and improvement of bilateral papilledema. Follow-up at 18 months showed a 67.5% excessive weight loss (weight: 94.5kg and BMI: 31.2kg/m^2) and complete resolution of PPTC symptoms.

Conclusion: Our case shows that bariatric surgery may be a valid alternative approach for those morbidly obese adolescent patients with refractory symptoms. Our patient presented complete resolution of PPTC signs and symptoms and experienced a 67.5% excessive weight loss after surgery.

P3-P148

Investigation of Pubertal Effect on Thyroid Volume and IGF-1 Changes in Morbid Obese Children

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Context: Thyroid growth and insulin like growth factor-1 (IGF-1) change depending on pubertal status and body mass index (BMI). The previous studies have reported some inconsistent results on association between thyroid volume (TV) and IGF-1 in terms of puberty and obesity.

Objective: The aim of present study is to investigate pubertal effect of on TV and IGF-1 in morbid obese children.

Design: The study population consisted of 250 children with aged 6-18 years. Children were classified into prepubertal and pubertal groups Children with BMI 97th percentile or greater were classified as the morbid obese group(n=145) and those with BMI less than 85th percentile served as the control group(n=105) by age and sex. The following parameters were assessed in children: BMI, pubertal status, TV and serum IGF-1, IGFBP-3 and IGF-1:IGFBP-3 molar ratio.

Results: Mean TV was larger in pubertal morbid obese than in those prepubertal group compared to their control groups(p=0.07, p=0.603). There was positive correlation of IGF-1 with TV in prepubertal and pubertal children(r=0,369, p=0,001; r=0.316, p=0.004). Correlation between IGF-1 and BMI was no found in prepubertal and pubertal groups (r=0.99, p=0.092; r=0.094, p=0.088). Serum mean IGF-1, IGFBP-3 and IGF-1:IGFBP-3 ratio increased significantly in pubertal group(p=0.023, p=0.042, p=0.031).

Conclusion: This study demonstrated in morbid obese children that thyroid size and IGF-1 increased in puberty and there was significant association of thyroid volume with IGF-1 independently from puberty. These results indicate that puberty significantly affects increase in thyroid growth and IGF-1 promotes enlargement of thyroid gland in morbid obese children.Keywords: childhood morbid obesity, insulin like-growth factor-1, thyroid volume, puberty

P3-P149

The Effect of Vitamin D Supplementation on Metabolic Syndrome Parameters in Overweight and Obese Children and Adolescents in Greece

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Background: Accumulating evidence suggests that decreased 25-hydroxyvitamin [25(OH)D] concentrations are associated with components of the metabolic syndrome.

Objective: The aim of our study was to investigate the effect of vitamin D supplementation on metabolic syndrome parameters in obese children and adolescents.

Patients and Methods: Two hundred thirty two (n=232) obese children and adolescents aged [mean ± standard deviation (SD)] 10.24 ± 2.50 years were studied prospectively for one year. Subjects were randomly assigned to either the intervention (n=117) or the control group (n=115). Participants in the intervention group received 50,000 IU vitamin D weekly for 6 weeks and were subsequently placed on maintenance dose. Blood samples for determination of 25(OH)D, bone profile, liver function and cardiometabolic parameters were obtained at baseline and 12 months later. Systolic and diastolic blood pressure were determined twice and the mean was calculated.

Results: Overall, 220 eligible children and adolescents completed the study (109 in the intervention group and 111 in the control group). A significant decrease was noted in the BMI (p=0.001) over the study period, with the intervention group demonstrating significantly lower BMI compared with placebo group (p=0.016). Moreover, the intervention group had significantly lower fat mass (p=0.007) and higher HDL concentrations (p<0.05) compared with the placebo group. No significant differences were noted between groups over the study period in relation to arterial blood pressure, HbA1c (%), HOMA-IR and QUICKI.

Conclusions: Vitamin D supplementation may have beneficial effects on alleviating certain complications of childhood obesity.

P3-P150

Mother's Obesity and High Child's Waist Circumference Are Predictive Factors of Severe Child's Obesity: An Observational Study in French Guiana

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Background: This study aims to describe the predictive factors of severe obesity in children followed in French Guiana

Methods: In this observational study, the patients from the French Guianese Childhood Obesity Group database were prospectively included**,** after giving a statement of patient's non opposition.

Results: Our group classifications revealed that 36 of 150 (24%) participants were classified as being Metabolically Unhealthy obesity (MUO), while 114 of 150 (76%) were categorized as metabolically healthy obesity (MHO). MUO-patients were older. Their mothers had more severe obesity. We also observed that their systolic blood pressure was higher. The median Z-score BMI of children with MUO was 4, 9 [4, 05-5, 38], which shows a more obese condition than the MHO group. The median waist-to-height ratio (WTHR) of our study population was high, either 0.63 [0.54-0.59]. No significant differences in the term of pregnancy, father's obesity, gender, birth weight, feeding, diastolic blood pressure and WTHR were found between the two groups. The predictors of MUO status, after adjusting for age and sex, were mother's obesity and high child's waist circumference.

Among the comorbidity, there were two Down syndrome, one Cornelia de Lange syndrome, one Nephrotic Syndrome and one Epilepsy.The leptin hormone and insulin levels were higher in MUO than in MHO, while 25-OH D-vitamin was higher in MHO.

Conclusion: This study indicates the need to incorporate waist circumference into routine clinical practice, in addition to traditional measures of weight, height, body mass index and waist-to-height ratio.

Key words: Mother's obesity, waist circumference, predictive factors, childhood obesity, observational Study, French Guiana.

P3-P151

Lipidogram, Leptin-and Adiponectinaemia in Teenagers and Adolescents with Metabolic Syndrome

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Introduction: Obesity leads to the development of hypertension, cardiovascular diseases, disorders of carbohydrate metabolism, which are components of the metabolic syndrome. The nature of the changes of lipid homeostasis, leptin and adiponectin levels in relation to the severity of metabolic syndrome are not well understood.

Materials and methods: 48 people with the metabolic syndrome (24, 16-18 years old and 24 young adults (19-22 years)) are recruited and classified according to body mass index and homeostasis model of assessment-insulin resistance index. The circulating concentrations of leptin, adiponectin and of several metabolic markers of obesity and insulin resistance are determined by standard methods.

Results and discussion: Total cholesterol in the first group and the comparison group is 6,89 ± 0,17 mmol/l and 4,11 ± 0,12 mmol/l, respectively. The cholesterol in the 2nd group is significantly higher (7,21 ± 0,18 mmol/L) compared to the 1st and in control. Triglycerides are significantly increased in both groups (3,9±0,09 mmol/L, 4,12±0,08 mmol/L) in comparing to the control group (0.76 ± 0.04 mmol/L). The amount of HDL statistically significantly reduced in 1st (1.02 ± 0,09 mmol/l) and in 2nd group (0.9 ± 0.08 mmol/l) compared to controls (1.44 ± 0 06 mmol/l). LDL values totaled 5,1 ± 0,05 mmol/l in the group 1 and 5,6 ± 0,06 mmol/l in the 2nd. It is established the direct correlation between LDL, depending on the severity of MS symptoms. Dyslipidemia is found in 85% of teenagers and 98% of young adults. 62.5% of adolescents and 79.2% young adults have atherogenic dyslipidemia of type 2b (hypertriglyceridemia, hypercholesterolemia, increase LDL and decrease HDL). Leptin is significantly different in the 1st and in the 2nd group and in the control (48,2 ± 11,6 ng/ml, 59,1 ± 17,4 ng ml and 11,2 ± 2,3 ng/ml, respectively). Significantly lower concentrations of adiponectin are detected in patients of 2 group compared with adolescents and the control group, respectively 6,1 ± 3,9mkg/ml, 8,9 ± 4,2mkg/ml and 17,1 ± 4,9 mg/ml ($p < 0.05$).

Conclusion: Type 2b atherogenic dyslipidemia (hypertriglyceridemia, hypercholesterolemia, high LDL and low HDL) is diagnosed in 62.5% of adolescents and 79.2% young people with metabolic syndrome.

P3-P152

Metabolic Endotoxemia in Egyptian Obese Children and Adolescents

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Background: Obesity is associated with metabolic abnormalities, which result in progression to insulin resistance and the metabolic syndrome. The underlying stimulus for these metabolic abnormalities in obesity is not clear, however, recent evidence suggests that systemic, low-level elevations of gut-derived endotoxin (lipopolysaccharide) may play a role in obesity-related metabolic abnormalities

Objective: To study the metabolic endotoxemia in obese children and adolescents and its potential relation to insulin resistance, lipid profile, and CRP.

Subjects & Methods: The Study included thirty obese children and adolescents aged 5–18 years and 20 non-obese children matched for age and sex as a control group. Lipid profile, liver function tests, CRP, and serum lipopolysaccaride (LPS) were done, Insulin resistance was calculated using Homeostasis model assessment (Homa-IR) and quantitative insulin sensitivity check index (QUICKI), Abdominal ultrasound was done for detection of fatty liver.

Results: The mean age in obese children was 10.23 ± 3.08 years compared to 9.15 ± 2.89 years in the control group. CRP and LPS were significantly higher in obese group compared to the control. There was a significant positive correlation between serum LPS with BMI, waist circumference, TG, cholesterol, fasting insulin, HOMA- IR, CRP, and frequency of eating junk food.Also, there was a significant negative correlation between LPS with physical activity and QUICKI.

Conclusions: Metabolic endotoxemia may have a role in cardio-metabolic disease risk factors associated with obesity in children and adolescents.

P3-P153

Resting Metabolic Rate and the Development of Metabolic Disorders in Obese Children

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Decreased resting metabolic rate (RMR) is a risk factor for the development and progression of obesity. Childhood obesity is accompanied by the development of metabolic disorders, which often persist in adults. The relationship between the rate of basal metabolism and development of childhood obesity complications is not well understood.

Objective and hypotheses: Measure resting metabolic rate in obese children and assess the pronouncement of metabolic disorders, depending on the rate of energy metabolism.

Method: A total of 150 children with simple obesity (SDS BMI +3.35 [2.98, 3.65]) aged from 10 to 17 years (14.5 [12.5, 15.9] years)

were studied. Obesity is diagnosed according to WHO criteria. RMR was measured using indirect respiratory calorimetry. The decrease RMR was determined at a difference > -10% between measured level and predicted value calculated by the Molnar formula. All children were evaluated fats, ALT and AST levels, glucose tolerance test with calculation of ISI Matsuda. % of body fat was estimated by bioelectrical impedance analysis.

Results: Children with lowered RMR have a greater degree of obesity compared to peers with normal RMR (SDS BMI 3.6 [3.2; 3.8] vs 3.3 [2.9; 3.5], p = 0.01) and a higher % of body fat (46.3 [41.1; 51.3] vs 43.2 [38.7; 47.2], p = 0.03). In the group of children with reduced energy metabolism, higher 2 hour glucose level after glucose loading (7.1 [6.8; 8.5] vs 6.1 [5.6; 7.4], p = 0.001), lower HDL cholesterol level (0.89 [0.8; 1.05] vs 1.02 [0.92; 1.18], p = 0.03) and decreased ISI Matsuda (1.54 [1.19; 2.64] vs 2.4 [1.99; 3.2], p = 0.02) were identified. Correlation analysis revealed a positive relationship between RMR and 2 hours glycaemic level after glucose loading (r = 0.43, p <0.05).

Conclusion: Decrease in resting metabolic rate is associated with more pronounced obesity and an unfavorable metabolic profile in children.

P3-P154

Relation of Screen-time (Phone-Computer-TV-Online Games) and Physical Activity with Childhood Obesity

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Objective: Sedentary lifestyle obviously increases the risk of obesity. Reduced physical activity and increased screen-time seem to act as major determinants of the rapid increase of childhood obesity. Prevention of obesity is easier and more practical in comparison with treatment of obesity and its complications. Treatment of childhood obesity not only carries positive biopsychosocial consequences for the child but also serves as an important public health issue by preventing complications which would emerge into adulthood. For this reason, we aimed to determine the relation of screen-time and physical activity with childhood obesity.

Method: This prospective cohort study was conducted in the pediatric primary care clinic of Ankara University School of Medicine between July 2017-November 2017. The children, aged between 6-18 years, without any underlying chronic disease and previous use of medications which increase the risk of obesity were included to study. A survey instrument was handed to families for the determination of daily physical activity and screen-time. Anthropometric values were calculated. Overweight (BMI>85%P) and obese (BMI> 95%P) children were identified. Data were evaluated by appropriate statistical methods.

Results: A total of 1949 children [1124 female, 826 male)] with a mean age of 11.1 ± 3.8 years were evaluated. The 41.1% of families signified that their children spent 1-2 hours and 42.6% denoted >2 hours of screen-time a day while 16.3% reported no screen-time. Obesity was detected in 12.6% of those who did not mention any screen-time whereas in 26.1% of those who spent > 2 hours a day (p <0,05). Physical activity findings revealed no participation in sports in 44.6%, 2 days/week in 25%, 3-4 days/week in 10.1% and >4 days/week in 20.3% of all children. The frequency of obesity was determined as 22% in children reported no exercise at all, and 11.2% in those who stated >4 days/week of exercise(p <0.05).

Conclusion: As compatible with previous research, this study showed that sedentary lifestyle serves as a serious risk for obesity. We observed that the risk of obesity increased with more daily screen-time. For this reason, we believe that physical activity starting from the family environment should be encouraged together with restriction of daily screen-time. In fact, increasing participation of social and physical activites is an effective measure to reduce screen-time. We suggest sufficient maintenance of playgrounds in school as well as public areas, more sports facilities and replication of jogging tracks.

P3-P155

Effect of Three-Month Diet and Physical Activity on Adipokines and Inflammatory Status in Children with Metabolic Syndrome

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The prevalence of metabolic syndrome (MetS) in young population continues to rise. Obesity is a chronic inflammatory disorder in which leptin, adiponectin and C reactive protein (CRP) play an important role. This study aimed to determine whether these adipokines are significant markers in defining MetS in pediatric population and to assess the effect of hypocaloric diet and physical activity on serum concentrations of adiponectine, leptin, and high sensitivity CRP (hs-CRP).

Material and methods: A prospective study was conducted over a period of 1 year, between January 2016 and December 2016, on 66 cases of obesity in children diagnosed at the Louis Ţurcanu Emergency Hospital for Children Timişoara. The patients diagnosed with MetS were put on diet and physical exercise for 3 months.

Results: MetS was present in 63.6% of obese children. There was a significant and positive correlation between MetS and both leptin and hs-CRP, and a significant, negative correlation between MetS and adiponectin. After diet and physical activity 3 patients no longer met the criteria for MetS. Leptin, adiponectin and hs-CRP concentrations statistically improved after a three-month diet and physical activity program.

Conclusions: hs-CRP, leptin and adiponectin can be used as predictors of cardiovascular risk in pediatric population. Diet and physical activity have an impact on the metabolic status.

P3-P156

Neck Circumference and Lipid Profile in Adolescents with Overweight / Obesity

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Introduction: Neck Circumference (NC) has been pointed out as an important indicator in the evaluation of overweight and may be useful to determine the level of obesity and metabolic alterations.

Objective: To verify the relationship between the NC and the lipid profile in adolescents with overweight or obesity.

Methods: A cross-sectional study with adolescents between 10 and 19 years old, of both sexes attended at the Endocrinology pediatric Unit in the Northeastern region of Brazil. The anthropometric nutritional status was classified according to World Health Organization reference curves (WHO). For evaluation of NC, it was used as cutoff point adapted for adolescents values>32cm for females and> 35,5cm for males. Total cholesterol, LDL-c, HDL-c, and triglycerides, were evaluated and classified according to the V Brazilian Guidelines on Dyslipidemias and Prevention of atherosclerosis (2017). Data were analyzed by the Software R x64 3.4.2. Statistical descriptive analysis and *Pearson* correlation were performed with adopted significance level of $p<0.05$.

Results: A total of 67 adolescents were evaluated, 52.2% of whom were male. From this sample, 20.9% individuals had overweight, 61.2% with obesity and 17.9% with severe obesity. It was observed that, of the total, 74.6% of the adolescents had elevated total cholesterol and 59.7% of the LDL-c, as well as 70.1% of the adolescents presented HDL-c below the recommendations. Girls presented higher mean values for total cholesterol 172 mg/dL (±28.32), LDL-c 106.81 mg/dL (±21.62), HDL-c 40.16 mg/dL (±7.74) and triglycerides 131.97 mg/dL (±67.79), with no significant difference between genders. 59.3% of the adolescents presented values above the cutoff point for NC. There was a negative correlation between NC and HDL-c ($p\leq0.01$) in males.

Conclusion: Adolescents presented high frequency of changes in total cholesterol, LDL-c and HDL-c, and there was a negative correlation between neck circumference and HDL-c in male adolescents.

P3-P157

A Not So "Simple Obesity"

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Childhood obesity is the consequence of a complex interaction among several factors: environment, genetics, endocrine disorders, medications and other conditions.

Genetic factors are described to be causal factors in up to 30-50% of overweight conditions.

Although polygenetic obesity is by far the most commonly observed, several obesity related syndromes associated with single gene defects have been identified.

Case presentation: A three year old girl referred to our Clinic with slightly increased TSH value (TSH 5.81 mcIU/ml, normal fT4) and excessive weight gain since she was 2. No anamnestic pathological features were referred. Family history included obesity, rheumatoid arthritis, high blood pressure, a maternal spontaneous abortion at 15w and T2MD.

Our first clinical evaluation (at 38 months old) revealed an important weight excess (BMI 25.6 Kg/m2, SDS3.78), flat feet, knock knees, pre-pubertal stages, no cognitive impairment or dysmorphic features. Blood biochemical examinations showed normal blood cells count, normal liver and kidneys function, high insulin resistance (G/I 4.64, HOMA index 3.75), normal thyroid function (slightly increased TSH (7.09 mcIU/ml), normal fT4 (14 pg/ml)), prepubertal hormone levels, normal adrenal secretion.

Further investigations revealed a normal female karyotype, no organic anomalies (negative brain MR, liver steatosis at abdomen ultrasound), prepubertal features at pelvic ultrasound examination and advanced bone age at X-rays.

Once excluded main secondary obesity conditions, a dietetic program was started and the little child was evaluated every 6 months at our center.

Although a good compliance to dietary plan and physical activity program, patient's weight continued to increase (BMI 26.6 Kg/m2 at 7 months of follow up, BMI 34.1 kg/m2 at 39 months). For this reason, CGH-array were performed and revealed a heterozygous deletion of 232 kb (arr[hg19] 16p11.2(28,819,028-29,051,191) x1 in the 11.2 region of chromosome 16 p arm.

Discussion: Loss or gain of material from 16p11.2 is increasingly recognized as one of the most common structural chromosome disorders. The deletion identified in our little patient concerns 12 genes and the most important possible causative gene of her obesity is related to SH2B1 gene. This gene protein is SH2 adaptor protein 1 (SH2B1), involved in leptin and insulin signaling. In literature the loss of this protein has been found associated to a serious early onset obesity with insulin resistance, these features were observed in our patient.

Conclusion: In essential-like obesity not responding to dietary treatment, CGH array could be useful for improve diagnosis.

P3-P158

Effect of Obesity on Bone Age and Hormonal Parameters in Indian Children

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Background: Obesity is one of the most common nutritional problems in developed countries. The prevalence of obesity is rapidly progressing in children. It is associated with serious health hazards in adolescence and especially in adulthood, like hypertension, coronary artery disease, diabetes mellitus, etc.

Methods: A study was conducted including the pediatric patients presented to Indraprastha Apollo hospital with signs of insulin resistance. All patients were investigated with oral glucose tolerance test, Fasting lipid profile, Liver function test, Vitamin D, Thyroid profile and bone age assessment using Tanner-Whitehouse method (RUS).

Results: Among the study population (n=100) 61 patients were pre-pubertal and 39 patients were pubertal. 55 patients were obese, 33 were overweight and 10 had weight between 50th and 23rd adult equivalent. Among obese patients mean chronological age was 9.16±3.25 while bone age 10.97±3.07($p<0.001$), among overweight patients mean chronological age was 11.16±1.95 while bone age 12.17±1.87($p<0.001$). All patients had insulin resistance calculated with HOMA IR index, Matsuda Index and Stumvoll Index. Among the obese patients only 18.4% had High triglyceride levels. All the patient had vitamin D deficiency, 5 had subclinical hypothyroidism.

Conclusions: obesity and overweight were associated with advanced bone age, which ultimately results in decreased final adult height. Hence bone age should be evaluated white treating obesity and require long term follow ups to predict the effects on adult height.

P3-P159

Compliance of Obese Children and their Family to the Directions of a Pediatric Endocrinology Medical Office

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Introduction: Childhood obesity constitutes one of the most serious public health concerns currently since its prevalence is increased rapidly worldwide and triggers raised morbidity and mortality in childhood and adulthood.

Objective and hypotheses: The present study is a prospective cohort survey which aim is to find risk factors of children and their parents' denial to compliant to the directions of a pediatric endocrinology medical office.

Method:A total of 106 obese Greek children were enrolled in this study.The age of the children ranged from 5 to 14 years. Family and medical history and demographic information was collected. Anthropometric measurements were obtained, including height, weight, and waist circumference at two programmed meetings and the scores were compared.

Results:84% of children were consistent to the next appointment and 16% did not showed up. Among them who came, 57% had raised their BMI and 43% had decreased BMI. 81% of children changed their diet customs, among them 53% had raised BMI at the second measurement and 47% had decreased BMI. From those who had improved BMI 53% had reduced the quantity of consuming food, 63% had reduced consuming junk food and 12% had increased the consumption of fruits and vegetables. 34% of children started or intensified their physical activity, among them 43% had raised BMI at the second measurement and 57% had decreased BMI. 19% of the children changed both their diet customs and physical activity, among them 47% had raised BMI at the second measurement and 53% had decreased BMI. 24% of the children increased sleeping time, among them 40% had raised BMI at the second measurement and 60% had decreased BMI. 50% of the children who started medical treatment with metformin (8) stopped receiving it because of the side effects. 43% of boys decreased BMI and 57% increased BMI and 45% of girls decreased BMI and 55% increased BMI. 62% of the children who reside at urban area decreased BMI and 38% increased BMI while 30% of those who live at city decreased BMI and 70% increased BMI.

Conclusions: Low financial incomes and lack of time prevent consistence to the appointments, improving diet and starting a sport activity. The harder part of compliance is starting physical activity. Physical activity, reducing quantity of food consumption and junk food are the most effective interventions of decreasing weight. Sufficient time of sleep assists the decrease of BMI. Urban residence supports the effort of children to lose weight.

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Risk Factors and Comorbidities of Childhood Obesity

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Introduction: The epidemic of childhood obesity has emerged as one of the most serious public health issues since this disease leads to multiple disorders in many systems of the human body and decreases the quality of life and the life expectancy. Plenty of studies have searched for risk factors which cause pediatric obesity and precocious markers of comorbidities which follow obesity.

Objective and hypotheses: This study is a cross-sectional and retrospective case- control survey which aim is to find risk factors and complications of childhood and adolescence obesity.

Method: The sample consists of 28 obese individuals and 17 individuals with normal weight as control group, aged 5 to 16 years old. Family and medical history was obtained and anthropometric details were measured. A physical examination was performed as well as blood sampling and ultrasound of the liver.

Results: Consumption of high food quantity, high amounts of junk food, skipping breakfast, low physical activity and sedentary behaviours of children and their parents are major risk factors of

childhood obesity. On the contrary, food quality appears not to influence the prevalence of childhood obesity. Sufficient amount of sleep is an important limiting factor of the obesity onset. This study does not reveal pre-natal and post-natal determinants. The socioeconomic position of the family and the area of residence does not influence the incidence of pediatric obesity. Obesity among family contributes to this disease, especially obese mothers develop high risk of having obese children and mother's pre-conception high BMI seems to be a risk factor.

Obese adolescents excibited higher risk to develop disorders of metabolic syndrome than the control group (high waist circumference, waist-to-hip ratio and waist-to-height ratio, low HDL, high levels of c-peptide and HbA1c in blood serum), elevated levels of CRP and TSH and low levels of SHBG in blood serum. The study also reveals a trend towards elevated levels of ALT in blood serum of obese children than children with normal BMI and a high percentage of obese adolescents (22%) appear to have NAFLD according to the findings of ultrasound of the liver.

Conclusions: More research in risk factors of childhood obesity is a high priority of public health for the purpose of prevention programs' development. It is urgent also to bring out predictors of obesity comorbidities in order that obese children enhance their quality of life and increased their life expectancy.

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Autonomic Nervous System - Inflammation Link: A New Independent Mechanism for Homeostasis

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Background: Translational research has provided evidence of autonomic nervous system (ANS) interactions with cytokines and gut hormones. In the gastrointestinal track, the crosstalk of the stimulated vagus nerve with immune cells enhances the cholinergic tone. In obesity, on the other hand, hyperinsulinemia and hyperleptinemia induce ANS activation.

Aim: To synthesize literature results exploring links among the autonomic nervous system, gut hormones, immune factors, and pancreatic β-cell function.

Methods: Literature search in PUBMED, Scopus.

Results: A study in animal models showed an association between ANS and inflammatory markers (Matteoli & Boeckxstaen, 2013). In obese patients with and without diabetes type 2, an association between ANS and inflammatory factors with, independent of BMI or fat loss, after bariatric surgery, was observed (Casellini 2016). Importantly, a meta-analysis after bariatric surgery that evaluated the interaction of ANS and insulin resistance, suggested a link betweenthe ANS, the gut, and pancreatic islet β-cells (Geronikolou 2017a). A separate interactions network within the so-termed "Obesidome" has been created to explore this interplay (Geronikolou 2017b). Our results show that there is an intricate communication network between the nervous and immune systems and that this interplay could be involved in the regulation of the immune response. TGF-beta and thymic stromal lymphopoietin produced by the GI enterocytes and/or immune cells may contribute to the maintenance of immune homeostasis. The interactions between the autonomic, inflammatory, and hormonal biomarkers and their encoding genes revealed that JAK2 serves as a key hub for leptin and insulin activity, thus, providing the basis for further investigation.

Conclusions: The autonomic nervous and immune system interplay may provide an independent mechanism of energy homeostasis warranting future research.

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Effects of a brief Physician Delivered Counseling on Childhood Obesity

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Introduction: In the resource constrained setting of a general endocrine clinic, a brief counseling session was offered to all overweight children.

Material: In the period 1996–2017, 2364 patients with obesity between the ages 5 and 18 years were seen. All gave consent for their data to be analysed. Patients with syndromic obesity or with a secondary cause for obesity were excluded.

Methods: The caregiver, usually a parent was instructed to never serve food to the child. The child was instructed to serve herself, never take a second helping and spend at least 20 minutes over a meal. The child was asked to eat in a fixed designated place, at fixed times and not to use a TV or mobile phone while eating. No anti obesity pharmacotherapy was given, but coexisting problems were treated. Follow up visits were scheduled every 6 months. BMI was calculated at each visit.

Setting: A prospective observational study in a secondary referral centre in Kolkata, India.

Results: A total of 2364 patients (1447 males and 917 females) were seen. Of these, 85% did not revisit. The reason for drop out was lack of efficacy, ascertained through random phone calls. There was a significant fall of BMI in almost all the children who returned for follow up. However over the next 5 years all the responders had regained weight. The first 30 responders were chosen for further study. The BMI of these patients at baseline was paired with the BMI obtained on their next visit. Wilcoxon's ranked sum test was used to compare the pairs. The fall in BMI between the first visit and the second (median 25.2 kg/m^2 to 24.2 kg/m^2), is statistically significant ($p < 0.001$). Longer term follow-up of the patients, some over 5 years, showed that in every instance the BMI increased.

Discussion: A small subset (15%) of children appear to lose weight after physician led counseling. Although the weight loss is not sustained, these children are motivated to attend on follow up visits. When there is no initial weight loss, there is no motivation to return for follow up. Thus the twin challenges are to produce an initial weight loss after counseling and then later, to sustain it.

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The Prevalence of Obesity in Boys in the Region of the Russian Federation

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Background: Obesity is one of the most frequent chronic diseases in the world, however the true prevalence of obesity in the RF remains at the moment insufficiently studied.

Aims: to study the age features of the prevalence obesity in boys in the Udmurt Republic - the region in European part of the Russian Federation with the children population of 335 000.

Methods: 4795 boys aged 1–17 years were surveyed, among them 2368 (49,4%) were city dwellers, 2427 (50,6%) - rural dwellers. Diagnostic criteria of overweight and obesity in children recommended by WHO (2007) were used. Age features of the disease were analyzed in groups of 1-3 years, 3-7 years, 7-12 years, 12-15 years, over 15 years. The prevalence of obesity was estimated at 100 surveyed.

Results: Overweight was detected in 17,2% (in age groups from 13,5% to 22,2%), obesity in 8,7% (in age groups from 4,4% to 12,4%). The results of the epidemiological study exceed the official statistics by 8,4 times. The peak of overweight prevalence was registered in boys of 1-3 years (22,2±1,6%), peak of obesity prevalence - in boys of 7-12 (12,4±0,9%). The lowest prevalence rates of both overweight and obesity are registered in the age group over 15 years (13,5±1,3% and 4,4±0,8%). No significant differences in the incidence of obesity between rural and city dwellers were registered (9,3±0,6% and 8,2±0,6%, P > 0,05). In patients with obesity BMI within 2–2,5 SD was registered in 58,7%, 2,6–3,0 SD – in 26,0%, 3,1–3,9 SD – in 12,6%, > 4,0 SD – in 2,7%.

Conclusions: The study shows a high prevalence of overweight and obesity among boys in the region and actualizes the problem for clinical.

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Obesity in Adolescents, Is Accompanied by a High Levels of Leptin and a Low Serum Ghr Level in the Blood Plasma. A High Degree of Obesity Is Accompanied by a Greater Higher Leptin Level and Decrease in the Ghr Level.these Changes Are More Significant Registered in Abdominal Ob

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Introduction: About 20 thousands of new cases of obesity (Ob) are first registered in children and adolescents in Ukraine annually (morbidity 2.72/1000, prevalence 13.50/1000 of the corresponding population on 01.01.2016). Adolescent Ob shows catastrophic rise (prevalence 8.9/ 1000 in 2001 vs 28.3/1000 in 2015). Completely unclear the role of Ghr in the etiopathogenesis of obesity in adolescents.

Methodology: A total of 39 obese children with HD (14 boys, 15,1 ± 1,4 y.) and 14 healthy control (mean age 14,6 ± 1,2 y.) were included into the study. Among patients with HD- 16 patients (41,03 %) had visceral abdominal obesity (VAOb), 23 patients (58,97 %) had gluteofemoral obesity (GFOb). Serum Leptin, Ghrelin, Insulin level, HOMA-IR were studied. Such studies are conducted in Ukraine for the first time.

Results: Overweightt was revealed in 15 (38,5 %) patients, ObI – in 8 (20,5 %) people, ObII – in 10 (25,6 %) persons, ObIII – in 6 people (15,4 %). The signs of insulin resistance (HOMA-IR > 2,77; IRI > 20 μIU/mL) were noted in 60 % patients. Level of leptin in children with obesity VAOb was 47.2 ± 5.54 ng / ml (BMI 35.2 ± 5.07 kg / m2) and was significantly higher (26.5 ± 7.13 ng / ml, p <0.05) than in children in the group with GFOb, in combination with similar metabolic disorders, BMI at the same time was 28.7 ± 2.4 kg / m2).

Serum Ghr level was found significantly lower in obese adolescents compared to that of control group and was dependent on the degree of Ob. The level of Ghr was the lowest (582,58 ± 59,37 ng/mL) in patients with ObIII. The level of Ghr was significantly lower (p <0.05) in patients with VAOb than with GFOb (656,63 ± 113,16 vs 1212,13 ± 114,6 ng/ml, respectively). The levels of hyperinsulinemia and insulin resistance were increased with an increase in the degree of obesity.

Conclusion: Obesity in adolescents, is accompanied by a high levels of leptin and a low serum Ghr level in the blood plasma. A high degree of obesity is accompanied by a greater higher Leptin level and decrease in the Ghr level. A significantly higher Leptin level and lower Ghr level was registered in abdominal Ob comparing to gluteofemoral type of obesity. Further studies the relationship of Leptin abd Ghr level, insulin resistance and hyperinsulinemia in obese adolescents are required

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Hidden Hunger in Overweight/ Obese Indian Adolescents

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Background and Objective: Overweight/ obese children may have unrecognized deficiency of several essential micronutrients owing to their faulty dietary habits. These may impair their physical and mental development. Deficiency of specific minerals and vitamins that co-factors in metabolic and signalling pathways, such as choline, zinc, magnesium, vitamins D and B12 may also predispose to insulin resistance, fatty liver and metabolic syndrome. This study was undertaken to assess the macro- and micronutrient intakes of overweight/ obese Indian adolescents.

Methods: This was a cross-sectional hospital based study. Dietary assessment was done using 24 hours recall and quantitative food frequency questionnaires in 214 overweight/ obese adolescents aged 10 to 16 years. Daily intakes of fat, protein, carbohydrates, fibre, iron, calcium, magnesium, zinc, choline, folic acid, vitamin B12 and vitamin C were calculated and compared to the age and gender-specific recommended dietary allowances (RDA) for Indian adolescents. Intake < 90% of RDA was considered low

Table 1. (for Abstract no P3-P165)

Dietary component	Daily intake Mean ± SD	Intake in comparison to recommended daily allowance		
		High N (%)	As per RDA N (%)	Low N (%)
Energy (Kcal)	2922.3±837.5	148 (69.2)	46 (21.5)	20 (9.3)
Protein (g)	82.5±25.1	200 (93.5)	10 (4.6)	4 (1.9)
Fat (g)	88.6±32.0	209 (97.7)	2 (0.9)	3 (1.4)
Fibre (g)	8.6±3.8	0	1 (0.5)	213 (99.5)
Iron (mg)	22.7±8.9	47 (22.0)	39 (18.2)	128 (59.8)
Calcium (mg)	973.3±493.4	109 (51.0)	37 (17.2)	68 (31.8)
Magnesium (mg)	591.6±235.3	213 (99.5)	1 (0.5)	0
Zinc (mg)	9.0±3.7	53 (24.7)	31 (14.5)	130 (60.8)
Choline (mg)	262.8±223.3	35 (16.4)	15 (7.0)	164 (76.6)
Folic Acid (μg)	288.8±119.3	192 (89.8)	11 (5.1)	11 (5.1)
Vitamin B12 (μg)	0.82±1.0	39 (18.2)	19 (8.9)	156 (72.9)
Vitamin C (mg)	91.3±67.3	175 (81.8)	19 (8.9)	20 (9.3)

and > 110% as high. Serum 25 hydroxyvitamin D was measured in a subset (n=66) by electrochemiluminiscence, <20 ng/ml was considered as deficiency.

Results: The daily intake of energy, fat and proteins exceeded the RDA but that of fibre and several micronutrients was low. Intake of choline, vitamin B12, zinc, iron and calcium was low in 76.6, 72.9, 60.8, 59.8, and 31.8%, of the adolescents, respectively. Biochemical vitamin D deficiency was present in 74.3%.

Conclusion: Hidden hunger is common in obese adolescents. This should be identified and rectified by appropriate nutritional advice.

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Assessment of Obesity in Children with Achondroplasia and Hypochondroplasia

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Introduction: Obesity is one of common complications in achondroplasia (ACH) and hypochondroplasia (HCH). Obesity can be a risk factor for excessive load on joints or lower spines in aged, worsen sleep apnea and develop a metabolic syndrome. Thus, it is critical to maintain their proper weight from early childhood. ACH specific growth charts and BMI has been used to evaluate their overweight and obesity. Due to disproportional short stature, the assessment by BMI could lead an overestimation of body fat. Dual X-ray absorptiometry has been known to be a powerful tool to assess body compositions accurately. In this study, DXA as well as anthropometric measurement were performed to evaluate the degree of obesity in our cohort.

Objective: Our objective is to assess their obesity using % body fat by DXA and body index obtained from anthropometric measurement and to find a useful parameter which reflects an adiposity

Subjective and Methods: Thirty-one participants of our University Hospital were recruited in this retrospective study. Their anthropometric measurements (height, weight, hip circumference and waist circumference) were extracted from the medical records. Then, we calculated BMI, waist height ratio and waist hip ratio. Whole body DXA scans were performed on a Hologic Discovery A DXA scanner (Hologic Inc., Waltham, MA). % body fat was also measured by Tanita DC320 dual frequency body composition analyzer (Tania Corp. Tokyo, Japan) using bioelectrical impedance analysis (BIA). All statistical analyses were performed using IBM SPSS Statistics software. The definition of obesity was made the following conditions; boys with more than 25% body fat, girls under 10 years of age with more than 30% body fat and girls over 11 years old with more than 35% body fat.

Results: It was 25.8% that met the criteria of obesity (27.8% in boy and 23.1% in girl). Whereas, subjects with BMI over 85% accounted for 83.9%. (83.3% in boy, 84.6% in girl). Moreover, as much as 45.2% of all was above 95% BMI (50% in boy, 38.5% in girl). Our data showed no age dependency to fulfill obesity criteria from the point of %BF.

Discussion: There was a discrepancy between BMI percentile and %BF (DXA) in number of patients satisfied obesity criteria. It seems to be unreliable to predict a quantity of adiposity from BMI. The relationship between obesity and insulin resistance is the next issue to be examined.

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Correlation of Lipoprotein(a) Levels and Family History of Cardiovascular Disease in a Sample of Overweight/Obese Children and Adolescents

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Introduction: Children with positive familiar history (FH) of cardiovascular disease (CVD), consist a subpopulation in higher risk for early life cardiovascular events. Obesity represents a major risk factor for coronary heart disease and premature death. Recently published studies integrate high levels of lipoprotein (a) (Lp(a)) into the group of cardiovascular risk factors. According to the Bogalusa study, increased levels of Lp(a) (>30mg/dL) are associated with cardiovascular disease in early life.

Aim of the study: The aim was to investigate a possible correlation between Lp(a) levels and FH of CVD in a sample of overweight/obese (ow/ob) children and adolescents and compare them with normal weight controls.

Subjects and Methods: Data were collected from 147 ob/ow children and adolescents (66 boys, 81 girls) who attended the paediatric obesity clinic of a tertiary centre, and 59 healthy controls (25 boys, 34 girls) with normal weight for age. From all all participants a FH of CVD and a morning lipid profile including Lp(a) after a 12-hour fast was obtained, and a full physical examination was performed. Statistical analysis was performed with IBM SPSS 23, statistical significance set at p value <0.05.

Results: Mean age of ow/ob was 10 years (± 2.8), 10.2 (± 0.9) of controls. In the ow/ob group 23.1% were overweight, 44.2% obese, 32.7% had morbid obesity. The mean Lp(a) value in the ow/ob was statistically significant (p<0.05), 31.3mg/dl (± 40.8), and 24.2 mg/dl (± 34.2) in the controls. The ow/ob children and adolescents with positive FH of CVD (45,7%) had Lp(a) levels >30mg/dl, mean value 34.8mg/dl (± 37.4), the rest (70.7%) with negative FH of CVD had a mean Lp(a) 29.8mg/dl (±42.1), statistically significant difference (p<0.05). The association between level of obesity (overweight, obese, morbidly obese) and FH of CVD was also statistically significant (p<0.05).

Conclusions: In the ow/ob children and adolescents of our study raised L(a) levels were found to positively correlate with FH of CVD. Determining Lp(a) levels is important for evaluating obesity in paediatric populations as abnormal Lp(a) levels correlate with higher risk of cardiovascular events in early life. When high Lp(a) levels are found, a more intense intervention is recommended to establish normal weight and at the same time to establish healthier eating habits and a daily exercise routine.

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Beneficial Effect of Metformin Treatment in Obese Children and Adolescents

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Introduction: Obesity in children and adolescents is a growing global health problem. Obese children and adolescents provide the pediatric healthcare professionals management challenge. Obesity with insulin resistance, dyslipidemia and elevated blood pressure constitute the metabolic syndrome and each of these is an independent risk factor for cardiovascular disease,diabetes mellitus, non-alcoholic fatty liver disease.Lifestyle modification is a primary and main milestone in treatment, but often has short or limited effect. On the other hand metformin is well established oral hypoglycemic agent in the treatment of adult and young patients with type 2 diabetes.

Objective: To evaluate the effect of metformin treatment in children and adolescents on the body mass index(BMI), fasting serum glucose and insulin (calculated as Homeostasis model assessment for Insulin resistance – HOMA-IR) and blood glucose at the second hour of an oral glucose tolerance test (OGTT). In addition we examined secondary health outcomes as total cholesterol, tryglycerides, HDL- and LDL- cholesterol and blood pressure.

Methods: Investigation and follow up of 57 children and adolescents (16 boys), aged 7 years 6 months-16 years 9 months. Patients received Metformin for an average period of 14,6 months (6-36 months) twice daily dosage of 1000–1700 mg.Anthropometry (height, weight, waist circumference), clinical examination with regard to presence of acanthosis nigricans (AN) and hypertension (AH)(systolic and/or diastolic blood pressure above 95 percentile for age, gender and height), serum lipid level, liver enzymes, OGTT were performed at baseline, every six months and end of treatment period.

Results: At evaluation and beginning of treatment median BMI was 30,95 kg/m^2. After the treatment period BMI was reduced with 1,91 kg/m^2. AN was found in 51% of all patients and pretreatment HOMA-IR was 5,52. Metformin therapy had beneficial effect both on HOMA-IR which fall to 3,16 and the presence of AN which was found in 27 patients(47,3%).Of all patients 21%(12) were found to have Impaired glucose tolerance before treatment and only one at the end of treatment. Total cholesterol was average 4,34 mmol/l and fall to 4,11 mmol/l(p>0,05). Reduction of other lipids was found but also without statistical significance. AH was found in 26 patients (45,5%) at beginning and in 25,7%after treatment.

Conclusion: Metformin can be efficacious treatment that lead to improvement in BMI, HOMA-IR, IGT and AH in obese children and adolescents but although it has lowering effect on serum lipids it does not show statistical significance.

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Comparison of the Effectiveness of a Battery Powered and Manual Toothbrush in Removal of a Dental Plaque for Good Oral Hygiene in Adolesents with Over-weight

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Objective: Dental plaque removal is an important factor in preventing periodontal diseases and caries. Tooth brushing remains the most reliable method of controlling dental plaque. The purpose of this study was to compare the effectiveness of plaque control performed with a battery powered and manual toothbrushes in over-weight adolescents.

Materials and Methods: The twenty two adolesents with overweight were attended in this study. These patients were divided into two groups by randomly method (such as study and control). The study group; using a battery powered toothbrush twice a day, the control group; using manuel toothbrush twice a day.

Plaque was scored after brushing at the baseline of the study and three months later, using Patient Hygiene Performance (PHP). Statistical analysis was performed by Paired samples t-test and Independent samples t-test.

Results: According to statistical analysis of the obtained results, both toothbrushes mean differences between baseline and post-brushing plaque scores decreased. Especially in the lingual surfaces of the teeth and in the posterior regions of molar teeth, battery powered toothbrush was more active in over-weight adolescents ($p< 0,01$).

Conclusion: Battery powered toothbrushes should be recommended to provide good oral hygiene in overweight adolescents (just like people with disabilities and orthodontic patients).

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Cardiac and Vascular Assessments in Small- Versus Appropriate-for-Gestational-Age Infants at Ages 1 and 2 Years

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Background: Children born small-for-gestational age (SGA), especially those who experience spontaneous postnatal catch-up growth, are at increased risk for developing insulin resistance, central adiposity and cardiovascular abnormalities later in life. By age 3-6 years, SGA children have a broader aortic and carotid intima media thickness (aIMT and cIMT) which are markers of preclinical atherosclerosis.

Objective: To assess longitudinally -at age 12 and 24 months-, cardiac morphology and function, and markers of cardiac dysfunction and cell damage, together with body composition and endocrine-metabolic status, in catch-up healthy children born SGA and in age-matched appropriate-for-gestational age (AGA) children.

Subjects/ Methods: The study population consisted of 61 AGA (48% girls) and 26 SGA infants (50% girls), born after uncomplicated, term pregnancies; mean birthweight Z-scores: 0.0 and -2.3, respectively. Cardiac morphology, systolic and diastolic function (by M mode, 2D, doppler color echocardiography with a Vivid 7 model and 7MHz phased-array transducer), aIMT, cIMT, pre-peritoneal fat (by US), markers of cardiac dysfunction (homocysteine, Heart-type Fatty Acid-Binding Protein), endocrine-metabolic variables (glucose, insulin, IGF-I, HMW-adiponectin, leptin), and body composition (by DXA) were assessed at 12 and at 24 months.

Results: At age 12 months, SGA infants had a thicker carotida and less lean mass, as compared to AGA infants (both $p<0.001$). Cardiac morphology assessment disclosed a smaller aortic annulus and left ventricle diameter in systole; those differences disappeared after correcting for cardiac size. At age 24 months, the differences in cIMT and lean mass between subgroups persisted ($p<0.0001$); in addition, SGA children showed an increase in pre-peritoneal fat –a surrogate of visceral fat- ($p<0.01$ *vs* AGA), a decrease in the left ventricular ejection and shortening fractions, and a thinner interventricular septum in diastole (IVSd) (all $p<0.05$). The difference in IVSd disappeared after adjusting for cardiac size. Markers of cardiac dysfunction and endocrine-metabolic vari-

ables were similar between subgroups. cIMT correlated positively with pre-peritoneal fat at age 12 months (r=0.34, p=0.0016) and 24 months (r=0.35, p=0.0064), and negatively with lean mass (r=-0.40, p=0.0003) at age 12 months.

Conclusion: The present study appears to be the first to have longitudinally explored a series of cardiac and vascular markers in AGA and SGA infants at the ages of 12 and 24 months. Overall, SGA infants displayed reassuring results, but their early increment of cIMT (which was found to be linked to their early deficit of lean mass) and abnormal parameters of left ventricular function may deserve further attention.

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Bone Maturation as a Predictive Factor of Catch-up Growth During the First Year of Life in Born Small for Gestational Age Infants: A Prospective Study

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Background: About 85-90% of children born small for gestational age (SGA) experience a catch-up growth that occurs mostly during the first year of life and results in a full stature recovery by the age of 2. The remaining 10-15% do not undergo compensatory growth, achieving - if untreated - an adult height approximately 20 cm below their peers.

Objective: The aim of this prospective one-center study was to investigate the relation between bone maturation (BM) and catch-up growth during the first year of life in SGA infants.

Method: Newborns whose weight and/or length was <-2 SD for gestational age were classified as SGA. The study included a group of 32 SGA, 21 of which full-term (37-41 gestation weeks GW, subgroup A1) and 11 preterm (30-36 GW, subgroup A2). Control group (B) consisted of 19 full-term and adequate for gestational age (AGA) newborns. All the partecipants were born in the same hospital and period (2013-2014). Chromosomal disorders, major congenital defects and maternal chronic diseases were criteria of exclusion.

The study population underwent longitudinal evaluation of growth parameters and BM at 0, 3, 6 and 12 months. Assessment of BM was performed by ultrasonographyc (US) study of Beclard's nucleus (<3 mm at birth meaning intrauterine delay of BM).

Results: Mean 1st year height velocity (HV) was 25.5±13.2 cm. Significantly higher HV was observed in subgroup A2 versus A1 (32.4±8.0 vs 25.6±2.9 cm, p=0.01); nevertheless, subgroup A2 presented more frequently <-2 SD height outcome at 1 year than subgroup A1 (27.3% vs 0%, p=0.01). If compared with controls, HV was overall higher in SGA group, but without reaching statistical significance (28.6±6.5 vs 25.5±2.9 cm, p=0.10). Intrauterine delay of BM was more common in group A vs B (59.4% vs 21.2%, p=0.0078), and in subgroup A2 vs A1 (90.9% vs 42.9%, p=0.0086). SGA with intrauterine delay of BM showed a constant pattern of catch-up growth, with higher HV and better height gain (29.75±3.1 vs 23.8±2.7 cm, p=0.003) at 12 months evaluation.

Conclusion: Our results suggest for the first time that neonatal BM should be regarded as a predictive factor of SGA height gain during the first year of life.

US evaluation of Beclard's nucleus is a useful non–invasive technique to identify intrauterine delay of BM, which can positively influence early postnatal catch-up growth of SGA infants.

P1-P137

Neonatal Screening Tests in Premature Newborns in Southern Brasil

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Neonatal screening tests are used for the screening of genetic, endocrine and metabolic diseases. Preterm newborns have a higher false-positive and false-negative results in neonatal screening. The objective of this study was to estimate the prevalence of false-positive and false-negative results in the neonatal screening tests for phenylketonuria, congenital hypothyroidism, biotinidase deficiency and congenital adrenal hyperplasia (CAH) in preterm newborns in Curitiba, to analyze other factors that influences the results and to evaluate the adherence to the newborn screening guideline for preterm newborn. A cross-sectional study with prospective data collection was carried out in 11 hospitals from March to December 2015. The results were compared with the results of the screening tests performed on the term newborns. A total of 1,753 preterm newborns and 18,028 term newborns were included. Only 486 (28%) of the preterm newborn performed the second dried blood spot, according to guideline. The prevalence of false-positive in preterm newborn for phenylketonuria was 1:150, for congenital hypothyroidism was 1:133, for biotinidase deficiency was 1:447 and for CAH was 1:5,6. Early dried blood spots, collected before 48 hours postnatal age, showed a higher risk of false-positive results for congenital hypothyroidism and CAH (26.78 and 16.41, respectively). Early sample collection did not influence the results of the screening tests for phenylketonuria and biotinidase deficiency. Only one patient had delayed thyroid stimulating hormone (TSH) elevation. There were no reports of false-negative results.

Conclusions: Prematurity and early collection were considered as risk factors for higher frequency of false-positive in neonatal screening tests of CAH and congenital hypothyroidism. A second dried blood spot for screening test is recommended to diagnose cases of delayed TSH elevation. Efforts should be made to improve the proper collection of tests in preterm infants to avoid false-negative results.

P1-P138

Measurement of Estradiol and Testosterone in Umbilical Cord Blood by Gas Chromatography-tandem Mass Spectrometry (GC-MS/MS); Comparisons with Radioimmunoassay (RIA)

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Background: We have previously shown radioimmunoassay (RIA) and gas chromatography-tandem mass spectrometry (GC-MS/MS) to be comparable when analyzing estradiol and testosterone concentrations in prepubertal and pubertal children. However, the reliability for steroid hormone determination with RIA in umbilical cord blood is not known. In general, older studies using RIA show higher values of testosterone, than more recent ones using MS/MS.

Patients and methods: Umbilical cord blood was collected from 236 infants (133 boys, 103 girls). Estradiol and testosterone concentrations were analyzed using both RIA (Spectria, Orion Diagnostica, Espoo, Finland) and GC-MS/MS (Agilent, Montreal, Canada).

For estradiol the limit of detection (LOD) was 9 pmol/L for RIA and 2 pmol/L for GC-MS/MS. With RIA the intra-assay coefficient of variation (CV) was <8% whereas the interassay CV was <13% for concentrations ≥ 40 pmol/L. With GC-MS/MS the intra-assay CV was <4% and the interassay CV was 7% for concentrations ≥300 pmol/L.

For testosterone the LOD was 0.1 nmol/L for both RIA and GC-MS/MS. With RIA the intra- and interassay CV was < 7% for concentrations of ≥ 0.9 nmol/L. With GC-MS/MS the intra-assay CV was <4% and the interassay CV was 16% for 0.2 nmol/L and ≤8% for concentrations of ≥5 pmol/L.

Results and discussion: For estradiol, there was a good correlation between RIA and GC-MS/MS (r=0.92, p=0.000). The concentrations of estradiol were similar, RIA (range 413-71765, median 14044 pmol/L) versus GC-MS/MS (range 499-68825, median 15754 pmol/L).

For testosterone, there was also a correlation between RIA and GC-MS/MS (r=0.44, p=0.000). Umbilical cord blood testosterone concentrations determined with RIA were higher (range 0.7-15.0, median 3.3 nmol/L) than with GC-MS/MS (range 0.1-8.1, median 0.3 nmol/L), with linear fit functions; RIA = 0.99 x GC-MS/MS + 3.10 nmol/L.

Although RIA is as reliable as GC-MS/MS when analyzing serum from prepubertal and pubertal children, that is not the case in umbilical cord blood. We speculate that this is due to cross reactivity with other androgens, testosterone metabolites, or estrogens with the RIA.

Conclusion: We conclude that RIA is sufficient for determination of estradiol, but not testosterone, in umbilical cord blood.

P1-P139

Transient Neonatal Iatrogenic Hypothyroidism Due to Iodinated Contrast

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Introduction: Iodine is necessary for thyroid hormone synthesis, but when exposed to large quantities, iodine may have an inhibitory effect on hormone synthesis leading to hypothyroidism, known as the Wolff-Chaikoff effect. Newborns may be exposed to iodine through various events in early life. In 2012 three index cases with suspected iatrogenic hypothyroidism due to iodinated contrast exposure were discovered at the Neonatal department, The Queen Silvia Children´s Hospital, Gothenburg, Sweden. These three cases prompted us to regularly monitor thyroid function in patients who had been exposed to iodinated contrast via the gastrointestinal (GI) tract.

Method: Thyroid function was monitored in infants with gestational age ≤ 36 weeks at birth and exposed to iodinated contrast via the GI tract before 40 gestational weeks. We identified patients with elevated TSH (thyroid stimulating hormone). Patients with prolonged GI passage time were also identified.

73 patients born between June 2012 and December 2017 (48 males, 25 females) who met these criteria were identified.

Results: 33 patients (45%) had increased TSH levels after iodinated contrast exposure (9,2-484 mU/L). Seven patients (9,5%) had both elevated TSH, and decreased f-T4 (thyroxine). Mean TSH was 53,9 mU/L. TSH was spontaneously normalized after mean 18 days in 8 infants who were not given levothyroxine treatment. In 8/11 (73%) infants who were given levothyroxine, TSH was normalized during treatment. In the remaining infants, we lack TSH-results post x-ray.

We identified a few confounding factors. Three patients had Down's syndrome (9%) and four were born small for gestational age (SGA) (12%). 14/33 (42%) patients with elevated TSH had necrotizing enterocolitis (NEC).

28/33 (85%) patients with elevated TSH, had a prolonged GI passage time.

In this material, we were not able to identify a specific gestational age where patients would be more susceptible to thyroid dysfunction after iodinated contrast exposure.

Conclusion: We found elevated TSH levels after exposure to iodinated contrast via the GI tract. The expected incidence of congenital hypothyroidism is usually 1/3000, which makes these cases evidently more common. Both prematurity and prolonged exposure time to iodine may be risk factors for iodine induced hypothyroidism.

Even though this condition seems to be transient, follow-up studies are needed, especially investigations of cognitive outcome of these children.

We suggest that thyroid function is investigated before and after exposure to iodine-containing contrast solutions.

P1-P140

Sexual Dimorphism of IGF1 and IGF2 Expression in the Neonatal Rat Brain

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Insulin-like growth factor (IGF) 2 plays a fundamental role in prenatal growth and development. The *IGF2* gene is imprinted, with the paternally inherited copy being active and the maternal copy being silenced in most tissues. During development, the expression of IGF2 is sexually dimorphic in some tissues and this is thought to be involved in the development of some sexually dimorphic features. For example, IGF2 expression is reported to be higher in the male brain compared to females, but less is known regarding specific brain areas and cell types. As the hypothalamus is implicitly implicated in the control of sexually dimorphic endocrine functions and glial cells participate in this control, we asked whether their expression of IGF2 and other members of the IGF system is sexually dimorphic.

Our aims were to: 1) Determine if the overall expression of IGF2 is sexually dimorphic in specific brain regions, including the hypothalamus, and 2) Compare the expression of the IGF system in hypothalamic astrocytes from male and female neonatal rats. For tissue analysis, cerebellum, hypothalamus and frontal cortex were dissected from 2-day old Wistar males and females. Primary hypothalamic astrocyte cultures were prepared from 2-day old male and female Wistar rats and grown under standard conditions for 10 days. Total RNA was extracted, and RT-PCR performed. There were no differences between the sexes in expression of IGF1 or IGF2 in cerebellum or hypothalamus. In frontal cortex, IGF1 expression was higher in females ($p<0.05$) compared to males. In contrast, in hypothalamic astrocyte cultures IGF1 expression was higher in males ($p<0.01$) and IGF2 mRNA levels higher in females ($p<0.05$). None of the remaining IGF family members analyzed (pregnancy-associated plasma protein-A, IGF-binding proteins 2, 3, 4 and 5 and stanniocalcin-2) were different between the sexes at this age.

In conclusion, although overall IGF1 and IGF2 expression was not sexually dimorphic in the hypothalamus at post-natal day 2, the expression of these growth factors by hypothalamic astrocytes differed between neonatal males and females. Thus, these glial cells could participate in the development of sexually dimorphic neuroendocrine systems. It remains to be determined if this sex difference in IGF expression by astrocytes is age and anatomically specific.

Fetal, Neonatal Endocrinology and Metabolism P2

P2-P181

Clinical Characteristics of Congenital Hyperinsulinism Caused by Dominant *KCNJ11/ABCC8* Mutations

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Congenital hyperinsulinism (HI) is the most common cause of hypoglycemia in children and infants. It is characterized by a dysregulation of insulin secretion from pancreatic β-cells and mostly associated with recessive inactivating mutations in the β-cell ATP-sensitive potassium (K_{ATP}) channel genes - *KCNJ11* and *ABCC8*. Dominantly inherited mutations in these genes are usually associated with mild forms of diazoxide responsive HI. Recently monoallelic K_{ATP} genes mutations were reported to be a rare cause of severe diazoxide unresponsive diffuse forms of HI.

We report clinical and genetic characteristics of the group of patients with diazoxide unresponsive diffuse form of HI caused by a single heterozygous mutation in K_{ATP} genes.

A total of 187 patients with CHI were identified in Russia since 2009. 78 of them (41,7%) were found to have monoallelic or biallelic mutations in *ABCC8/KCNJ11* genes in 60 and 18 cases respectively. Most of these patients (49/78, 62,8%) were diazoxide unresponsive and 41 of 78 (52,5%) underwent pancreatic surgery. Focal form of the disease was diagnosed in 28 children (35,9%), all of them were found to carry heterozygous paternal mutation.

9 children (4 females) with diazoxide unresponsive diffuse HI from 6 different families were found to have a single *KCNJ11* (c.G868A:p.V290M and c.C761T:p.P254L (n=2); c.G617A:p.R206H (n=1)) or *ABCC8* (c.G2143A:p.V715M (n=1); c.G2470A:p.E824K (n=2); c.C4154G:p.S1385C; (n=1) c.4153_4155del:p.1385_1385del (n=2)) mutation. In 3 families mutation was on maternal site, in 1 case - on paternal site and 2 children had denovo mutations. All but one *KCNJ11* gene mutation (R206H) were previously described.

Diffuse form of the disease was confirmed either by 18F-DOPA PET/CT or by histology. All of the patients had a neonatal onset of hypoglycemia, 7 of 9 were born LGA. 2 patients underwent pancreatic surgery, others were controlled with Octreotide injections and/or frequent feeds.

Biochemical and clinical investigations of parents were possible in 3 families and included fasting test, standard OGTT and Hb1AC measurements. No one had hypoglycemia. In 2 families mothers who carried mutations were found to have either glucose intolerance or gestational diabetes. All the mutation carriers, including probands and those who were asymptomatic, were born LGA.

In our cohort dominant K_{ATP} genes mutations account for 18,3% of the children with diffuse diazoxide unresponsive CHI. The variability of clinical presentation in mutation carriers among the family is unclear. Additional studies of possible modifying genes are needed for better understating the behavior of dominantly acting mutations.

P2-P182

Clinical Characterstics, Genotype-phenotype Correlations and Follow Up of Patients with Congenital Hyperinsulinaemic Hypoglycaemia; Single Center Experience from a Southeastern City of Turkey

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Objective: Congenital Hyperinsulinism (CHI) is a clinically, genetically and histologically heterogenous diesease. In recent years substantial developements have been observed in the genetics, imaging techniques and treatment options. We herein present the clinical characteristics, genetics and follow-up of 31 CHI patients from a single paediatric endocrine center with a particular emphasis on the new treatment options.

Patients and method: Clinical characteristics, presenting complaints, biochemical features and molecular genetic analysis as well as treatment strategies for patients with CHI were collected from the patients' hospital files.

Results: The number of patients recruited was 31(18 females). A mutation was detected in 16 out of 23 (69.5%) patients who underwent genetic testing. Of these 15 had mutation(s) in *ABCC8* and one in *HADH*. All patients with an *ABCC8* mutation were diazoxide unresponsive. Five underwent surgery and two patients were managed with sirolimus until the age of 3 and 10 months when sirolimus was stopped due to hepatotoxicity. A post-sirolimus trial of octreotide treatment achieved normoglycaemia, neither patient required pancreatectomy.

The 8 remaining patients with *ABCC8* mutations are also being successfully managed with the long-acting somatostatin analogs, octreotide LAR/lanreotide with no severe side effects. A female with a homozygous *ABCC8* mutation developed diabetes at the 4th year of octreotide/LAR treatment, when she was 15 years-old (HbA1c:8%). Hyperglycaemia is now being succesfully managed with dietary intervention. One patient with *HADH* mutation has protein sensitive, diazoxide responsive CHI. She is currently 8 years-old and has a good neurodevelopemental outcome.

Conclusion: In this series of 31 CHI patients from a single center we detected a mutation in a high proportion of patients who underwent molecular genetics analysis. New therapeutic tools landreotide and sirolimus further improved the prognosis of our patients.

P2-P183

Congenital Hyperinsulinism: Management & Outcome in West of Scotland

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Introduction: Hyperinsulinemic hypoglycaemia (HH) is the most frequent cause of persistent hypoglycaemia in neonates and infants. The most severe forms of HH are inherited and referred to as Congenital Hyperinsulinism (CHI). Hypoglycaemia is the main feature of CHI, and early diagnosis and immediate management are essential to reduce the high risk of neurological damage. Diazoxide is the mainstay of medical treatment, with surgery being an option in appropriate cases.

Objective: To describe management and outcome of patients with hyperinsulinemic hypoglycaemia within our service.

Methods: Children diagnosed with HH were identified between 2009 and 2017. Clinical course, genetic data, interventions and follow-up data were documented.

Results: A total of 39 children (25males) were identified, with increasing frequency of referrals during the study period (24/39 – during 2015-2017). Seven patients with secondary and syndromic HH were excluded. 26/32(81.2%) presented within the first 72 hours of life, 27/32 (84.3%) were born at term. Median birth weight was 3201gm (range 1916-4610gm). Most were born with an appropriate weight for gestational age(62.5%), only (15.6%) were large for gestational age. Maximum glucose requirement ranged between 6.7-18.8 mg/kg/min (median 13.1). Median insulin level in critical samples was 11.9 mIU/L (range 1.3-110). Diazoxide was started in all patients. Most patients responded, however 7 did not and required octreotide/continuous feeding, with 6/7 requiring surgery. Adverse effects to diazoxide therapy requiring discontinuation were observed in 4 patients, mainly pulmonary hypertension. Genetic mutations were detected in 12/32(37.5%), (9 K-ATP channel mutations, 3 GLUD 1 mutations). Hyperinsulinism resolved in conservatively treated patients within 12 months in 11/32(34.3%) compared to 14/32 (43.7%) requiring more than 12 months of medication with 11/14 having no identifiable mutation. A total of 7 (21.8%) patients underwent pancreatectomy (3-subtotal/near-total, 4-focal). Patients with subtotal/near total pancreatectomy still required diazoxide/octreotide post-surgery, with 2/3 developing diabetes.

Conclusion: Although macrosomia and SGA are risk factors, most babies in our cohort were of normal birth weight. Initial glucose requirement and insulin level at diagnosis do not influence disease outcome. Genetic mutation does not exclude medical remission; long-term conservative treatment of CHI is feasible as surgery doesn't guarantee complete remission but carries risk of pancreatic dysfunction. The need for ongoing treatment in absence of gene mutations suggests that there may be other novel genetic mechanisms involved in regulating insulin secretion. Early management of hypoglycaemia remains critical to prevent long term neurological deficits.

P2-P184

20 Cases of Congenital Hyperinsulinism in Ukraine

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Background: Congenital hyperinsulinism (CHI) is a rare heterogeneous disease. Genetic testing is crucial as identifying the underlying aetiology can guide clinical management.

Objective and hypotheses: We investigated the clinical characteristics and genetics of 20 Ukrainian patients with CHI.

Methods: Routine clinical and laboratory investigations were performed on 20 patients with hypoglycemia and unsuppressed C-peptide and p-insulin, diagnostic for CHI. Patients were sub grouped according to whether the hypoglycemia was persistent (n=12) or transient (n=8). *KCNJ11* and *ABCC8* were sequenced in all patients. Targeted next generation of all the known CHI genes was undertaken in 2 patients with persistent CHI. In one case features of Beckwith-Wiedemann Syndrome prompted methylation and dosage analysis of chromosome 11p15.5. ^{18}F-DOPA PET-CT was performed on 9 cases (75%) with persistent CHI.

Results: Those with persistent CHI were diagnosed earlier compared to those was transient disease (22.5 days [1,8; 54] vs 89.5 days [1.75; 284] p=0.01) and had a higher birth weight (3845g [3625; 4373] vs 3475g [3205; 3937] p=0.001). There was no difference in gender, blood glucose levels, p-insulin or C-peptide at presentation between the groups.

A genetic diagnosis was possible for 12/20 (60%) patients (*ABCC8* n=10, *KCNJ11* n=1, pUPD 11p15.5 n=1). The pick-up rate was higher for those with persistent versus transient CHI (10/12 (83.3%) vs 2/8 (25%) p=0.004).

Of the 9 patients who underwent ^{18}F-DOPA PET-CT scan 5 cases with a paternally inherited KATP channel mutation had a focal lesion, whilst diffuse disease was observed in 2 cases with a compound heterozygous *ABCC8* mutation and one case with a dominant *ABCC8* mutation. Two patients without a mutation had atypical histology.

Eleven patients with persistent CHI (91.6%) were treated with short-acting octreotide and/or diazoxide versus 5 patients with transient CHI (62.5%), p>0.05. Nine (75%) patients with persistent CHI underwent surgery due to poor response to medical therapy. Postoperative complications included transient fasting hyperglycemia (n=1), subclinical exocrine insufficiency (n=1) and a cicatricial hernia (n=1). Hypoglycaemia persisted following surgery in 2 patients (with atypical and diffuse disease). Both are currently treated with long acting release octreotide.

Conclusion: Despite persistent CHI being associated with an earlier age at diagnosis and higher birth weight the overlap in the range of these features between those with persistent and transient CHI means that it is not possible to use clinical characteristics to predict disease duration. Genetic testing should therefore be performed in all individuals with CHI to ensure optimal treatment.

P2-P185

Nifedipine Therapy in Hyperinsulinaemic Hypoglycaemia Due to Mutations in the *PMM2* Gene Improves Fast Tolerance, Stabilises Blood Glucose Profile, and Enables Rationalisation of Treatments for Glycaemic Control and Hypertension: the First Reported Trial in 3 Patients in a Tertiary Centre

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Background: Hyperinsulinaemic hypoglycaemia (HH) is the most frequent cause of severe and persistent hypoglycaemia in infancy. Prompt recognition and successful management are critical to ensure prevention of hypoglycaemic brain injury and neurological sequelae. The incidence of HH varies from 1:50,000-1:2,500, and mutations in at least 12 different genes involved in β-cell insulin release have been described. Recently, the spectrum of genetic causes for HH has been extended, with the reported co-existence of HH and congenital polycystic kidney disease (PCKD) in 17 children, caused by a promoter mutation in the phosphomannomutase 2 gene (*PMM2*). Previous reports have documented the effectiveness of L-type calcium channel blockers, such as nifedipine, for treating different forms of HH. In some cases nifedipine was introduced to avoid the side-effects of other medications such as diazoxide/octreotide, or with a concomitant antihypertensive purpose. Closure of adenosine triphosphate (ATP)-sensitive potassium channels (K_{ATP} channels) channels in the membrane of pancreatic β-cells initiates depolarisation of the cell membrane and opening of calcium channels. This results in an influx of calcium, and the rise in intracellular calcium triggers insulin release.

Objective: To report the first trial of nifedipine therapy in 3 patients with HH due to mutations in *PMM2*.

Methods: Nifedipine was initiated at a dose of 0.5mg/kg/day and increased to 1mg/kg/day after 48 hours, with close blood pressure monitoring. Glycaemic response was assessed by a blood glucose profile and fast test.

Results: Treatment with nifedipine enabled Patient 1 to come off overnight feeds and fast for 16 hours (6 hours prior to treatment), with no hypoglycaemic episodes on profile. Furthermore, his diazoxide dose was weaned by 20%. Patient 2 had an increase in fast tolerance from 13 to 16 hours with no hypoglycaemia on treatment. Patient 3 was able to fast for 18 hours with no hypoglycaemia on profile, and his dose of diazoxide was weaned by ~40% on Nifedipine.

Conclusions: This is the first report of glycaemic response to nifedipine therapy in 3 patients with HH due to mutations in *PMM2*. Nifedipine therapy has enabled these patients to achieve a stable blood glucose profile with increased fast tolerance, and to wean diazoxide. Furthermore, control of blood pressure improved to the extent that, in one case, nifedipine is now used as monotherapy. Nifedipine may therefore prove useful as first line therapy in patients with HH and PCKD due to mutations in *PMM2*.

P2-P186

Potentially Modifiable Predictors of Adverse Neonatal Outcomes in Women with Gestational Diabetes Mellitus (GDM)

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Introduction: GDM prevalence is increasing worldwide. The aim of the study was to identify potentially modifiable predictors of adverse neonatal outcomes in women with GDM.

Methods: This prospective observational study included 576 singleton multiethnic women diagnosed with GDM after 13 weeks of gestational age, followed in the Diabetes and Pregnancy Unit of the CHUV between 4/2012 and 2/2017.

Predictors included HbA1c at booking after GDM diagnosis and at the end of the pregnancy, treatment requirement (treatment vs no treatment), excessive gestational weight gain (GWG) according to the Institute of Medicine guidelines and BMI at booking after GDM diagnosis.

Neonatal and maternal outcomes included macrosomia (birth weight (BW)>4kg), LGA (BW-centile≥90), SGA (BW-centile≤10), hypoglycemia (glycemia<2.5mmol/l), prematurity (gestational age<37 weeks), hospitalisation in a neonatal care unit, respiratory distress requiring ICU admission, and need for cesarian section. Data were analysed using logistic regression analysis, adjusting for sex and gestational age at birth.

Results: Mean HbA1c was 5.5±0.4% at booking after GDM diagnosis, and 5.6±0.4% at the end of the pregnancy; 42% of women did not require treatment.

Mean BMI at booking after GDM diagnosis was 30±5.5kg/m^2 and gestational weight gain 12.6±7.2kg, with 41% of women having excessive GWG.

The mean gestational age at birth was 38.9±2 weeks and mean birth weight was 3242±587g. 7.6% had macrosomia, 17% were LGA, and 9.4% SGA. 11% had hypoglycemia, 8.2% were premature, 12% were transferred to a neonatal care unit, and 5% had respiratory distress requiring ICU admission. Cesarian delivery rate was 38%.

HbA1c at booking after GDM diagnosis and at the end of pregnancy predicted macrosomia and LGA. HbA1c at booking after GDM diagnosis was also correlated with cesarean section requirement, and at the end of pregnancy with prematurity.

Treatment requirement predicted macrosomia, LGA, hypoglycemia and cesarean section requirement. BMI at booking was correlated with macrosomia and LGA, and inversely correlated with SGA. Excessive GWG predicted macrosomia.

Conclusion: HbA1c at booking after GDM diagnosis and at the end of pregnancy constitutes a simple marker which can help clinicians in the management of women with GDM, but is currently not systematically used. Weight gain in pregnant women should be carefully monitored. Precise universal guidelines for maternal and neonatal follow-up and interventions (cesarean section, timing of delivery, neonatal glucose monitoring) depending on clinical predictors including treatment modality, excessive GWG, and HbA1c levels, are needed.

P2-P187

A Boy with Diazoxide Unresponsive Congenital Hyperinsulinism Due to a Homozygous ABCC8 Missense Mutation Previously Reported to Be Dominant

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Background: Congenital hyperinsulinism possesses considerable clinical heterogeneity attributed partly to its diverse genetic causes.

Objective: To present a boy with diazoxide unresponsive hyperinsulinaemic hypoglycaemia due to a homozygous recessive ABCC8 missense mutation, previously reported to be dominant acting and being inherited by his unaffected heterozygous parents.

Material and results: The boy was a third preterm child of a 27-year-old mother, born at 37 weeks of gestation with a weight of 3600 g (+1.49 SDS) and retarded cardiopulmonary adaptation. Hypoglycaemic episodes with generalized seizures had appeared in the first hours after birth and the baby had been commenced on i.v. glucose infusions. Although the high glucose infusion rate (GIR) (above 8 mg/kg/min), the blood glucose values had varied between 1.0-2.0 mmol/l and at the age of 14 days the patient was referred to our Endocrine center for further investigations and treatment. He had normal cardiopulmonary function, with no liver enlargement or hemihypertrophy and did not display any features of syndromic hyperinsulinism. A "critical sample" was obtained at blood glucose level of 1.3 mmol/l showing increased insulin (31.4 mIU/ml), undetectable ketone bodies, normal cortisol and growth hormone concentrations at the time of hypoglycaemia. All other laboratory and imaging tests were normal. We commenced treatment with i.v. glucose with GIR of 8.5 mg/kg/min, diazoxide and chlorothiazide. However, the patient did not respond to this therapy and i.v. glucagon was initiated in order to control the blood glucose above 3.5 mmol/l. At the age of 1 month the patient was successfully commenced on octreotide therapy (18.5 mcg/kg/day) given as 4 s.c. injections. A genetic testing with sequence analysis of ABCC8 and KCNJ11 genes was performed showing that the boy was homozygous for a ABCC8 missense mutation (p.Gly92Asp) inherited from his unaffected parents. They were heterozygous for the same mutation which has previously been reported as a dominant one.

Discussion: The result of our patient is consistent with the diagnosis of autosomal-recessive congenital hyperinsulinism due to a homozygous loss-of-function mutation in the SUR1 subunit of the ATP-sensitive potassium channel confirming the diazoxide unresponsive diffuse disease. Further genotype-phenotype association studies in congenital hyperinsulinism are needed due to the variability in its inheritance and clinical presentation.

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Diazoxide Unresponsive Congenital Hyperinsulinism Due to a Novel Abcc8 Missense Mutation

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Background: Congenital hyperinsulinism is a frequent cause of persistent hypoglycaemia in neonates. Mutations of the K_{ATP} channel subunit are the most common molecular defects. We report here a novel ABCC8 gene mutation causing a severe form of CHI in a newborn.

Case report: A 10-day-old boy born to consanguineous parents was referred for persistent hypoglycaemia. He was born by normal vaginal delivery at 38 weeks gestation, birth weight was 4.46 kg, birth length 54.5 cm with severe perinatal asphyxia. Hypoglycaemia started early needing high dose of glucose infusion (>15mg/kg/min) and investigations showed hyperinsulinimic hypoglycaemia with insulin levels of 22.9 µU/ml (2.7 - 10.30) and C peptide: 8.55 ng/ml (N: 1.10- 4.40). Heart ultrasound revealed hypertrophic cardiomyopathy. Diazoxide was started and increased to 20 mg/kg/day, he then became unresponsive and was started on octreotide at 20 mc/kg/day. Genetic testing revealed a novel ABCC8 missense mutation, p.Asp861Tyr that has never been reported previously but predicted to be pathogenic. Our patient is homozygote for this mutation and both his parents are heterozygote, confirming the diagnosis of autosomal recessive congenital hyperinsulinism. Now aged 5 years, the patient shows good glycaemic control on octreotide in combination with frequent feeding. However, he has developmental delay with epilepsy, requiring multiple anticonvulsivant drugs.

Conclusion: A novel ABCC 8 gene mutation was responsible for congenital hyperinsulinism in our patient. Birth asphyxia due to macrosomia caused by the disease has worsened the neurological outcome.

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Neonatal Hypoglycaemia: Unchanged Risk of Neurodevelopmental Impairment, But Sex-specific Decreased Fine Motor Function and Increased Internalizing Behaviour at School Age

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The neurodevelopmental consequences of neonatal hypoglycaemia are sparsely studied. We included neonates with blood glucose <1.7mmol/L, but no severe perinatal risk factors, in a follow-up with blinded Wechsler's Intelligence Scale for Children-IV (WISC-IV), Movement ABC-2 tests and child behaviour checklist (CBCL). Neurodevelopmental impairment was defined as psychomotor retardation, blindness, epilepsy, cerebral palsy, WISC-IV score <70, or Movement ABC-2 <15th percentile. Seventy-one children with neonatal hypoglycaemia aged median (range) 7.75(6.0-8.45) years were compared with 32 control siblings aged 9.17(3.75-16.0) years. Neurodevelopmental impairment was observed in 15% vs. 8.7% (p=0.25). In univariate analysis, the hypoglycaemia group had lower total motor and fine motor scores compared to controls, 48(40.5-72.4) vs. 61(49.1-72.4) percentile (trend p=0.07), and 43(34.8-50.3) vs. 57(45.6-68.7) percentile (p=0.03), respectively. Multivariable regression analysis showed a trend towards lower fine motor score after hypoglycaemia, β -11.3, p=0.10, driven by boys within the hypoglycaemia group, β -16.4, p=0.048, Furthermore, girls had a higher internalizing CBCL score in the hypoglycaemia group, p=0.02.

Conclusion: Neonatal hypoglycaemia was not associated with neurodevelopmental impairment at 7.75 years. However, boys had lower fine motor score and girls had higher internalizing score after hypoglycaemia, suggesting a novel identified, sex-specific, differential vulnerability in neonates with hypoglycaemia.

P2-P190

Atypical Hepatoblastoma and Wilm's Tumour in an Infant with Beckwith-Wiedemann Syndrome and Diazoxide Resistant Congenital Hyperinsulinism

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Introduction: Beckwith-Wiedemann Syndrome (BWS) is a rare genetic disorder that could be associated with embryonal tumours. Genotype based categorisation of patients enables better screening strategies. We present a patient with BWS who de-

veloped atypical congenital hepatoblastoma and atypical Wilms tumour in infancy.

Case Report: A 2 day old infant was referred with recurrent hypoglycaemia and high intravenous glucose requirement [>12mg/kg/min]. He was born at 36 weeks gestation by an elective LSCS, being large for gestational age. A hypoglycaemia screen confirmed congenital hyperinsulinism (CHI) [blood glucose 1.6mmol/L, plasma insulin 97pmol/L, c-peptide 523pmol/L, free fatty acids <176umol/L and B-hydroxybutyrate <23umol/L]. Following unresponsiveness to maximum dose of diazoxide [15mg/kg/day], he was commenced on subcutaneous octreotide with a good response [22mg/kg/day]. He was subsequently switched to once monthly Lanreotide injections. Genetic analysis for *ABCC8* and *KCNJ11* were negative. He was noted to have features of BWS [macroglossia, hepatomegaly and single earlobe crease]. Genetic analysis revealed hypomethylation at *KCNQ1OT1:TSS-DMR* and hypermethylation at the *H19/IGF2:IG-DMR* consistent with mosaic paternal isodisomy of the 11p15 region without copy number changes. Screening ultrasound on day 4 of life revealed bilateral renal enlargement and a focal mass in the left lobe of liver, the biopsy of which revealed hepatoblastoma showing exclusively epithelial component. He was resistant to chemotherapy. He underwent ultrasound guided resection as the tumour was not readily identifiable and the histology was more consistent with hepatocellular carcinoma. MRI abdomen at 3 months of age revealed a lesion in left kidney suggestive of Wilms Tumour that was confirmed on biopsy [Immunohistochemistry was positive for CD56 and WT1]. He was started on induction chemotherapy with Vincristine and Actinomycin D but showed no response. Post-nephrectomy histology at 5 months of age revealed mixed type, intermediate risk, stage 3 disease. In view of the poor response to initial chemotherapy, treatment was changed to Cyclophosphamide with Doxorubicin and Carboplatin with Etoposide. He is planned for post-operative radiotherapy.

Conclusion: We report, for the first time, a rare association of atypical hepatoblastoma and atypical Wilms tumour in an infant with BWS, who also had diazoxide resistant CHI. Patients with BWS, should be screened for embryonal tumours as early as possible. Early onset tumours may show more atypical features and be resistant to chemotherapy.

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Association between Rubenstein-Taybi Syndrome and Hyperinsulinaemic Hypoglycaemia

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Introduction: Rubenstein-Taybi Syndrome (RSTS)is a rare multiple congenital anomaly syndrome with a prevalence of 1:100,000 to 1:125,000. It is classically characterized by postnatal growth deficiency, microcephaly, learning difficulties, increased risk of tumour formation, broad thumbs and halluces and dysmorphic facial features including highly arched eyebrows, long eyelashes, downslanting palpebral fissures, broad nasal bridge, beaked nose, high arched palate and characteristic grimacing or abnormal smile. The majority of cases are caused by haploinsufficiency of the CREBBP gene. However, variants disrupting the paralogous gene, EP300, are found in up to 10% of patients. An expanding phenotype for RSTS is being recognised. Hyperinsulinaemic hypoglycaemia (HH) has been identified as a novel association, and there have been two case reports of HH in patients with RSTS in the literature so far. Here, we present two further patients with RSTS and HH.

Case reports: Patient 1 was born at 38-weeks gestation with a birth weight of 2.60Kg. She had mild dysmorphic features, bilateral choanal atresia requiring nasal stent insertion in the neonatal period, gastro-oesophageal reflux disease, unsafe swallow and developmental delay. A gastrostomy was inserted at 18 months. She had persistent episodes of hypoglycaemia and was diagnosed with HH at 1.54 years. Genetic testing was negative for mutations in known genes causing HH and imaging showed diffuse uptake of 18F-DOPA on PET scan. The HH was unresponsive to diazoxide, octreotide and nifedipine. She was subsequently started on sirolimus therapy and demonstrated a good response. She was eventually diagnosed with RSTS, due to a truncating mutation in the EP300 gene, at 2.38 years following genetic testing as part of the Deciphering Developmental Disorders (DDD) study.

Patient 2 was diagnosed with RSTS (heterozygous mutation c.1044delT in CREBBP) in the neonatal period with typical facial appearance, broad and angulated thumbs, broad halluces and undescended testes. He was found to have persistent post-prandial HH and was started on diazoxide at 38 days. Diazoxide was stopped and he had a Nissens fundoplication and gastrostomy insertion at 0.77 years. Following gastrostomy insertion he was started on continuous feeds. He was subsequently diagnosed with dumping syndrome at 4.38 years and was started on acarbose with feeds.

Conclusion: A number of conditions involving histone modification such as RSTS and Kabuki syndrome are associated with hyperinsulinism. Additional cases are needed to confirm the association between RSTS and HH, particularly in EP300 mutations which have a wider phenotypic spectrum.

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Hyperinsulinemic Hypoglycemia in Congenital Disorder of Glycosylation Type-1a (CDG-1a)

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Introduction: Congenital disorder of glycosylation type-1a is a multi-system disease involving neurological, gastrointestinal, ophthalmologic, cardiac or endocrine systems. In addition to hypothyroidism and hypergonadotropic hypogonadism, rare occurrences of hyperinsulinemic hypoglycemia in CDG patients have been reported. In the present report, we describe a patient diagnosed with CDG type-1a accompanied by hyperinsulinemic hypoglycemia, and whose responsive to diazoxide.

Case: The female patient was referred to our hospital at the age of 8 months with the complaint of failure to thrive. She was born at term as the first child of healthy non-consanguineous par-

ents. Her weight was 6 kg(<3p), height was 63 cm(3p). She had strabismus, axial hypotonia, a hepatomegaly of 3 cm below the margin, inverted nipples and an abnormal distribution of subcutaneous fat. Routine investigations revealed hypoalbuminaemia, hypertransaminasemia, minimally raised prothrombin time. The patient's serum glucose was 36 mg/dl, and the concurrently measured insulin:3.1 μIU/ml, c-peptide:1 ng/ml, cortisol:6.19 μg/dl, ACTH: 25.8 pg/ml, GH:8.01 ng/ml, lactic acid:14 mg/dl (N:4.5-19.8), ammonia:33 μg/dl(N:20-120), tandem mass spectrometry, plasma and urine amino acid profiles, urine organic acid analyses were normal. Low dose ACTH stimulation and thyroid function tests were normal. As the patient was hypoglycemic, IV glucose infusion was given at a rate of 8 mg/kg/min. Hyperinsulinism was considered, since the levels of insulin and c-peptide were elevated while the patient was hypoglycemic, and exaggerated glucose response was seen in the glucagon test, and the patient was started on diazoxide. The patient experienced no new episodes of hypoglycemia after treatment. Transferrin isoform electrophoresis, requested following a preliminary diagnosis of CDG, based on the appearance of bilateral inverted nipples and abnormal distribution of subcutaneous fat, was abnormal with type 1 pattern. A homozygous mutation was detected in a PMM2 gene analysis(c.385G>A). Cranial MRI showed cerebellar atrophy and diffuse volume loss in the brainstem, echocardiography demonstrated pericardial effusion and increased echogenicity in the myocardium, and the lipid profile showed hypertriglyceridemia and low HDL levels, which were consistent with the CDG.

Conclusion: Hyperinsulinemic hypoglycemia accompanying CDG type-1a has been reported in very few cases, and its etiology is still to be clarified. Based on a previously suggested hypothesis, an abnormal glycosylation of the KATP channels may result in hyperinsulinism, and so patients respond well to diazoxide, as an agent with proven activity in KATP channels.

P2-P193

A Rare Cause of Hyperinsulinemic Hypoglycemia: Costello Syndrome

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Introduction: Costello syndrome is a rare RASopathy that is associated with such characteristics as prenatal overgrowth, postnatal growth retardation, mental-motor retardation, coarse face appearance, loose skin on the neck, hands and feet, cardiovascular abnormalities, deep palmar and plantar lines and a predisposition to various types of cancer. Several endocrine disorders, including growth hormone deficiency, adrenal failure, glucose intolerance, hyperprolactinemia and hypoglycemia, have been defined in cases with Costello syndrome. In the present report, we describe a patient diagnosed with Costello syndrome accompanied by a clinical picture of hyperinsulinemic hypoglycemia and whose responsive to diazoxide.

Case: A 36-week-old female patient with a birth weight of 3,800 grams showed postnatal growth and developmental retardation, and a physical examination revealed a body weight of 6,120 grams, a height of 63 cm, coarse face appearance, and deep palmar and plantar lines. Echocardiography showed pulmonary valve stenosis. A whole exome sequencing was performed to rule out storage diseases and to confirm the diagnosis of Costello syndrome which was suspected based on clinical findings. The Costello syndrome was confirmed by the presence of a heterozygous missense mutation in *HRAS* gene. The cranial MRI showed a diffuse thin appearance in corpus callosum. The patient was examined by the endocrinology department at the age of 13 months because of hypoglycemia. The patient's serum glucose was 38 mg/dl, and the concurrently measured insulin:2.8 mcIU/ml, c-peptide:1.8 ng/ml, cortisol:26 mcg/dl, growth hormone(GH): 8.72 ng/ml, NH3:123 mcg/dl (N:20-120), lactic acid:13.69 mg/dl (N:4.5-19.8), pyruvate:1.62 mg/dl (N:0.3-0.9), tandem mass spectrometry, plasma and urine amino acid profiles, and urine organic acid analyses were normal. Hyperinsulinism was suspected, since the levels of insulin and c-peptide were elevated at the time of hypoglycemia, and an exaggerated glucose response was seen in a glucagon test. Thyroid function tests and prolactin levels were normal. IGF-1:4.66 ng/ml(<-3SD), IGFBP-3:1082.93ng/ml (<-3 SD), and peak GH at glucagon stimulation: 9.07 ng/ml. Blood glucose monitoring indicated episodes of fasting hypoglycemia and postprandial hyperglycemia. Diazoxide of 10 mg/kg/day was initiated for hyperinsulinemic hypoglycemia, which was resolved, with no new episodes of postprandial hyperglycemia occurring. Conclusion: Very few cases of Costello syndrome accompanied by hyperinsulinemic hypoglycemia have been reported, and the etiology of this condition is yet to be understood, although patients respond well to diazoxide.

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Molecular Defects Identified by Whole Exome Sequencing in a Chinese Boy with Fructose-1,6-Bisphosphatase Deficiency

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Background: Fructose-1,6-bisphosphatase (FBPase) deficiency is a rare autosomal recessive inherited disorder of gluconeogenesis, which caused by the mutations in the *FBP1* gene. FBPase deficiency is characterized by recurrent episodes of hypoglycemia with metabolic and lactic acidosis. If diagnosed early, the prognosis of this disorder is excellent by the prevention of hypoglycemia and avoidance of intake of fructose and sucrose. However, the misdiagnosis of FBPase deficiency is not rare in clinical practice because of the limited experiences in Chinese patients. This misdiagnosis could be avoided by using next generation sequencing, which have

been shown an excellent performance for detecting mutations in suspected cases of inborn errors of metabolism in previous studies. Here, we report a Chinese boy with FBPase deficiency detected by whole exome sequencing (WES).

Methods: The clinical and laboratory data of this Chinese boy were collected retrospectively. WES was performed to identify his potential genetic etiology and the putative pathogenic variants were validated by Sanger sequencing.

Results: A 16-month-old boy was repeatedly admitted to hospitals with recurrent onset of lethargy every time after febrile infectious disease and recurrent vomiting during 6 months. His physical examination showed mild hepatomegaly, and he had normal physical and mental development. The laboratory findings revealed severe hypoglycemia, metabolic acidosis, hyperlactacidemia and abnormal liver function. After intravenous infusion of glucose, bicarbonate and antibiotics, there was a dramatic clinical improvement in a short time. WES identified compound heterozygous mutations in the *FBP1* gene of c.841G>A (inherited from his father) and c.778 G>A (inherited from his mother). Both the mutations were known pathogenically. After the diagnosis was established, the boy was prescribed dietary restrictions. In the last 6 months follow-up, he had no attack.

Conclusions: FBPase deficiency needs to be considered in individuals with recurrent hypoglycemia and metabolic acidosis. Our results illustrate that WES could become a powerful tool for molecular diagnosis of Mendelian disease with unknown etiology, which may contribute to better treatment, genetic counseling and prenatal diagnosis.

P2-P195

The Benefit of Universal Neonatal Screening for Hypoglycemia

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Introduction: Hypoglycemia is a common problem in neonatal period associated with adverse neurological outcome and brain injury if treatment was not provided. AAP and PES recommended screening for hypoglycemia only in newborns with risk factors but many others neonates may present episodes of asymptomatic hypoglycemia without any known risk factor.

Objectives: To assess the incidence of hypoglycemia in healthy full term neonates without any risk factors in our medical center and to correlate it with mother's BMI, the initiating time of feeding and the difference between breast feeding and formula. To prove the benefit of universal neonatal screening of hypoglycemia in saving many full term newborns without any risk factors.

Materials and methods: A hospital based, prospective longitudinal study involving 300 healthy full term asymptomatic neonates. Blood glucose level was measured at 60 and 90 minutes of life using reagent strips and Glucometer independent of feeding time.

Results: According to the definition of hypoglycemia by the AAP (glycemia< 40 mg/dL) and PES (glycemia<50 mg/dL), the overall incidence of hypoglycemia in asymptomatic healthy full term newborns was 12,1% and 30.9% at 60 min respectively, while it was 1.1% and 17% at 90min respectively. There was no significant statistical association between BMI of the mother and hypoglycemia in neonates. However, the frequency of hypoglycemic episode in babies born at 37 weeks of gestation was higher than those born at 38 weeks and above with a significant P value of 0.0001. Neonates who were breastfed presented much less hypoglycemia than formula fed neonates with statistically significant P value of 0.0001.There was a higher incidence rate of hypoglycemia when feeding was initiated above 1 hour after delivery.

Conclusion: Delayed initiation of feeding, gestational age below 38 weeks and bottle fed infants were significantly associated with hypoglycemia. It is preferable to do a universal glycemic screening for all newborns to prevent transient neonatal hypoglycemia, which could have some deleterious consequences on the central nervous system and to start breastfeeding within 1 hour after delivery.

Keywords: Hypoglycemia, neonates, breastfeeding.

P2-P196

Prematurity of 23 or Less Weeks' Gestation is a Risk for Transient Late-onset Hyperglycemia in Neonates

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Background: Appropriate management for hyperglycemia is essential in preterm infants, because hyperglycemia increase the risk for intracranial hemorrhage, sepsis, retinopathy of prematurity, impairing long outcome to mortality and morbidity. In general, transient neonatal hyperglycemia is frequently observed during glucose infusion therapy, and it may not require interventions other than reducing glucose infusion. On the other hand, extremely preterm infants (EPIs GA<28weeks) have been reported to occasionally develop transient hyperglycemia in the absence of glucose infusion. The glucose infusion independent hyperglycemia occurs after nutritional transition from parenteral to enteral feeding is completed. Such "transient late-onset hyperglycemia" should be clinically differentiated from general neonate hyperglycemia, because it tends to be prolonged and requires appropriate intervention, such as insulin therapy. Despite of its clinical significance, clinical details of the transient late-onset hyperglycemia are not elucidated.

Aim: Identifying risks for transient late-onset hyperglycemia in EPIs.

Subjects and Methods: We retrospectively analysed 25 EPIs who were born in a single medical institute from April 2015 to March 2018. The patients with severe complications, such as requiring cardiac or gastrointestinal surgery, or lethal cases were excluded. "Hyperglycemia" was defined as more than 180mg/dL (10 mmol/L) of blood glucose levels were documented in two or more sequential measurements.

Results: Among 25 subjects, 8 infants (32%) developed transient late-onset hyperglycemia. The prevalence of the late-onset hy-

perglycemia was significantly higher in the infants who were born 23 or less weeks of gestation (6/8 in =<23 weeks VS 2/17 in >=24 weeks, p=0.01), and the odds ratio was 24.0. The mean duration of hyperglycemia was 37.0 days (25th percentiles: 19.3days, 75th percentiles: 52.5 days). The median of postmenstrual age at disappearance of hyperglycemia was 30.1 weeks (25th percentiles: 29.5 weeks, 75th percentiles: 32.4 weeks). Early(≦5 days after birth) minimal enteral nutrition was performed for 7 out of 8 infants with late onset hyperglycemia, and 5 out of 8 infants received insulin therapy.

Discussion: Our data suggested that EPIs born at 23 or less weeks' gestational age is a risk for transient late-onset hyperglycemia. Further, the hyperglycemia was prolonged more than 30days that would seriously affect growth and development of the infants. Early minimal enteral nutrition for premature infants has been considered to be favorable for preventing hyperglycemia, but, according our data, for preventing transient late-onset hyperglycemia, the treatment was not efficient and different nutritional approach could be considered for EPIs born at 23 or less weeks.

P2-P197

An Unusual Cause of Neonatal Hyperglycemia – Case Report

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Introduction: Hyperglycemia is a common event in neonates, frequently associated with specific clinical conditions (sepsis, drugs or intravenous fluids) other than neonatal diabetes. Unusual endocrino-metabolic syndromes must be considered whenever initial studies are inconclusive.

Case report: Newborn term female was admitted at the NICU for intrauterine growth restriction with fluxometric changes and low birth weight (1710g). Gestational history included oligoamnios and maternal hypertension and autoimmune thyroiditis.

At day 11 tachycardia and hyperglycemia occurred, resolving with enteric pause and intravenous fluids with glucose 5mg/Kg/min; complete blood count and acid base status were normal and cultures were sterile. After returning to enteric feeding hyperglycemia recurred, and insulin therapy was maintained for 24 hours with normoglycemia; ketonemia and ketonuria were negative and glycated hemoglobin was 4.7%.

At day 28 tachycardia and hyperglycemia recurred, resolving with enteric pause and intravenous fluids; blood chemistry showed severe hypertriglyceridemia (1589mg/dL) and she initiated a very low lipid formula and supplementation with soy and corn oils. Genetic testing for congenital diabetes was negative; abdominal ultrasound and echocardiogram were normal. She was discharged at day 34, with a net weight increase of 20g/day.

In the next months, diet was managed targeting triglyceride levels, with continuous adjustments in the oils, low lipid formulas, LC-PUFAS and carbohydrates supplements. Glucose levels were normal, and apolipoproteins A, B and lipoprotein(a) were normal. Hyperinsulinemia (>100uU/ml) was noted.

At physical examination she progressively developed a lipodystrophic phenotype, with absent subcutaneous fat, muscle hypertrophy, hepatomegaly and phlebomegaly. At 8 months-old a breast button was noted, with no progression of sexual characters, normal growth velocity, and concordant skeletal and chronological age.

At this time, Bernardinelli-Seip congenital lipodystrophy (BSCL) criteria were met, and genetic testing confirmed a compound heterozygous in BSCL2 gene: c.604C>T (p.Arg202*) and c.399C>A (p.Tyr133*). Echocardiogram revealed non-obstructive hypertrophic cardiomegaly, and abdominal ultrasound confirmed severe hepatomegaly with hepatic steatosis. Hypoleptinemia was found, and she is waiting authorization to start metreleptin therapy.

Discussion: The authors present a case of BSCL as the primary cause of neonatal insulin resistance and hyperglycemia. BSCL is characterized by the absence of functional adipocytes with storage of lipids in muscle and liver. Besides early insulin resistance, other endocrine manifestations that should be regularly surveilled include diabetes mellitus of difficult control, hirsutism, and precocious puberty.

P2-P198

Neonatal Hypocalcemia due to Maternal Hypovitaminosis D: A Cohort of Children in a Region of Northern Spain

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Background: Neonatal hypocalcemia is defined when the total calcium levels are under 8mg/dl (Ionic Ca < 1.1 mmol/L) in the full-term newborn, and under 7 mg/dl (Ionic Ca < 1 mmol/L) in the preterm. The fetus entirely depends on the maternal contributions of 25-OH-vitamin D, whose levels are directly correlated with diet and solar exposure. The largest transfer in calcium and vitamin D occurs in the third trimester of gestation, so prematurity is an important risk factor.

Objective: To evaluate the clinical characteristics of 11 neonates diagnosed with hypocalcemia due to maternal hypovitaminosis D in the last 3 years.

Method: Retrospective study of medical records. Statistical analysis with SPSS v.24.

Results: 11 patients: 5 females, 6 males. Gestational age: 7 full-term and 4 preterm neonates. Discrete winter predominance (4 cases). All appropriate for gestational age (AGE). Only two mothers received vitamin D supplements during pregnancy (200 UI per day). Feeding: 7 formula feeding, 4 cases breastfeeding plus formula. Average age at diagnosis 3.8 days. Clinical presentation: 3 distal fine tremor; 8 asymptomatic, diagnosed in blood test for another reason. All cases: total calcium at lower limit of normality, mean 7.2 ±0.5mg/dl (average ionic Ca 0.99 ±0.05 mmol/L). 25-OH-vitamin D median 10 ng/ml (range 7-26 ng/ml), a case of insufficiency (20-30 ng/ml) and 10 deficiencies (<20ng/ml). PTHi median 52.4 pg/ml (range 6-165pg/ml) (normal value 10-45pg/ml). Maternal

study: 25-OH-vitamin D mean 11, 1 ±4.5mg/dl, deficiency in all cases. Treatment: 4 intravenous calcium (mean 6 days) and 3 oral calcium. Vitamin D supplements, doses of 800 IU/day in 10 cases and 400UI/day in the patient with insufficiency. Ten patients in follow-up by pediatric endocrinology, 6 with normal values of 25-OH-vitamin D at 2 months, 4 patients at 5 months.

Discussion: Although current recommendations in our country only include maternal supplementation with iodine and folic acid during normal pregnancy, it may be necessary to modify them in the contribution of vitamin D, especially in regions of northern Spain where there is scarce solar exposure. It is important to consider that the effects of the vitamin D deficiency are extended far beyond the phospho-calcium metabolism. Longer studies are required. Many cases of neonatal hypocalcemia and hypovitaminosis course asymptomatically, so it could be an underdiagnosed entity.

P2-P199

Evaluation of Vitamin D Status and Its Correlation with Gonadal Function in Children at Mini-Puberty

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Objective: Most recent evidence from conducted in human and animal studies suggests that vitamin D has a potential role in the physiology of reproductive function in both genders. We investigate the role of vitamin D in male and female gonadal function at mini-puberty period with particular emphasis on production of sex steroids and gonadal peptide hormones. Additionaly, this study evaluated serum levels of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol (E2), total testosteron (TT), anti-müllerian hormone (AMH), and inhibin B in a large prospective cohort of infant at mini-puberty period.

Subjects and Methods: We analyzed data from a prospective cohort of a 180 (94 boys and 86 girls) unselected, healthy infants aged 30 to 45 days. Nonfasting peripheral venous blood samples were taken between 08.00 and 10.00 a.m. Serum LH, FSH, E2, TT, AMH, inhibin B and 25-OH Vitamin D levels were measured.

Results: All the boys and girls were divided into three groups including vitamin D deficiency (<10 ng/ml), vitamin D insufficiency (10-20 ng/ml), and vitamin D sufficiency (>20 ng/ml). Among the groups no statistically significant difference was found between the age, birth weight, current weight and height (p>0.05). Their average age was 39,75 ± 3,79 days. The findings from all subjects that, out of 180 infants, 29 (16.1%) had vitamin D deficiency, 59 (32.7%) had vitamin D insufficiency, 92 (51.1%) had a sufficient level. In boys, no significant correlation was found between Vitamin D levels and gonadal hormones in three groups. In girls, no significant correlation was found between Vitamin D level and LH, FSH, E2, and AMH in three groups. But there was a statisticaly significant difference between the testosterone levels of the three groups (p =0.007). >20 ng/ml vitamin D group showed a significantly low total testosteron levels compared to <10 ng/ml and 10-20 ng/ml vitamin D groups (p =0.003, p=0,025). Moreover, there was a statisticaly significant difference between inhibin B levels of the three groups (p=0,021). <10 ng/ml vitamin D group showed a significantly low inhibin B levels compared to 10-20 ng/ml and >20 ng/ml vitamin D groups (p=0,012, p=0,02).

Conclusion: More studies are needed to confirm a direct cause-and-effect relationship between vitamin D and gonadal function and to evaluate the potential therapeutic benefits of vitamin D supplementation on reproductive outcomes.

P2-P200

Systemic Pseudohypoaldosteronism Type 1 due to 3 Novel Mutations in *SCNN1A* and *SCNN1B* Genes; Report of 3 Cases

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Objective: The systemic form pseudohypoaldosteronism type 1 (PHA1) is an autosomal recessive disorder characterized with defective sodium transport in many organ systems including kidney, lungs, colon, sweat glands and salivary glands. Homozygous or compound heterozygous loss-of-function mutations in the genes encoding amiloride sensitive epithelial sodium channel (ENaC) account for genetic causes of systemic PHA1.

Case 1: Male patient presented with vomiting, poor feeding, discomfort and skin rash. He had normal male external genitalia, no hyperpigmentation and normal blood pressure. In laboratory investigations severe hyponatremia (NA:106 Eq/l), hyperkalemia (K:11.8mEq/l), metabolic acidosis (pH:7.16, HCO3:9mEq/l), elevated plasma renin (98.2ng/ml; N:.4-37), elevated aldosterone (3173pg/ml; N:86-1340) and positive sweat test (147mEq/l) suggested the diagnosis of systemic PHA1. In the molecular genetics analysis a novel compound heterozygous [c.87 C >A(p.Tyr29*)/IVS9+1G >A (c.1346+1G >A)] mutation was detected in *SCNN1B* gene.

Case 2: A female admitted with vomiting, poor feeding, and weight loos. She was appeared unwell, agitated and restless. She had a normal female external genitalia with no hyperpigmentation. In laboratory investigations severe hyponatremia (Na: 117 mEq/l), hyperkalemia (K:9.8 mEq/l), metabolic acidosis (pH:7.24, HCO3:12.1 mEq/l), elevated plasma renin (96.9 ng/ml; N:.4-37), elevated aldosterone(3032 pg/ml; N:86-1340) and positive sweat test (112mEq/l) suggested the diagnosis of systemic PHA1. In the molecular genetics analysis a homozygous [p.T663A(c.1987A>G] mutation was detected in *SCNN1A* gene.

Case 3: A female neonates admitted to our clinic with the complaints of weakness and poor feeding. At presentation she was unwell, had 3/6 systolic murmur, decreased skin turgor-tonus and dyspnea. She had normal female external genitalia with no skin pigmentation. In laboratory investigations severe hyponatremia (Na:109mEq/l), hyperkalemia (K:10.9mEq/l), metabolic acido-

sis (pH:7.11, HCO3: 8.2mEq/l), elevated plasma renin(104.2ng/ml; N:.4-37), elevated aldosterone(5882pg/ml; N:86-1340) and positive sweat test (134mEq/l) suggested the diagnosis systemic PHA1. In the molecular genetics analysis a homozygous p.A200Gfs*6(c.598dupG) mutation was detected in *SCNN1A* gene.

Conclusion: In patients presenting with hyponatremia, hyperkalemia and metabolic acidosis, particularly with absence of disorders of sexual differentiation and hyperpigmentation systemic form PHA1 should be considered in the differential diagnosis. Present cases with 3 novel mutations would add novel insights into our understanding the pheotype-genotype relationship of systemic PHA1 and expand the mutation database.

P2-P201

Postnatal Growth of Infants with Neonatal Diabetes: Insulin Pump (CSII) versus Multiple Daily Injection (MDI) Therapy

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Background: Permanent neonatal diabetes mellitus (PNDM) is a persistent hyperglycaemia diagnosed within the first 6 months of life. A correct genetic diagnosis can affect treatment and clinical outcome. Clinical manifestations at the time of diagnosis include intrauterine growth retardation, hyperglycemia, glycosuria, osmotic polyuria, severe dehydration and failure to thrive. Insulin production is inadequate, requiring exogenous insulin therapy. The treatment corrects the hyperglycemia and results in improvement of growth. However, there are no studies reporting the longitudinal growth of these infants (head circumference, length and weight gain) after starting insulin therapy.

Aim of the study: was to measure linear growth parameters in infants with PNDM on insulin therapy during their infancy period.

Patients and methods: Growth parameters: weight (Wt), Length (L) and head circumference (HC) were assessed in 9 infants with PNDM during the first 2 years of their postnatal life. Five infants were on insulin pump therapy (CSII) and 4 infants were on multiple daily injections (MDI) therapy.

Results: After 20 ± 4 months of insulin therapy a growth catch-up occurred in the majority of them. L standard deviation score (SDS) increased from -1.45 to -0.65, HCSDS increased from -2.3 to -0.51 and WtSDS increased from -1.94 to -0.7, after starting insulin therapy, at the end of the 20 ± 4 months of age. Two out of 9 infants had a LSDS < -2, in 4 WtSDS was < -2 and 1 the HCSDS was <-2 at ± 4 months of postnatal growth. Growth parameters in infants on CSII therapy were better than those on MDI therapy. The mean level of HbA1C was non-significantly lower in the CSII group versus the MDI group (9.6 ± 1 % vs 10.3 ± 2 %; p: ns).

Conclusions: The majority of infants with PNDM exhibit significant good catch up growth within the first two years of life irrespective of the etiology of their neonatal diabetes. Further studies are needed to confirm our preliminary observations and to explain the persistent slow growth parameters in some of them in spite of insulin treatment.

P2-P202

Serum Vaspin Concentration in Full-term, Appropriate-for-Gestational-Age Newborns: Effect of Early-Onset Infections

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Objective: Vaspin plays an important role in the foetal and postnatal development of children. The effect of early-onset infection in neonates on vaspin levels is not well known.

The aim of the study: 1) evaluation of serum vaspin concentrations in full-term appropriate-for-gestational-age (AGA) newborns, according to their gender, birth asphyxia, type of delivery, occurrence of early-onset infections; 2) analysis of correlations between serum vaspin concentrations and neonatal anthropometric parameters.

Material and methods: The study involved 183 full-term AGA newborns aged from 3rd and 6th day of life (75 girls, 108 boys; 119 delivered vaginally and 64 by cesarean section), among them 102 with severe infection (24 septic, 78 local infection, predominantly with congenital pneumonia) and 81 healthy controls. Serum vaspin concentrations (SVC) were measured by the ELISA method (Bio Vendor Research and Diagnostic Products, Czech Republic).

Results: Infected newborns had significantly increased SVC than healthy ones. In septic newborns SVC were significantly higher than in local infected ones. No significant differences between infected male and female newborns either between children born by cesarean section and vaginally were noted. The healthy females had statistically higher SVC than the healthy male newborns. Significant negative linear correlation between SVC and the gestational age of infected babies was noted. No correlations between SVC and body length, head or chest circumferences in healthy and infected newborns either between Apgar score in 1st minute of life and SVC in infected children were found.

Conclusion: Early-onset infections, especially sepsis, increase SVC in full-term AGA newborns independently of their sex, birth asphyxia and type of delivery.

P2-P203

First Three Years of the Congenital Adrenal Hyperplasia Neonatal Screening Program of the State of Parana, Southern Brazil

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Introduction: The diagnosis of Congenital Adrenal Hyperplasia (CAH) is a challenge due to the complexity of its pathophysiology and the variety of clinical manifestations. Female newborns

(NB) with classical forms present virilization of the external genitalia while in boys it is usually normal. Salt-losers boys and girls are highly susceptible to develop acute adrenal insufficiency and death in the first weeks of life; for these reasons, Neonatal Screening (NS) programs have included CAH among the diseases surveyed. In the State of Parana, Brazil, NS for CAH started in 2013.

Objectives: to determine the prevalence of CAH in Parana; to characterize interfering factors related to false positive results for CAH; and to determine sensitivity, specificity, accuracy, positive and negative predictive values and false positive rate of the 17-OHP dosing method.

Patients and Methods: Clinical and laboratorial evaluation of NB tested positive for CAH in the period of August/2013-July/2016; 17-OHP in blood spot was measured by immunofluorymetric assay and in serum by either RIA or ELISA. NB were followed at the Pediatric Endocrinology Unit of the Department of Pediatrics of the Federal University of Paraná School Hospital.

Results and Conclusions: Of 474,890 NB in the period, 475 tested positive for CAH; of those, 403 were evaluated and 392 were included in the study; of these 369 (94.1%) were false positive, while 23 (5.9%) had confirmed CAH. Among the 23, twenty-one are salt-losers, the other two with simple virilizing and non-classical forms, respectively. Prevalence of the classical form of CAH in the period is 1:21,596 live births, with higher prevalence in the west and southwest regions of the state. The female to male ratio was 1.4:1.0. Prematurity and neonatal stress were related to false positive screening. Sensitivity of the 17-OHP method for filter paper was 100%; specificity and accuracy were 99.9%; the positive predictive value was 5.1%; the negative predictive value was 100%; the recall rate was 0.99% and the false positive rate 0.08%. There are challenges in the program: to standardize the method to measure serum 17OHP, to minimize errors in the collection of the blood spot and to provide adequate treatment to all children with CAH.

P2-P204

Assessment of the Stretched Penile Length in Sri Lankan Newborns

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Background: Evaluation of the external genitalia is very important in the routine neonatal examination, since abnormalities of the genitalia give clues to underlying endocrine disorders or serious structural malformations. This is the first report regarding the stretched penile length (SPL) of newborns from Sri Lanka.

Objective and hypotheses: The objectives of the study were to document the SPL of healthy term neonates born following an uncomplicated delivery at a tertiary care hospital in Sri Lanka, and to establish the normative data for the SPL for Sri Lankan neonates.

Method: This was a cross sectional observational study, carried out at post natal wards of the Castle Street Hospital for Women, Sri Lanka. The study was done on 369 stable newborns delivered at the gestational age of 37 to 42 weeks.

A complete neonatal examination was performed by the principal investigator and the measurements of the weight, lenght, haed circumference and streached penile length were obtained.

Mean penile length and statistically significant difference of penile length (SD) values were calculated. The correlation of mean penile length, period of gestation, birth weight and length were analyzed.

Results: The SPL positively correlated with the length of the baby. There is no statistically significant correlation of birth weight, head circumference and gestational age with the SPL. The mean SPL for term Sri Lankan newborns was 3.03cm ± 0.37cm and the -2SD value was 2.29cm.

Recommendations: Since the -2SD of SPL was 2.29cm, measurements less than this should be considered as micropenis.

Key words: stretched penile length (SPL), Neonates, Sri Lankan newborns

P2-P205

Auxological Catch Up Growth and Evaluation of Spontaneous Motility in the Term Newborn Small for Gestational Age Employing the Prechtl Assessment of General Movements

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Introduction: Term newborns Small for Gestational Age (SGA) have an increased risk for minor neurological impairment at pre- and school age. The general movements (GMs) assessment, in particular at Fidgety (F+) age, has been increasingly used to predict neurological dysfunctions. Aim of our study was to evaluate, in a population of term newborn SGA (gestational age >37 weeks) the growth recovery, the presence of F+ at 3 months of age, and the neurological outcome at 2 years, compared to term AGA newborns.

Methods: Prospective evaluation of SGA newborns (birth weight and/or length < 3° percentile according to national growth charts) and AGA controls. At 3 months we evaluate: the auxological parameters (AP) (weight, length, head circumference) and the assessment of spontaneous motility according to the Prechtl's evaluation of GMs method, the neurological examination (NE) according to Amiel-Tyson. At 6-12-24 months we evaluate AP + NE + neurodevelopment assessment by the Griffiths mental development scales.

Results: We enrolled 38 SGA and 20 AGA controls. At three months, 13% of SGA presented at least one auxological parameter < 3° percentile, despite a significant catch up growth both for

weight and length (p<0,001; p<0,001, respectively). 100% of AGA newborns presented F+ at three months, while in SGA children 23.7% (4M, 5F) did not show F+ (p<0.001). No substantial differences were recorded in weight (p=0.53), length (p=0.32) and cranial circumference (p=0.24) at birth and at 3 months (respectively p=0.49, p=0.84, p=0.84) between SGA F+ and SGA F-. Cranial circumference at birth was noticed to be a positive predictive factor for F+ (p=0.039). At 2 years of age, a difference statistically significant between SGA and AGA was detected in each item of the Griffiths mental development scales.

Conclusion: Independently from the growth recovery, at three months of age, about 1/4 of SGA newborns do not show Fidgety movements. At 2 years of age the neurodevelopmental assessment reveal differences in each domain of evaluation between SGA and AGA children, although within the normal ranges. We may assume that intrauterine growth restriction and the reduction of cranial circumference could have a negative effect on neuropsychological development and that SGA children may need an attentive neurological follow-up.

Fetal, Neonatal Endocrinology and Metabolism P3

P3-P170

A Rare Case of Congeintal Hyperinsulinemina With ABCC8 Missense Mutation Presenting with Focal Pancreatic Lesion

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Introduction: Congenital Hyperinsulinemic hypolglycemia (CHI) is a rare genetic disorder resulting severe hypoglycaemia secondary to excessive insulin release from the pancreatic cells. Its early diagnosis is imperative to prevent irreversible brain damage by hypoglycemia. Genetic testing and 18-F-DOPA scan help to confirm the diagnosis.

Case: A 2.7kg male baby was born at term to non-consanguineous parents by normal vaginal delivery. On day 4 of life the child was excessively lethargic for which was taken to a hospital, where he was detected to have blood sugar of 40mg/dl.

On day 6 of life the baby had seizures and was taken to the emergency where he was diagnosed to have hypoglycemia without any ketonuria. The critical blood sample taken at a time of hypoglycemia revealed C-peptide 2.72ng/ml, blood sugar 22mg/dl, serum insulin 13.3uU/ml, with thyroid, cortisol and growth hormone being in normal range. He was started on oral diazoxide at 10mg/kg/day and escalated to 15mg/kg/day.. The child was started on injectable subcutaneous octreotide at a dose of 2ugm/kg and increased to 4ugm/kg. Oral diazoxide was slowly tapered and stopped.a genetic study was done which showed that the child was heterozygous for the ABCC8 mutation missense variant., p.(Gly 111Arg). The father heterozygous for ABCC8 variant and the mother did not have any genetic mutations.

Conclusion: We report the first heterozygous, paternally inherited ABCC8 missense mutation with focal pancreatic lesion from India. This mutation has been reported to present mostly with diffuse pancreatic lesions, requiring surgery.

P3-P171

Comparison of Metabolic Parameters of Children's Blood Depending on the Level of Mother's Glycemia During Pregnancy

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Introduction: The impact of gestational diabetes mellitus (GDM) on fetal development and the future health of the child need further studying. In accordance to the criteria by Hyperglycemia and Adverse Pregnancy Outcome Study, GDM can lead to a number of negative consequences, including the impact on disturbance of metabolic parameters.

Aim: To compare the impact of glycemia during pregnancy on the children's metabolic status.

Methods: GDM was confirmed by determining the level of glycemia during the oral glucose tolerance test in pregnant women. Women were treated with insulin or diet therapy. Depending on the achievement of the target glycemia, the women were divided in 2 groups. All women were not achieve the targer levels of fasting glucose (FG) less than 5,1 mmol/L or 1 hour postprandial less than 7,0 mmol/L. Target glycemia was considered FG less than 5.3 mmol / L and / or 7.8 mmol / L after 1 hour postprandial more than 70% of the measurements. Non-target - FG more than 5.3 mmol / l and / or 7.8 mmol / l after 1 hour postprandial more than 30% of the measurements. The study included 43 children at the age of 6 months, born to mothers with GDM. Group 1 (n = 28) included children, from pregnancies with target glycemia, Group 2 (n = 15) - non-target. The level of FG, insulin, cholesterol and triglycerides of children's plasma was studied. The statistical treatment was carried out by evaluating the significance of differences in mean values using Student's t-test.

Results: No differences were find out when comparing the FG level between groups (group 1 4.63 ± 0.56 mmol/L, group 2 4.78 ± 0.55 mmol/L, p = 0.42). The level of insulin (group 1 16.05 ± 14.07 mmol/L, group 2 1.07 ± 11.3 mmol/L, p = 0.79) also did not differ. A similar situation was observed in the evaluation of cholesterol (group 1 3.93 ± 0.66 mmol/L, group 2 3.53 ± 0.73 mmol/L, p = 0.41) and tryglecerides (group 1 1.1 ± 0.75 mmol/L, group 2 0, 95 ± 0.54 mmol/L, p = 0.31).

Conclusions: There was no evidence of the influence of mothers glycemia during pregnancy on changes in the level of FG, insulin, triglycerides, cholesterol in children of 6 months. Perhaps in the study of children from mothers with strict target glycemia criteria during pregnancy, other results will be obtained.

P3-P172

Forty Patients with Persistent, Non-focal Congenital Hyperinsulinism: Urgent Need for New Treatment Modalities

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Background: Congenital hyperinsulinism (CHI) is a rare, heterogeneous disease with a focal, diffuse, or atypical histological form and a high risk of cerebral injury due to severe hypoglycemia.

Methods: We retrospectively evaluated the treatment and outcome of a cohort of patients with non-focal, persistent CHI admitted to the International Hyperinsulinism Center, Denmark from January 2000 to May 2017. Data were extracted from hospital files.

Results: In our cohort of 68 patients with persistent CHI, 40 (59%) had non-focal CHI, diffuse; n=36, atypical; n=4. Twenty-two patients (55%) could not be managed with medical monotherapy (diazoxide or octreotide) and six (15%) patients developed severe potential side effects to medication, hypertrophic cardiomyopathy; n=4 (potentially due to hyperinsulinism itself),thrombocytopenia after diazoxide; n=2. Surgery was performed in 17 (43%) patients with resection of 66%-98% of the pancreas (median=90%). Surgically treated patients had more frequently K_{ATP}-channel mutations (surgical; 12/17 *vs*. conservative treatment; 6/23, p=0.013), highly severe disease (15/17 *vs*. 13/23, p = 0.025) and clinical onset <30 days of age (15/17 *vs*. 10/23, p = 0.004). Ten out of 17 (59%) had mild (n=9), or severe (septicemia and multiorgan failure, n=1), early post-surgical complications.

At last follow-up with a median (range) age of 5.3 (0.3-31.3) years, 32 (80%) patients still received medical treatment, including 12 (71%) after surgery. One patient had diabetes after a 98% pancreatic resection. Problematic treatment status (lack of hypoglycemia control, severe medical side effects, tube feeding, or diabetes) was seen in 17.5%. Only 20% (n=8, pancreatic surgery in five) had clinical remission. Neurodevelopmental impairment (n=12, 30%) was marginally associated with disease severity (p=0.059).

Conclusion: Persistent, non-focal CHI remains difficult to manage. Neurological impairment in 30% suggests a frequent failure of prompt and adequate treatment. A high rate of problematic treatment status at follow-up demonstrates an urgent need for new medical treatment modalities.

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P3-P173

Outcome of Eight Patients with Congenital Hyperinsulinism (CHI) Studied With 18[F] Dihydroxyphenyl-Alanine Positron Emission Tomography Imaging (^{18}F-DOPA-PET-CT) in Argentina

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Congenital hyperinsulinism (CHI) results from inappropriate insulin secretion most commonly caused by mutations in the *ABCC8* and *KCNJ11* genes which encode for the pancreatic β-cells-ATP-sensitive-potassium channel (KATP) subunits SUR1 and KIR6.2 respectively. Diagnosis of CHI is based on the presence of detectable plasma insulin during hypoglycemia, suppressed β-hydroxybutyrate and NEFA. Diazoxide is the major treatment for CHI, sirolimus had also been used. Focal/diffuse disease are differentiated by ^{18}F-DOPA-PET-CT scanning. In the former a lesionectomy can resolve hyperinsulinism. Monoallelic recessively-acting *ABBCC8/KCNJ11* mutations predict focal disease with 69-97% sensitivity. Within a focal lesion uniparental disomy unmasks the paternal mutation. Objective: To report a retrospective series of 8 patients with CHI, describing clinical outcome, laboratory, genetic an ^{18}F-DOPA-PET-CT findings.

Materials and methods: A clinical diagnosis was made in the presence of glucose<50mg/dl (2.8mmol/l), with detectable plasma insulin. Transient and syndromic forms were excluded. Age, laboratory results, response to treatment, side effects, *ABCC8/KCNJ11* sequencing and 18F-DOPA-PET-CT results were recorded. Response to diazoxide was considered positive if normoglycemia was maintained after 6 hours of fast (maximum dose of 15mg/kg/day).

Results: 8 patients presented with hypoglycemia (6-40mg/dl), within 6-48 hours of life (except one detected at 5 months). Maximum glucose infusion rate required was: 8-21mg/kg minutes. Laboratory during hypoglycemia: insulin: 5-60.6uUI/l, β-hydroxybuturate: 0.07-0.3O mmol/l(NV:0.03-0.35), NEFA:0.13-0.5mmol/l (NV:0.1-0.9), normal ammonia. Four patients responded to diazoxide, one presented with fluid retention. One patient treated with sirolimus presented persistent diarrhea, vomiting without improvement in glucose levels.

Six patients had ^{18}F-DOPA-PET-CT evaluation, 4 had diffuse and 2 had focal disease. *ABCC8* mutations were detected in 6 of 8 patients; 3 of the 4 diazoxide-responsive patients and 3 of the 4 diazoxide-unresponsive.

Two diazoxide-unresponsive patients had a monoallelic recessive ABCC8 mutation; one had focal disease whereas the other had diffuse disease. In the later LOH of pancreatic DNA to exclude a giant focal lesion was not performed.

In one patient with focal disease analysis of leukocyte DNA did not identify a mutation, although a somatic mutation within the pancreas was not excluded.

Hypoglycemia was not detected in patients with focal disease after the surgical remove of the lesion, whereas incidental hypoglycemia was found in patients under medical treatment. Conclusions: the small pancreatic resection guided by ^{18}F-DOPA-PET-CT in the focal disease allowed normal blood glucose homeostasis. Patients receiving medical treatment should maintain long-term surveillance to avoid hypoglycemia

P3-P174

Congenital Hyperinsulinism and Maple Syrup Urine Disease a Challenging Combination

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Background: Congenital hyperinsulinism (CHI) is the most common cause of persistent hypoglycemia in infancy, characterized by unregulated insulin secretion. CHI is a challenging disease to diagnose and manage. Moreover, complicating the course of the disease with another metabolic disease like Maple syrup urine disease (MSUD) adds more challenges to the already complex management.

Case: we report a term male neonate with uneventful birth history. He developed symptomatic hypoglycemia with a blood glucose (BG) level of 1.9 mmol/l at 21 hours of life. A critical sample at that time showed high serum insulin level of 167.7 pmol/L, C-peptide > > 1160 pmol/L and low ketones confirming the diagnosis of hyperinsulinism. Amino acid profile on dried blood spot by tandem mass spectrometry part of critical sample was done and showed high leucine and isoleucine levels indicating the diagnosis of MSUD. MSUD is then confirmed by HPLC which showed the presence of allo-isoleucine at 101 umol/L, and elevated levels of the three branched chain amino acids (leucine 724 (45.00-160.00), isoleucine 240 umol/L (28.00-95.00), and valine 390 umol/L(60.00-294.00).

The diagnosis of CHI and MSUD was afterward confirmed by molecular genetic testing. The finding of a known pathogenic homozygous mutation in the ABCC8 gene (c.3748C>T, p.Arg1250*) confirmed CHI diagnosis. The presence of a homozygous mutation in the BCKDHA (c.1087, p.Arg363Trp) confirmed the MSUD diagnosis.

The baby's case is very challenging managing two rare autosomal recessive disorders. Managing his hypoglycemia with high glucose rate through intravenous fluids, frequent feeds with special MSUD formula, and medications for hyperinsulinism (Diazoxide and octereotide). Unfortunately his hyperinsulinism did not respond to all medical measures and he needed to go to a near total pancreatectomy.

Through all his complicated course, he required very meticulous monitoring of his BG and amino acid profile (3 times/week on average) aiming to maintain the BG at 3.9 mmol and above and levels of the three branched chain amino acids at the disease therapeutic targets for a neonate.

Conclusion: This patient is perhaps the only known case of the occurrence of two rare life threatening disorders. Both hypoglycemia and Leucine encephalopathy can result in death or permanent neurological damage. This is complicated by the fact that both disorders have direct effect on the body metabolism of glucose and branched chain amino acids and there management in combination is very challenging.

[DANA1]Need the reference values.

P3-P175

Neonatal Diabetes Mellitus in Vietnam National Children Hospital

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Introduction: Neonatal diabetes mellitus (NDM) is a rare (1:300,000–400,000 newborns) but potentially devastating metabolic disorder characterized by hyperglycemia combined with low levels of insulin. Two main groups have been recognized, transient NDM (TNDM) and permanent NDM (PNDM).

Objective: To describle clinical features and laboratory manifestations of patient with NDM and evaluate outcome of management.

Subject and methods: clinical features, biochemical finding, mutation analysis and management outcome of 38 cases from 38 unrelated families were study. All exon of *KCNJ11*, *ABCC8* and *INS* genes were amplified from genomic DNA and directly sequenced. If the mutation of *KCNJ11*, *ABCC8* and *INS* has failed to detect, methylation – specific PCR will be done to detect the loss of methylated region on chromosome 6q24. If the mutaion of these genes has failed to detect, whole genome sequencing will be done to detect mutaion.

Results: 37 cases (16 girls and 21 boys) onset at 7-357 days of age (median: 44.5) with gestation age of 39.1 ± 1.9 weeks and birth weight of 2705.5 ± 526.4 gram. 9/38 cases admitted with the feature of polydipsia, polyuria and 29 cases with diabetes keton acidosis with pH of 7.12 ± 0.19, blood glucose of 36.24 ± 11.1 mmol/l, HbA1C of 7.86 ± 2.89 %. Mutation analysis showed 10 patients with heterozygous for a *KCNJ11* missense mutation, 12 patients with *ABCC8* mutations, 6 patients with abnormal of chromosom 6, and six patients with *INS* mutation, one patient with *EIF2AK3* gene mutation, one patient with *FOXP3* gene mutation and one patient with *EIF2B1* gene mutation. The patients have been follow up during 54.4 ± 46.6 months (4 months – 14 years). Ten patients with TNDM stop insulin at 8.25 ± 5.8 months of diagnosis: 6 cases have abnormal of 6q24, two cases has *ABCC8* mutation and two cases has *KCNJ11* mutation. Now all cases have normoglycemic (blood glucose: 5.0 and 5.9 mmol/l), one patient has mild development delay and 4 patients has normal development. 27 patients with PNDM: 18 cases successfully transferred onto sulfonylureas and did not need insulin injections, 8 cases require insulin, one

case with *FOXP3* gene mutation died for immunodeficiency. In there, 2 case with DEND syndrome have development delay, others cases have normal mental development.

Conclusions: It is important to perform screening of gene mutations for patients with diabetes before 12 months of age to control blood glucose and follow up the patients.

P3-P176

Axillary Temperature Relation to Blood Serum Insulin-like Growth Factor-I in The Not-Life-Threatened Newborn: Relevance of Preterm Birth

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Introduction: Preterm delivery may comport blood serum Insulin-like Growth Factor-I(IG1) decrements and lower body temperature during the first days of postnatal life of the human newborn (NWB). We evaluated the role of preterm delivery in associations between axillary temperature(TEMP) and IG1 in NWBs without life-threatening disease.

Methods: NWBs with any among total parenteral nutrition, blood transfusion, therapeutic hypothermia, life-threatening disease, diabetes mellitus(DM), endocrine diagnosis out of DM, malformation, and mother with DM were excluded. Each of 78 included NWBs had complete data availability for 1) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z) of postnatal age(PNA; unit:day), TEMP(unit:°C), caloric intake (kcal/kg/24hrs or kcal/kg/postnatal life hrs for PNA<1 day; K), and IG1 RIA measurements(unit:uM/dl), and for 2) gender(SEX), birth gestational age(GA; unit:complete week; range=28–42), preterm birth defined as GA<=36(PTB), BW(unit:g; range=1200–4150), BW<=10.th centile for GA(SGA) (numerosity; male SEX, 43; PTB, 46; SGA, 20). An arithmetical mean was calculated over x-y-z((x+y+z)/3), for TEMP(TEMPM), IG1(IG1M) and K(KM). The normal score of IG1M according to van der Waerden(IG1M-NS) resulted near-normally distributed. Mann-Whitney Test, Spearman Correlation and Multiple Linear Regression(MLR) were used for analyses(MLR computations; male SEX, PTB, SGA; condition absent=0, condition present=1).

Results: TEMPM ranged between 36.07°C and 37.00°C. Mann-Whitney Test showed significantly higher values of TEMPM in NWBs without PTB(TM-NWBs) than in NWBs with PTB(PT-NWBs)(p=.01), but similar values between TM-NWBs and PT-NWBs for PNA at x(PNAx). Spearman Correlation; GA vs. TEMPM, rho=. 295, p=.009. MLR partial correlation of TEMPM with outcome IG1M-NS(pc) was significant in a MLR model bearing SEX+SGA+PNAx+KM+TEMPM as predictors(pc coefficient=.269, t=2.373, p=.020), but was not significant in a MLR model bearing SEX+SGA+PTB+PNAx+KM+TEMPM as predictors. R^2 of each considered MLR model was significant.

Conclusions: PTB could be involved in TEMPM-IG1M associations not explained by SEX, SGA, PNAx and KM in NWBs free of life-threatening disease.

P3-P177

Birth Estimated Brain Weight Relation to Ratios Between Insulin-like Growth Factor-II and Insulin-like Growth Factor Binding Protein-3 in the Not-life-threatened Newborn: Relevance

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Introduction: Body temperature determinants include head-brain thermal homeostatic mechanisms and, in the human newborn(NWB), birth gestational age(GA). Estimated birth brain weight(BRW) ratio to birth body weight(BW)(BBR) resulted associated with GA and blood serum Insulin-like Growth Factor(IGF)-II(IG2) ratio to blood serum IGF Binding Protein-3(IB3)(IG2 through chronologically-corresponding IB3, IG2/IB3R) in our previous NWB observations. Here we evaluate BRW, BW, BBR and axillary temperature(TEMP) relations to IG2/IB3R in NWBs.

Methods: NWBs with any among total parenteral nutrition, blood transfusion, therapeutic hypothermia, life-threatening disease, diabetes mellitus(DM), non-DM endocrine diagnosis, malformation, and mother with DM were excluded. 78 included NWBs presented complete data availability for 1) same-day records at one of the first 5 postnatal days(x), 5 days after x(y) and 10 days after x(z), of postnatal age(PNA, unit:day), TEMP(unit:°C), caloric intake (kcal/kg/24hrs, or kcal/kg/postnatal life hrs for PNA<1 day; K), and IG2-IB3 RIA measurements(unit:uM/dl), and for 2) gender(SEX), GA(unit:complete week; range=28–42), GA<=36(PTB), BW(unit:g; range=1200–4150), head circumference (HC; unit:cm; range = 27.0-36.0), BW<=10.th centile for GA(SGA)(numerosity; male SEX, 43; PTB, 46; SGA, 20), BRW(unit:g) and BBR(calculations according to Lindley-McLennan; „$BRW=0.037 \times HC^{2.57}$"; "BBR=100 x (BRW/BW)"). IG2/IB3R was calculated at x, y and z. Arithmetical means were calculated over x-y-x((x+y+z)/3) for TEMP(TEMPM), K(KM) and IG2/IB3R(IG2/IB3RM). IG2/IB3RM van der Waerden normal

score(IG2/IB3RM-NS) resulted near-normally distributed. Spearman Correlation and Multiple Linear Regression(MLR) were used (MLR computations; male SEX, SGA; condition absent=0, condition present=1).

Results: TEMPM range: 36.07°C-37.00°C. Spearman Correlation as rho/significance; BRW vs. TEMPM:. 306/p=.006; BRW vs. IG2/IB3RM: -.391/p<.001); BW vs. TEMPM:. 204/p=.073; BW vs. IG2/IB3RM: -.511/p<.001; BBR vs. TEMPM: -.059/p=.606; BBR vs. IG2/IB3RM:. 468/p<.001. BRW MLR partial correlation with outcome IG2/IB3RM-NS(pc) was significant in MLR with predictors SEX+SGA+BRW+PNA at x(PNAx)+KM(pc coefficient=-.300, t=-2.669, p=.009) but not in MLR with predictors SEX+SGA+BRW+PNAx+KM+TEMPM(R^2 always significant).

Conclusions: TEMPM could be involved in BRW-IG2/IB3RM-NS relationships in not-life-threatened NWBs.

P3-P178

Congenital Hyperinsulinism in Children with Beckwith-Wiedemann Syndrome

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Introduction: Beckwith-Wiedemann syndrome (BWS) is a multisystem imprinting disorder. Approximately 50% of patients with BWS develop congenital hyperinsulinism (CHI). In this report, we describe the main clinical features in a group of patients with BWS and CHI.

Study: Clinical and laboratory data was collected from all patients with BWS under the care of endocrine units at Alder Hey Children's Hospital (Liverpool, UK) and Endocrine Research Centre (Moscow, Russia). The group included 12 children (8 males) with BWS and CHI. Median age is 1 year 5 months (range: 3 months – 11 years 8 months). All patients were under the follow up of multidisciplinary team and received require surveillance once every 3 months. Common clinical features of BWS included macroglossia (91%), large birth weight for gestational age (66%), ear crease/pit (58%) and umbilical hernia (58%). Methylation specific multiplex ligation-dependent probe amplification (MS-MLPA) was performed to confirm the diagnosis in 10 out of 12 children. In 3 patients methylation abnormality of 11p15.5 region was not found. Hence the diagnosis of BWS was made based on clinical features. Seven patients had genetically confirmed BWS (6 patients had ICR2 hypomethylation and 1 patient had mosaic paternal isodisomy of 11p15.5 region). All BWS patients were sporadic in origin. One patient with paternal uniparental isodisomy of 11p15 had two histologically proven embryonic tumors (hepatoblastoma and Wilm's tumor) in the infantile period. All patients had presented with recurrent hypoglycemic episodes with elevated plasma concentration of insulin during hypoglycaemia confirming CHI (median insulin level was 66pmol/l; range: 20.5–251). Diazoxide was effective in 10/12 patients (one patient was treated with octreotide and the data from the other patient was not available). The median dose of diazoxide was 6.9mg/kg/day (range: 3-10mg/kg/day). The median duration of diazoxide therapy was 8 months (range: 3 months to 11 years 8 months) and 7 patients are still on treatment.

Conclusion: The majority of BWS patients with CHI were responsive to diazoxide. One patient with mosaic paternal UPD of 11p15 [considered as high risk for tumour] developed Wilm's tumour and hepatoblastoma in the infantile period. Genetic analysis would be helpful for disease prognosis in patients with BWS.

P3-P179

Comparison of the Phenylketonuria Phenotypes in Qazvin Province Before and After Neonatal Screening Until 2017

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Background: Phenylketonuria (PKU) is an autosomal recessive disorder that primarily affects the brain. Patients are at risk for intellectual disability, developmental disorder, hyperactivity, seizure, autism, and so on. The aim of this study was to compare the PKU phenotypes in Qazvin province, Iran before and after neonatal screening until 2017.

Methods: All children with PKU (61 patients) in Qazvin province, Iran who had been diagnosed before and after neonatal screening until 2017 were examined. Data were analyzed using descriptive statistics and Chi-square test.

Results: Of 61, 31 (50.8%) were female. Patients were among 2.5 months to 18 years old. Of 61 patients, 7 (11.5%), 33 (54.1%), and 21 (34.4%) had malignant, classic, and HPA form of PKU, respectively. 23 (37.7%) were identified in neonatal screening and 38 (62.3%) were diagnosed before screening by clinical findings. The incidence rate of PKU was one in 4858 live births in Qazvin province. The most frequent clinical manifestations were delay in motor (57.4%) and language (54.1%) development, seizure (36.1%), restless (34.4%), hyperactivity (29.5%), eczematous rash (29.5%), and severe mental retardation (8.2%). All clinical manifestations in patients identified after neonatal screening was significantly lower than patients diagnosed before screening (P< 0.001).

Conclusion: Intellectual disorders, developmental delay, and seizure were the most frequent phenotypes in patients with PKU in Qazvin Province. Neonatal screening is necessary to prevent brain damage in patients with PKU.

P3-P180

From Hypoglycemia to Hyperglycemia

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A full-term baby girl born with birth weight of 2.75kg (10^{th}–25^{th} percentile) had an uneventful perinatal course and no history of gestational diabetes. She was admitted to nursery on day 4 for poor feeding. Physical examination was unremarkable. Blood glucose was 0.6mmol/L upon admission and urine ketone was negative. Electrolytes and blood gas were normal. Glucose infusion rate of 11mg/kg/min was required to maintain euglycemia. Critical samples revealed insulin of 42mIU/L while other investigations including cortisol, growth hormone, ammonia and metabolic workup were normal. Diagnosis of hyperinsulinemic hypoglycemia was made. Diazoxide at 5mg/kg/day was started together with hydrochlorothiazide. It was further titrated up to 7mg/kg/day and intravenous dextrose could be taken off. Full enteral feeding was later established and she was discharged on day 42 with home blood glucose monitoring.

Euglycemia was maintained with the same dose of diazoxide while the child grew. At 3.5 months, blood glucose was high at 11.5mmol/L. She was admitted for a trial of stopping diazoxide. It was successfully weaned off. At 4.5 years, she was noted to have language delay, rigid and hyperactive behavior. She was assessed in Child Assessment Service, clinical psychology and child psychiatry and diagnosed attention-deficit-hyperactivity-disorder, Asperger's syndrome, specific learning disorder with low average intelligent quotient. She had low mood and anxiety symptoms, and was put on atomoxetine and sertraline.

At 17 years, she presented with 2-week history of polyuria and polydipsia. Physical examination was unremarkable. Her body weight was 42.8kg (3^{rd}–10^{th} percentile), body height was 146.5cm (<3^{rd} percentile), and body mass index was 19.9kg/m^2. Blood glucose was 17.1mmol/L and urine ketone was 4+ at emergency room. Repeated blood glucose was 19.1mmol/L and blood β-hydroxybutyrate was 0.5mmol/L at paediatric unit. Blood gas showed no metabolic acidosis. After 2 hour of rehydration with normal saline, blood glucose was still high at 16.4mmol/L and urine ketone was moderate. She was then put on multiple daily insulin injections at 0.8unit/kg/day. A1c was 13.5%, insulin was 3.8mIU/L and anti-islet cell antibody was negative. Sanger sequencing revealed heterozygous HNF4A mutation at c.1001_1004dupAGTT p.(Phe335Leufs*12). It was a novel frameshift variant which was absent from normal controls. It was predicted to create a premature stop codon. The girl was switched from insulin to gliclazide and glycemic control was satisfactory with latest A1c of 6.1%.

P3-P181

Population Screening of Hypophosphatasia. A Metabolopathy to Consider. National Multicentric Study

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Hypophosphatasia is a congenital disease, characterized by a defect in bone and dental mineralization, secondary to a deficiency in the biosynthesis of the non-specific tissue isoenzyme of bone, liver and kidney alkaline phosphatase (TNSALP).

Clinical phenotype varies with age and its clinical expression is sometimes very latent.

There is a small but significant number of pediatric patients NOT diagnosed with hypophosphatasia. The values of low phosphatases may go unnoticed in routine clinical practice.

Objective: Identify those patients who gave values below normal (HYPOPHOSPHATASE) and assess whether these values can be biomarkers of rare disease. It is the first population screening study of these characteristics carried out in the region and at the national level.

Establish cut-off points adjusted for age and sex for alkaline phosphatase levels in relation to rare metabolic disease.

To evaluate the utility of retrospective studies in the diagnosis of rare diseases.

Material and Methods: Retrospective search during a 12-month period of the very low alkaline phosphatase values at pediatric age in the databases of Central Laboratory of the hospitals participating in the study. It will be verified also present low levels in the analytical carried out in other dates to discard, since the levels of alkaline phosphatases. Detected the case, will contact the pediatrician of children to know if they have any clinical data that is indicative of this disease. Normal values were considered as Clinical Chemistry Study 2012.

Results:

Population size: 16,555 Expected proportion: 0.0005%

Confidence level: 95.0%

Cases studied with initial PA + 3.480, confirmed potential cases 102. Sent to genetic study and CCEE of Metabolopathies 14.

Exclusion data: Anorexia nervosa, Oncology / hematology, Neuromuscular disease

Psychiatric pathology, Obesity, Traumatology, Complex cardiology Endocrinology (poly ovary, growth retardation)

Cases studied (14):8 cases associated with scoliosis (traumatology), 1 case associated with precocious puberty, 1 case of short stature, 1 case of liver disease and myasthenia, 1 case of teething problems

Conclusions: Pending genetic confirmation, we present the first study of these characteristics in our territory

Low FA levels in many cases are transient

In patients with low AF the clinic should be evaluated, in order to select the possible cases.

PPH with little clinical phenotype may be more at the level of trauma.

IT alert could be assessed, in values lower than 20% to the limit of normality adjusted to sex and age

The therapeutic approach includes cornstarch, pectin, octreotide, and dietary modification.

Infrequently reported in children, most of the cases of DS are related to Nissen fundoplication, we report a neonate with dumping syndrome after correction of a congenital malformation.

P3-P182

Dumping Syndrome in a Neonate with Esophagical Atresia Surgery

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Introduction: Dumping Syndrome (DS) has been recognized as a major complication of Nissen fundoplication in young children. Althougth other causes have been recognized.

We describe a children with esophageal atresia who presented with late DS caused by a surgical complication, Dumping and Horner syndrome were diagnosticated after his surgery.

Case description: A male newborn with prenatal diagnosis of right Aortic Arch was born by vaginal delivery, radiological and clinical findings confirm distal esophagical atresia and distal tracheoesophageal fistula (Gross type C, Vogt type 3B); at 2 days of life he underwent correction and primary esophagical anastomosis with closure of fistula.

After procedure palpebral ptosis and diaphragmatic paralysis are noted (ipsilateral to surgical incision).

Following a week of fasting with no hypoglycemia (parenteral nutrition was iniciated before surgery), he starts oral feeding with progressive tolerance, but with postprandial hypoglycemia associated with diaphoresis, tachycardia, pallor and hypotonia, always 2 hours after oral feeding and related with faster administration of feeding bottle, at physical examination his diaphoresis was asymmetrical (left side face), miosis and ipsilateral palpebral ptosis, followed by adbominal distension relieved by abundant diarrhea and emesis. Such episodes continue during the hospitalization, and getting worst until his referal to our unit.

Dumping syndrome was suspected and confirmed by a glucose tolerance test, which showed a postprandial 1 hour glycemia of 155mg/dL, and 2 hours post-feeding of 58mg/dL with elevated insulin values related to this value.

The boy was treated with frequent and reduced feeding with important improvement of glycemic values and autonomical symptoms, now receiving anti-reflux formula with no hypoglycemic episodes and adequate weight gain.

Discussion: DS must be suspected in neonates with congenital gastrointestinal malformations who underwent surgical manipulations and present postprandial hypoglycemia related to autonomical symptoms, such manipulation can cause alteration of gastric emptying mechanisms, related to its anatomy or its intrinsic innervation.

According to the time of hypoglycemia DS can be classified into 2 types: early and late, the first related to rapid delivery of hyperosmolar nutrients into the bowel and the second one as result of a reactive hypoglycemia induced by incretin response to carbohydrate ingestion.

P3-P183

Diagnosis and Treatment of Persistent Hyperkalemia in Newborn Twins – Rare Case Report of Gordon Syndrome

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Objectives: To summarize the diagnosis and treatment course of hyperkalemia in twins, review the diagnosis approach of hyperkalemia in neonate and guide clinical practice. Methods: The clinical manifestation, laboratory examination, the course of diagnosis and treatment of the two cases were summarized.

Results: A pair of twin girls, 38 days after birth, came to our department because of «Hyperkalemia more than one month». Twins were MCDA, with the gestational age 37 weeks. Postnatal routine biochemical examination showed hyperkalemia. Laboratory test in local hospital showed that arterial blood gas analysis, urine routine and renal function were normal, Doppler ultrasound of kidney was normal. For further diagnosis and treatment, the twins were administrated in NICU of our hospital.Since the onset of the disease, no vomiting or diarrhea. Mother of the twins was found high blood pressure and elevated blood potassium at the time of pregnancy. When admitted to our hospital, the physical examination showed that B1: BP 93/46mmHg, BP93/61mmHg. According to the family history of hyperkalemia and no dehydration, the twins gained 1.1kg and 1.2 kg body weight on 38 days after birth respectively, blood pressure increased, serum renin activity decreased obviously, so they were clinically diagnosed as Gordon syndrome. Twins and mother had the same heterozygous c. 230c > a mutation in exon 3 of the KLHL3 gene in chromosome 5, conforming the diagnosis of Gordon syndrome. Twins were treated with hydrochlorothiazide 2mg/kg.d orally. Serum potassium and blood pressure decreased gradually.

Conclusions: The family history of hyperkalemia, accompanied by hypertension, no dehydration, low renin activity, is highly indicative of Gordon syndrome.

P3-P184

Mutation in *UCP2* Gene: A Rare Cause of Hyperinsulinemic Hypoglycaemia Syndrome in a Small-for-Gestational Age Newborn

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Hyperinsulinism is a common cause of severe and persistent hypoglycaemia during the neonatal period. Eleven genes have been identified that lead to unregulated insulin secretion and hyperinsulinemic hypoglycaemia (HH). Inactivating mutations in *UCP2* gene have been described in a very small number of patients with HH. UCP2 protein is an inner mitochondrial carrier protein and its loss of function causes enhanced glucose oxidation and increased intracellular ATP synthesis leading to HH.

Case Report: Male newborn who presented hypoglycaemia since the first hour of life.

Family history: no consanguinity. Mother with hypertension. No history of hypoglycaemia nor diabetes mellitus.

Obstetric history: First gestation of 34 weeks' duration. O'Sullivan test and TORCH serologies were normal. Third trimester ultrasound detected intrauterine growth retardation and signs of hemodynamic redistribution. Birth by caesarean section. Apgar 8/9, weight 1630g (-1.92 SD), length 41cm (-2.23 SD) and cephalic perimeter 29cm (-1.28 SD). Physical examination was normal barring an umbilical hernia of less than 1cm.

The patient presented persistent asymptomatic hypoglycaemia that required administration of intravenous glucose boluses and continuous enteral feeding by nasogastric tube thereafter. Carbohydrates were progressively increased up to 17.4 mg/kg/min. There were no clinical-biochemical markers of infection.

Complementary tests: The study conducted during hypoglycaemia (35mg/dl) revealed detectable insulin level (1.72 mU/mL), slightly high serum ammonium levels (88 mcmol/L, normal value <53), normal cortisol (16 µg/dL), low levels of total free fatty acids (0.18 mmol/L, nv 0.6-1.3), normal ß-Hidroxibutirat (140 µmol/L) and a normal lactate (1.2 mmol/L). Providing the diagnosis of HH.

Serum amino acids, urine organic acids profile, acid-base equilibrium, liver and renal functions were normal; echocardiogram and abdominal ultrasound were also normal.

Genetic study included *ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A, UCP2, HK1* and *PGM1* genes; finding an inactivating mutation in *UCP2 (*c.127-1G>T), a splicing mutation that had not been previously reported.

Evolution and treatment: Diazoxide was started at a dose of 5mg/kg/day at the age of one month with a positive response. It allowed carbohydrate requirements to be significantly reduced, withdrawing the feeding by gastroclysis and prolonging the interval between takes. Diazoxide was well tolerated and suspended at age of 3 months. Currently the patient tolerates normal fasting time for age.

Conclusion: We have described the case of a small-for-gestational age newborn who presented transitory HH caused by mutation in *UCP2* gene that responded to diazoxide treatment.

P3-P185

Hyperinsulinemic Hypoglycaemia Syndrome in Small-for-gestational Age Newborns: Clinical Characteristics and Genetic Study

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Hyperinsulinemic hypoglycaemia (HH) is a common cause of severe and persistent hypoglycaemia during the neonatal period. Risk factors for neonatal transient hyperinsulinism are small-for-gestational age (SGA), perinatal asphyxia and maternal diabetes mellitus. This state of hyperinsulinism in SGA newborns could persist from weeks to years, resulting in an important comorbidity; its pathogenesis remains unknown.

Objective: To describe the clinical-genetic characteristics of SGA newborns with HH.

Methods: Review of our HH patient database and selection of SGA patients who presented hypoglycemia during neonatal period for more than 3 weeks. Definitions: SGA as birth weight and/or length ≤-2 SD. HH as insulin and/or C-peptide detectable during hypoglycaemia and/or suppressed or low concentrations of free fatty acids during hypoglycaemia, in patients with carbohydrate requirements >12mg/kg/min.

Genetic study included *ABCC8, KCNJ11, GLUD1, GCK, HADH, SLC16A1, HNF4A, HNF1A, UCP2, HK1* and *PGM1* genes.

Patients with history of maternal diabetes mellitus, perinatal asphyxia and clinical-biochemical markers of infections were excluded.

Results: Eight patients (3 girls). Mean gestational age 35.98 weeks (range 30-39), 4 preterm newborns. Mean Z-scores of weight at birth -1.9 (range -1.23 to -3.25) and length -2.08 (range +0.78 to -3.01).

All patients presented asymptomatic hypoglycemia from the first week of life (range 1–4 days). Echocardiographic study showed 3 patients with patent ductus arteriosus (PDA) (patient 2, 5 and 8), 2 of them were premature.

Mean carbohydrate requirement was 17.63mg/kg/min (range 14-21). Five patients received diazoxide with a good response to treatment. Two patients continue on treatment (patients 5 and 8, currently aged 11 and 3 months respectively). In patient 5 the dose was reduced due to ductus reopening with subsequent spontaneous closure. In patient 2 treatment was suspended after 6 days due to pulmonary hypertension that required intubation (she had history of surgical ligation of PDA at 7 days of life).

Nutritional and/or diazoxide treatment duration: mean 13.8 months (range 27 days– 28 months).

Genetic study was conducted in 6 patients with one positive result (patient 7): mutation c.127-1G>T in *UCP2* gene.

Conclusions: SGA newborns risk presenting transitory hyperinsulinism. The treatment with diazoxide was effective in all patients. Two complications were attributed to diazoxide: ductus reopening and pulmonary hypertension, observing high prevalence of adverse effects in this population.

The genetic study was positive in only 1 of 6 patients (16.6%) in contrast to 60% of non SGA patients from our database.

P3-P186

Pediatric Insulinoma: A Case Report

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Aims: To report case presenting with pediatric insulinoma

Methods: A case with pediatric insulinoma was reviewed including demographic and clinical data.

Results: A 11-year-old boy was referred from private hospital due to hypoglycemia. He has a 1- month history of increased hunger, increased 10 kilograms of weight, confusion and fainting after fasting 10 hour. On examination, height was 50th centile, weight was 90th centile, there were no cushingoid appearance, no hirsutism, normotension, systematic examinations were normal. Initial investigation from private hospital showed low blood glucose (BS 10 mg/dL) and return to normal after giving intravenous glucose bolus. We performed fasting study and found hypoglycemia 6 hours after fasting. Blood was drawn and found low glucose with high insulin(10 μU/mL) levels but normal cortisol level. An abdominal contrast-enhanced computed tomography scan show 2 small well-demarcated heterogeneously enhancing lesion within the body and tail of pancreas without dilatation of pancreatic duct. The patient was diagnosis as having insulinoma. Minimally invasive surgery endoscopic laparotomy was operated to remove pancreatic mass and found 3 mass at pancreas (the last one is in the pole of pancreas). Histopathology confirmed insulinoma. Blood glucose and insulin are in normal level within a month after surgery. Three years times follow up has complete recovery and no evidence of tumor recurrence.

Conclusions: Pediatric insulinoma should be considered in any young child presenting with hypoglycemia symptoms. It is managed effectively with tumor removal using minimally invasive procedures.

P3-P187

Mutations in Indian Children with Neonatal Diabetes

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Objective: to evaluate the genetic mutations prevalent in Indian children with Neonatal diabetes.

Methods: All infants, less than 6 months of age with hyperglycemia requiring insulin were included in the study and their genetic testing were done.

Results: 10 infants with ND were included; there were 3 females and 7 males. The age of presentation ranged from 4 weeks to 28 weeks of age. of all the children tested 5 children were detected with mutations FOXP3, KCJN11, HNF1B, EIF2AK3, INS.

Conclusion: we report 5 mutations out of 10 children diagnosed with neonatal diabetes, out of which one was a novel mutation, one IPEX syndrome, one Wolcott Rallison syndrome.

Table 1. Neonatal diabetes (for Abstract no P3-P187)

S.no	Gene	Location	Mutation	Mutation DNA level	Zygosity	Sex	No.	Age at presentation	Diagnosis
1	FOXP3	Exon 10	missense	c.1040G>A	Hemizygous	M	1	4 weeks	IPEX syndrome
2	KCJN11	Exon 1	missense	c.685G>A	Heterozygous	M	1	8 weeks	Transient ND
3	HNF1B	Novel	missense	p.S19C	Heterozygous	M	1	24 weeks	ND
4	No mutation detected	–	–	–	–	M	1	26 weeks	ND
5	EIF2AK3	Exon 5,13	frameshift	c.287G>A,/c.2511_2514del	Heterozygous	F	1	17 weeks	Wolcott Rallison syndrome
6	INS	Exon 3	missense	c.287G>A	Heterozygous	F	1	22 weeks	ND
7	No mutaion detected	–	–	–	–	F	1	16 weeks	ND
8	No mutaion detected	–	–	–	–	M		28 weeks	ND
9	No mutaion detected	–	–	–	–	M		24 weeks	ND
10	No mutaion detected	–	–	–	–	M		20 weeks	ND

P3-P188

Weight Outcome in Infants with Prolonged Hyperinsulinemic Hypoglycemia Treated with Diazoxide Versus Those with Spontaneous Resolution

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Background: In newborns, physiological transition of glucose metabolism is typically completed within 48-72h of life, yet prolonged hyperinsulinemic hypoglycemia (HH) beyond 5d of life is not uncommonly encountered, especially in infants at-risk of hypoglycemia. Management includes intravenous dextrose while awaiting spontaneous resolution (SR) of HH or Diazoxide (DZX) therapy. Since DZX acts by suppressing insulin release, concerns arise whether weight gain in infancy will be suppressed.

Aim: To compare weight change patterns in infants with prolonged HH managed with dextrose infusion awaiting SR and those who received DZX treatment.

Methods: HH was diagnosed in infants >48h of life needing GIR >8mg/kg/min to maintain blood glucose (BG) >3.4mmol/L, who had hypoketonemia and inappropriate insulin levels with BG <3mmol/L. These infants also failed to achieve full oral feeds after 5d of life without hypoglycemia. Data on demographics, birth weight, gestational age, treatment modality and duration, and follow-up body weight were collected. Resolution of HH in SR infants was confirmed by normal home glucose for 2 weeks following discharge and DZX infants passed fasting studies on completion of treatment. Birth weight z-scores were determined using Fenton 2013 tables and follow-up body weight z-scores were derived from WHO 2006 standards. Changes in weight z-score were analyzed.

Results: 46 infants met the inclusion criteria. The SR group included 22 (13 male, 9 preterm) with birth weight 2647±927g (SDS -0.56±1.50) at GA 36.2w; and follow-up weight 4539±1545g (SDS -0.83±1.19) at corrected age (CA) 3.8m. The DZX group included 24 (16 male, 11 preterm) with birth weight 2133±626g (SDS -1.36±1.02) at GA 36.8w; and follow-up weight 4673±1707g (SDS -1.5±1.11) at CA 3m. Median length of stay was 16d (7-41d) and 18d (10-50d) in SR and DZX babies, respectively. Median DZX dose was 3mg/kg/day (3-12mg) and duration of treatment was 56d. There was no difference in weight SDS change (-0.27 vs -0.13, p=0.69) between SR and DZX treated infants. In a sub-analysis of SGA infants, no weight change difference between 11 SR and 16 DZX infants (0.00 vs 0.29, p=0.36) was observed.

Conclusion: In this cohort of HH infants, the use of DZX therapy did not suppress weight gain and resulted in weight gain patterns similar to those of SR infants.

P3-P189

Neonatal Hyper- and Hypoglycaemia; Widening the Clinical Phenotype of Transient Neonatal Diabetes Mellitus Due to 6q24 Methylation Defects

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6q24 methylation defects are the most common cause of Transient Neonatal Diabetes Mellitus (TNDM). The clinical picture is one of impaired insulin secretion, small for gestational age and diabetes mellitus aged <6months. This case illustrates the fluctuation between both hyper- and hypoglycaemia that can been seen in 6q24 methylation defects.

A term, small for gestational age baby boy was noted to have hypoglycaemia (BSL 1.8mmol/L) at 1.5 hours of life which resolved with oral formula and intravenous (IV) dextrose. Then on day 9 whilst tolerating breast milk feeds 160 ml/kg/day (glucose utilisation rate (GUR) 8mg/kg/min) he was noted to have hyperglycaemia (BSL 22.7mmol/L). Fluctuating hyper/normoglycaemia continued between days 9-13 of life; nadir BSL 2.9mmol/L on day 11. On day 14, after 24 hours of persistent hyperglycaemia IV insulin infusion was commenced, and DNA sent for investigation of Neonatal Diabetes Mellitus. Insulin was weaned over 6 days and ceased completely following 48 hours of normoglycaemia on combination enteral feeds and IV dextrose (GUR 9.5mg/kg/min).

At 4 weeks of age the baby was again noted to be hypoglycaemic (BSL 2.8mmol/L), with suppressed ketones 3-hydroxybutyrate 0.04mmol/L (RR 0-0.61) and inappropriately recordable insulin 1.2mU/L. Treatment with diazoxide was considered, however normoglycaemia was achieved on large-volume breastmilk feeds (TFI 280 ml/kg/day, GUR 12.4mg/kg/min). He was discharged home on day 35 with ongoing glucometer finger-prick monitoring.

Initial genetic testing excluded possible pathogenic mutations in KCNJ11, ABCC8 and INS genes but subsequent methylation-specific analysis of chromosome 6 detected paternal uniparental disomy (UPD) of 6q24 locus. The phenotypic variations of TNDM due to 6q24 mutations is being broadened, with the novel clinical observation of hypoglycaemia following remission of 6q24 TNDM was first described in 2013 by Flanagan et al. The mechanism for hypoglycaemic in 6q24 methylation defects is not understood, however a more severe hypoglycaemic-phenotype appears to occur in the paternal UPD cohort compared to parternal duplication defects.

Our patient was readmitted at 6 and 7 weeks of age for symptomatic hypoglycaemia. He continues to experience symptomatic hypoglycaemic episodes presenting as irritability, floppiness, and mood changes at 22months of age. These are unrelated to intercurrent illness or protein-rich meals, which have both been described. Hypoglycaemia has been managed orally. Our case further describes the phenotypic variation of TNDM due to 6q24 methylation defects and management difficulty this cohort presents.

P3-P190

Clinical and Molecular Genetic Characterization of Two Patients Due to Mutations

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Background: The Phosphoglucomutase 1 (PGM1) enzyme plays a central role in glucose homeostasis by catalyzing the inter-conversion of glucose 1-phosphate and glucose 6-phosphate. Recently, PGM1 deficiency was recognized to cause the congenital disorders of glycosylation (CDGs). PGM1 deficiency is a rare, autosomal recessive inherited disease which can cause the extreme variability of clinical symptoms multi-organ dysfunction, including ketotic hypoglycemia, dilated cardiomyopathy, cleft palate, growth retardation, and hepatopathy.

Methods: The present study describes the clinical features of two Chinese Han pediatric patients who presented with recurrent hypoglycemia, hepatopathy and growth retardation.Patients' medical histories were recorded. Blood biochemical indices, oral glucose tolerance test, continuous glucose monitoring, hormonal assays, echocardiography, abdomen ultrasound, and brain MRI scan were performed and analyzed. Targeted gene sequencing (TGS) using the Agilent SureSelect XT Inherited Disease Panel was performed to screen for causal genetic variants, and the relevant mutations identified by TGS were verified by Sanger sequencing in the patients and their parents.

Results: Serum electrolyte and thyroid hormones levels were within normal ranges in both patients. They did not have dilated cardiomyopathy. The subscore in the patients according to the Tulane PGM1-CDG Rating Scale (TPCRS) was 4 (patient 1) and 8 (patient 2). In patient 1,an abdominal ultrasound demonstrated mild hepatic steatosis, while a brain magnetic resonance imaging(MRI) scan demonstrated that the pituitary was slightly thinning. Patient 1 did not have cleft palate.Patient 2 presented with cleft palate and micrognathia.Her cortisol levels during hypoglycemia was low. Prothrombin time(PT) and activated partial thromboplastin time(APTT) were prolonged slightly.Here, DNA sequencing identified three variations of the *PGM1* gene (NM_002633.2) in the two patients.Patient 1 had a novel homozygous mutation (c.119delT, p.Ile40Thrfs*28) in exon 1.In patient 2,we found a compound heterozygous mutations of c.1172G>T(p.Gly391Val) (novel) and c.1507C>T(p.Arg503*) (known pathogenic).

Conclusions: This report deepens our understanding of the clinical features of *PGM1* mutation. The early molecular genetic and multisystem assessment was essential to provide the timely and proper treatment.

P3-P191

Transient Central Hypothyroidism due to Maternal Graves' Disease

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Context: Maternal Graves' disease (GD) may lead to not only thyrotoxicosis but also hypothyroidism in neonates. We describe a case of transient central hypothyroidism (CH) due to undiagnosed maternal GD.

Case presentation: A 4-month old Japanese girl visited our hospital for the treatment of hypothyroidism. She was born after 37-week gestation, weighting 2320g. She developed hypoglycemia and admitted to the prior hospital. She exhibited hypothyroxinemia without elevation of thyroid-stimulating hormone (TSH) at 33-day old (free-T4: 0.6 ng/dL, TSH: 1.05 μIU/mL). Her thyroid was proved to be normal both in size and in location by ultrasonography. Thereafter, she underwent 5μg/kg/day of oral levothyroxine (L-T4) and referred to our hospital.

Laboratory data in the prior hospital indicated CH. We evaluated her anterior pituitary functions. Although we could not evaluate TSH secretion accurately because of L-T4 supplementation, it showed impaired secretion (peak value of 0.186 μIU/mL). The result indicated isolated TSH deficiency.

She showed no increase in L-T4 demand despite weight gain. We continued her treatment by the same dose as it was started. When she was 5-month old, her mother was made a diagnosis of GD. Her struma was mild and no other suggestive symptoms were observed. However, it was revealed that she had noticed tachycardia and slight tremor from the early weeks of pregnancy. These facts showed that the girl might be exposed to thyrotoxicosis through almost whole pregnancy period, indicating that her thyrotroph function was suppressed and this dysfunction may be transient.

Afterward, we decreased L-T4 carefully. Her thyroid function remained normal and adverse events such as growth retardation were not observed. She was discontinued the drug at 17-month old successfully. A thyrotropin-releasing hormone challenge test revealed normal reaction of TSH.

Discussion: Our case showed transient CH. Although the pituitary function showed the possibility of isolated TSH deficiency, it is rather rare condition. The diagnosis of her mother's disease indicated transient thyrotroph suppression. The mother's objective symptoms were mild, and she thought her symptoms as effects of pregnancy. These resulted in delayed diagnosis of GD. If her thyroid were checked when the child's hypothyroidism was noticed, the etiology might have become apparent earlier.

Conclusion: Maternal GD may cause transient central hypothyroidism of the child. We recommend that mothers whose neonates have thyroid dysfunction should be routinely evaluated their own thyroid. This may lead accurate diagnosis of their child's disease.

P1-P141

Autosomal Dominant Growth Hormone Deficiency due to a Novel c.178G>A Mutation in the *GH1* Gene Causing Instability of the Mutant GH Protein (p.Ala34Thr)

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Background: The most frequent cause of familial growth hormone deficiency (GHD) is Type II autosomal dominant GHD (isolated GHD type II) due to several heterozygous *GH1* mutations.

Method: Genomic DNA from patients with familial GHD was enriched for the coding exons using hybrid capture technology and *GH1* was sequenced using Next Generation Sequencing technology. Plasmids containing genes for WT and A34T GH1 were transfected into NCI HEK295 cells. RNA was analysed by RT PCR. The p.A34T mutant protein was expressed in bacteria and studied by chemical denaturation and proteolysis. Denaturation was quantified using fluorescence spectroscopy. Proteolysis was determined by SDS-PAGE and western blot.

Results: GHD was identified in three female siblings aged 3.25-6.33 years (Ht SDS -3.21 to -1.13, peak GH 2.9-6.6 ng/mL); their mother had previously been diagnosed with GHD at age 12.33 years (Ht SDS -3.44, GH peak <2 ng/mL). Sequencing of GH1 identified a heterozygous variant (c.178G>A; p.Ala34Thr) that had not been previously described, and was not found in the Broad ExAc dataset representing >60,000 children without severe childhood-onset disease. Functional studies of the mutant GH protein showed reduced stability to denaturation and proteolysis compared to native GH. This mutation leads to alternate splicing resulting in increased expression of the smaller isoform of GH missing exon 3. PCR analysis of RNA revealed loss of signal for the A34T mutant of *GH1*.

Conclusion: The presence of a heterozygous *GH1 variant* (c.178G>A, p.Ala34Thr) in four individuals with GHD suggests that this is a novel cause of IGHD type II. In addition, functional studies of the mutant GH protein show reduced stability to denaturation and proteolysis. The mutant RNA is unstable. Binding studies of the mutant protein to the GHR are underway to determine the mechanism causing the dominant negative phenotype.

P1-P142

Growth Hormone Deficiency Due to Whole-gene Deletion of *GHRHR*

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Introduction: Various types of mutations in *GHRHR* cause isolated growth hormone deficiency type 1B. Here, we report the clinical features associated with deletion of whole *GHRHR* gene for the first time.

Case: A four-year–and-nine-month-old otherwise healthy girl was admitted due to short stature. She was born at term with a birthweight of 3750 gr. Her height velocity slowed down after 2 years of age. The mother (157.8 cm, -0.82 SDS) and father (162 cm, -1.99 SDS) were second-degree cousins. Her weight was 11.8 kg (-3.54 SDS) and height 91 cm (-3.38 SDS). Infantile facial appearance and prominent forehead were noted. Biochemistry, blood count, and thyroid function tests were normal and bone age was compatible with 2.5 years. IGF-1 and IGFBP-3 levels were low. The peak GH levels following L-Dopa and ITT were 0.280 ng/mL and 0.420 ng/mL, respectively. Magnetic resonance imaging revealed pituitary hypoplasia. Somatropin treatment was commenced. At the most recent follow-up when she was 12-years and 7-month-old, her height was 152.2 cm (-0.45 SDS), BMI 17.5 (-0.37 SDS), and pubertal development compatible with Tanner stage 3. *GH1* sequencing was normal but homozygous whole-gene deletion of *GHRHR* was found. Both parents were heterozygous for this mutation. IGF-1 levels were low in the father and low-normal in the mother. Glucagon stimulation tests revealed normal peak growth hormone responses in the mother (4.85 ng/mL) and father (10.4 ng/mL).

Conclusion: The clinical features of homozygous whole-gene deletion of *GHRHR* are comparable with those of other types of *GHRHR* mutations. The carrier parents demonstrated normal growth hormone responses to the stimulation tests despite low IGF-1 levels.

P1-P143

Severe Pre- and Postnatal Growth Retardation in a Child Harboring a Novel Homozygous *Igf1* Gene Mutation

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Background: Human *IGF1* gene defects are characterized by intrauterine and postnatal growth retardation, sensorineural deafness, microcephaly and intellectual disability. Seven cases have been reported so far, and the underlying pathophysiology has been characterized in only three.

Objective: To describe a patient with severe short stature presenting a novel homozygous *IGF1* gene mutation and its underlying pathogenic mechanism.

Case: Born from consanguineous parents at 40 weeks of gestational age with IUGR. Birth weight was 1910 g (-3.06 SD), length 38 cm (-6.3 SD), and head circumference 34 cm (-0.4 SD). His mother and father were born with low weight (1900 g and 2500 g, respectively) and had short stature (height -1.92 SD and -2.6 SD, respectively).

Results: At 3.2 years of age, the patient´s height was 74 cm (-6.15 SD), weight 6.1 kg (-5.1 SD), head circumference 41 cm (-6.05 SD). Physical examination revealed proportionate short stature, microcephaly, and facial dysmorphism (frontal bossing, triangular face, bulbous nose, full lips, retrognathia). He also presented bilateral sensorineural deafness, mild global developmental delay, and hyperactivity behavior. Basal levels of GH and IGF-I were variable (GH: 1.9 to 29 ng/ml; IGF-I: 47 to 206 ng/ml), and normal-high IGFBP-3 (2.3 to 5.3 μg/ml). Karyotype was normal (46, XY). MLPA for subtelomeric regions showed a duplication in the Xq28 region. SNP array showed multiple chromosomal regions of homozygosity, including 12q23.2 where *IGF1*, a potential candidate gene for the patient´s phenotype, maps. *IGF1* coding and known regulatory regions were analyzed by High Resolution Melting. Fragments displaying abnormal melting pattern were sequenced. The patient was homozygous and his parents heterozygous for a novel missense variant (NM_001111285.2: c.322T>C, p.Tyr108His). The change of a highly conserved Tyr residue (Tyr60 in the mature IGF-I peptide), was consistently predicted as pathogenic by multiple bioinformatic tools. Tyr60 has already been described to be critical for IGF-I interaction with type 1 IGF receptor (IGF-1R). We performed *in vitro* studies using HEK293T cells, that showed marked reduced phosphorylation of IGF-1R after 10 minutes stimulation with serum from the patient compared to control serum.

Conclusion: This novel *IGF1* mutation may result in diminished affinity of mutant IGF-I for its receptor, resulting in the observed clinical condition. In addition, the duplication in the Xq28 region may also contribute to the patient´s clinical and dysmorphic features.

P1-P144

A New p.(Ile66Ser*fs**93) IGF2 Variant Is Associated with SRS-like Phenotype

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The Silver-Russel syndrome (SRS) is characterized by an intrauterine growth retardation accompanied by postnatal growth deficiency. Affected individuals typically have proportionately short statue, finger deformities as well as typical facial features. About 10% of individuals with SRS have maternal uniparental disomy for chromosome 7 (UPD7) and 35%-50% showed hypomethylation of the parental imprinting center region 1 (ICR1) of chromosome 11p15.5. In the recent past also paternally inherited *IGF2* mutations have been identified in patients with a SRS-like phenotype with evidence of pathogenicity. Here, we identify a novel *de novo* c.195delC *IGF2* genevariant [NM_000612, p.(Ile66Ser*fs**93)] in a patient with a SRS like phenotype using NGS sequencing. The patient exhibited severe pre- and postnatal growth retardation in combination with dystrophy, facial dimorphism, finger deformities as well as a patent ductus. Cloning and sequencing of a long-range PCR product harboring the deletion and a SNP informative site chr11:2153634 (rs680, NC_000011.9:g.2153634T>C) demonstrated that the variant resided on the paternal allele. This finding is consistent with the known maternal imprinting of IGF2. 3D protein structure prediction and overexpression studies demonstrated that the p.(Ile66Ser*fs**93) variation resulted in an altered protein structure that impaired ligand/receptor binding and thus prevents IGF1R activation.

In summary, our patient has an IGF2 deficiency due to a biologically inactive IGF2 protein that associated with pre- and postnatal growth retardations. The severity of the phenotype and dominant mode of transmission indicates that the p.(Ile66Ser*fs**93) variation might be responsible for the clinical picture of the patient, which argues for the inclusion of *IGF2* in gene panels designed for routine diagnostics of intrauterine growth failure. The identification of such new mutations in combination with a detailed description of the phenotype could increase the awareness of physicians on the pathophysiological relevance of IGF2 which will facilitate early diagnosis and the initiation of an adequate treatment in order to avoid serious long-term effects.

P1-P145

Response to Growth Hormone in Patients with Isolated Familial Growth Hormone Deficiency Due to *RNPC3* Mutations

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Background: We recently reported three children with severe isolated growth hormone (GH) deficiency and pituitary hypoplasia due to biallelic mutations in the *RNPC3* gene, which codes for a minor spliceosome protein required for U11/U12 small nuclear ribonucleoprotein formation and splicing of U12-type introns. Although it is clear that these patients are GH deficient, the underlying mechanism for this deficit is not totally understood.

Objective: We aimed to analyze the effect of recombinant human GH (rhGH) therapy in the first three patients identified with this condition.

Results: Three sisters with extremely short stature and phenotypical features of severe GH deficiency due to compound heterozygous mutations in *RNPC3* were studied. They were siblings from a Romanian family with parents of normal stature. Treatment with rhGH (0.025-0.035 mg/kg/day) was initiated at 15.5, 8.1 and 6.0 years of age, with heights at onset of -5.9, -5.0 and -6.7 height-SDS, respectively. The eldest sister achieved adult height within her familial target, continuing to respond to treatment until 20 years of age when GH was discontinued. Her body fat content normalized and bone mineral density and trabecular bone structure significantly improved after 4.5 years on therapy. The two younger sisters are showing an even better response to rhGH after 6.5 years, with no side effects.

Conclusion: Long-term treatment with rhGH in patients with GH deficiency (GHD) due to *RNPC3* mutations dramatically improves growth, bone mass, bone microarchitecture, and body composition, with no side effects.

P1-P146

Laron Syndrome Patients Have an Abnormal Plasma Amino Acid Pattern

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Background: Laron syndrome (LS), (OMIM#262500) is a rare recessively inherited disease caused by deletions or mutations of the GH receptor, and is characterized by low or undetectable serum IGF-I. This deficiency leads to a series of metabolic abnormalities including of the proteins.

Subjects & Method: This study presents for the first time the amino-acid analysis of two untreated and one IGF-I treated LS patients using the LC-MS/MS method (Waters TQS Micro system).

Results: The main findings are summarized in the following Table:

The untreated LS patients have an increase in the plasma Aspartic, Alla-isoleucine, Carnosine, Aminoadipic and Sarcosine acids, while Glutamine was decreased compare to the LS treated patient and normal control. We also found that both the untreated and treated LS patients have an elevation in plasma Lysine (244 Isomer) and Ornithine acids, compared to the control.

Conclusions: Congenital IGF-I deficiency alters the plasma amino acid composition changes which are partial reversible by long term IGF-I therapy.

Table 1. (for Abstract P1-P146)

Pt	Asp	Gln	Asn	Lys244	Orn	AILeu	Car	Aad	Sar
*	↑10.7	↓214.7	90.15	↑782.65	↑1048.45	↑7.57	↑2.9	↑9.55	↑5.6
*	↑10.1	↓309.65	69.1	↑430.25	↑1016.75	↑16.85	↑7.45	↑21.35	↑13.9
**	6.5	395.75	↑109.45	↑653.15	↑1463	0.1	0.1	1.25	1.65
C	9.8	184.5	43.7	103.0	58.5	0.4	0.4	2.6	2.3

*LS untreated, **LS IGF-I treated, C- control.

P1-P147

Serum IGFBP-2 Concentration in Neonates with Potential Diagnosis of Growth Hormone Deficiency (GHD)

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In a retrospective study *(1)*, we found that a GH<6.5 µg/L, IGF-I-WHO87/518 <30 µg/L and IGFBP-3<0.8 µg/mL confirmed GHD diagnosis with high diagnostic accuracy in neonates with clinical suspicion of GHD. GH and insulin negatively regulate IGFBP-2, and it was proposed to reflect GH status in the diagnostic work-out of GHD in childhood and adults. The accuracy of IGFBP-2 has not been set for neonates.

Objective: To prospectively validate own GH/IGF-I/IGFBP-3 cut-off values and to investigate the usefulness of IGFBP-2 for diagnosing GHD in neonates.

Methods: The study included 16 neonates that were referred with clinical suspicion of GHD from March 2017 to March 2018 and 18 control neonates (median: 21 days). GHD diagnosis was based on growth retardation, other pituitary hormone deficiencies or brain MRI. Neonates in whom GHD was ruled out were diagnosed as congenital hyperinsulinism or with transient disorders (non-GHD). A new cut-off for current IGF-I-WHO 02/254 by Siemens was calculated (26 ng/mL). Main outcomes (ROC): sensitivity, specificity, negative and positive predictive values (NPV; PPV) of IGFBP-2 (ELISA-MyBioSource).

Results: GHD was diagnosed in 6 neonates; hyperinsulinism in 3 and 7 had transient disorders. GH was <6.5 µg/L in 6/6 GHD and 2/8 non-GHD patients. IGF-I was <26 µg/L in 4/6 GHD, 1/7 non-GHD and 2/3 neonates with hyperinsulinism (undetectable IGF-I concentrations in 5/17 neonates). GH was significantly lower in GHD than the other groups (p<0.001). No differences were obtained for IGF-I or IGFBP-3. GH and IGFBP-2 presented an inverse correlation (r= -0.79; p<0.01). IGFBP-2 concentration was significantly higher in GHD (median: 314 µg/L) compared to non-GHD (97 µg/L) or hyperinsulinism groups (68 µg/L) (p< 0.001). Most non-GHD and hyperinsulinemic neonates had IGFBP-2 concentrations within control range (210 µg/L). IGFBP-2 outcomes by ROC (cut-off: 230 µg/L) were sensitivity: 1.0; specificity: 0.90; PPV: 0.83; NPV: 1.0 (p=0.002). 1/2 non-GHD that failed to reach GH cut-off presented IGFBP-2 <230 µg/L.

Conclusions: This study reaffirms that GH >6.5 µg/L excludes GHD with high diagnostic accuracy. IGF-I seems to be less useful, probably due to methodological sensitivity. The inclusion of IGFBP-2 strengthens GHD diagnosis. A larger sample size should be study to further consider IGFBP-2 measurement as a reliable biomarker to rule out GHD in neonates. *(1) Horm Res in Paediatrics 2017;P2-804.*

P1-P148

GH Treatment Causes an Increase in Klotho Concentration in Children with Growth Hormone Deficiency

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Introduction: Klotho is a protein which may serve as a regulator of GH secretion. Growth hormone deficiency is diagnosed in children with growth restriction when GH secretion in two GH stimulation tests do not exceed the level of 10 ng/ml.

Aim: The objective of the study was to investigate Klotho and FGF23 in children with growth hormone deficiency (GHD) and their responce to the treatment with recombinant human growth hormone (rHGH).

Patients and methods: The study group consisted of 78 patients (boys 45, girls 33) with GHD diagnosed in one pediatric tertiary center. Their median age was 7.43 years [4.88;10.48]. The control group consisted of 28 children of a similar age and sex.

Prior to and following a period of 6 months of treatment with rHGH anthropometrical data were recorded, and biochemical parameters were measured: Klotho, FGF23, IGF-1, IGFBP-3, 25-OH vitamin D, PTH, calcium, phosphate, alkaline phosphatase. Blood was sampled in the morning in fasting conditions. SDS for height, BMI, IGF-1S, and IGFBP-3 was calculated.

Results: Klotho levels in the group of children with GHD before treatment with rHGH (1664.4 pg/ml [1233.14;2125.87]) was lower than in the control group (2081.82 pg/ml [1372.13;2730.81]). The difference was statistically significant (p=0.046). The treatment with rHGH caused acceleration of height velocity from 5.05 +/- 1,54 to 9.35 +/- 2.02 cm/yeat (p = 0.000) and IGFSDS from -1.64 [-1.99;-1.31] to -0.75 [-1.31;-0.17]. After 6 months of treatment with rHGH in children with GHD Klotho levels increased to 2939.85 [1867.03;3853.04], p = 0.000. We did not observed similar trend for FGF23. In children with GHD on rHGH treatment Klotho correlated positively with PTH (p = 0.001), and IGF1 (p = 0.007).

Conclusion: Klotho protein can be used as a sensitive marker of GHD. It also can be used as a marker of the response to the treatment with rHGH.

P1-P149

Assesment of SDF-1 and Ang-1 and Ang-2 in Children with Growth Hormone Deficiency Before and After 1– Year Therapy with Recombinant Growth Hormone

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Introduction: Angiopoietins are necessary for development, differentiation and stabilization vessels progress. Angiopoient 1 (Ang-1) is responsible for vascular integrity, through stimulation of endothelial cell migration and adhesion, and inhibition of apoptosis. Action of angiopoietin 2 (Ang-2), in the absence of VEGF it Leeds to vascular regression, but in the presence of high VEGF concentration it stimulates angiogenesis. Stromal derived factor (SDF-1) play an important role in stem cells mobilization from bone marrow to the peripheral blond, what increases as a result of tissue injury. During therapy recombinant growth hormone (rGH) in patients with growth hormone deficiency (GHD) supply of increasing growth factors and a lot of processes development of cells.

Aim: The aim of the study was to estimate the concentration of angiopoietins 1 (Ang-1) and 2 (Ang-2) and stromal derived factor (SDF-1) in children with growth hormone deficiency before and after 1-year therapy with recombinant growth hormone.

Materials and methods: Anthropometric parameters (height, weight, BMI) and levels of angiopoient (Ang-1 and Ang-2) and stromal derived factor (SDF-1) were measured in 32 children with GHD before and during GH therapy. The control group comprised 16 healthy, age and sex matched children. Ang-1, Ang-2 and SDF-1 levels were determined with ELISA.

Results: Comparing to control group SDF-1 level decreases statistically significant (p<0,05) in the group with GHD and was demonstrated tendency to slightly decrease without statistical significance (p<0,05) in group treated with GH. Without statistically significant correlations (p<0,05) Ang-1 and Ang-2 decrease in group with GHD comparing to control group. Increasing levels of Ang-1 and Ang-2 (Ang2>Ang-1) was observed after 1-year therapy.

Conclusion: In conclusion, GHD connect with decreasing stromal derived factor (SDF-1) and angiopoient and play an important role in impaired regeneration and development new cells. SDF-1, Ang-1 and Ang-2 could be monitoring of patients response to therapy with GH.

P1-P150

Total Sum of Growth Hormone Values Obtained from Growth Hormone Stimulation Test May Be Useful in the Diagnosis of Prepubertal Children with Idiopathic Growth Hormone Deficiency

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Background & objective: The peak GH value plays a crucial role in the diagnosis of idiopathic growth hormone deficiency (iGHD). However, the prediction of peak GH in iGHD diagnosis is known to be limited.The purpose of this study was to evaluate the clinical and diagnostic usefulness of the total sum of GH values obtained from the GH stimulation test.

Materials & Methods: We retrospectively reviewed 178 prepubertal children who were diagnosed with iGHD in the Department of Pediatric Endocrinology at Kyungpook National University Children ,s Hospital for the past 5 years. Of these, 108 were boys and 97 were girls. The iGHD diagnosis was classified as ,complete iGHD' for peak GH <5 ng / mL and ,partial iGHD' for 5 ≤peak GH <10 ng / mL in the L-dopa and insulin stimulation test (ITT). To investigate the clinical significance of ,sum of GH' during GH stimulation test, peak GH value, sIGF-I at the time of diagnosis, delayed bone age (CA-BA), anthropometric data were retrospectively analyzed.

Results: The peak GH value and the sum of GH values in the GH stimulation test were highly correlated in both L-dopa and ITT ($r = 0.9$, $p < 0.000$). The sum of GH in ITT was significantly correlated with sIGF-I in boys ($p = 0.033$). However, peak GH in ITT did not show a significant correlation with sIGF-I. In ITT, the sum of GH values showed significantly inverse correlation with CA-BA (yr) in the partial iGHD group ($r = -0.28$, $p = 0.031$). However, peak GH in ITT did not show a significant correlation with CA-BA. This suggests that the sum of GH values in ITT seems to be significantly associated with bone maturation.

Conclusions: Total sum of growth hormone values obtained from growth hormone stimulation test may be useful in the diagnosis of prepubertal children with iGHD. Additional large-scale studies are needed.

P1-P151

Growth of Premature Infants Born Small by Gestational Age

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Premature infants born small by gestational age (SGA) represent a potential cohort for growth retardation. However, up to the present time, questions of the frequency and severity of the growth deficit, the timing of the growth rate, the age of achievement of the population standard depending on the gestational age have been discussed.

Aim: to assess the dynamics of growth of preterm infants born small by gestational age within 5 years of life, taking into account the gestational age.

Materials and methods: A total of 43 preterm infants with SGA and 44 preterm infants appropriate for gestational age (AGA) were included in the control group with a distribution of them depending on the gestational age: 22-31 weeks and 32-36 weeks. SGA was diagnosed at a mass and/or body length below the 10th percentile for gestational age (Fenton T.R.). Growth rates were estimated taking into account the adjusted age at 6 months, 1, 2, 3, 4, 5 years with SDS counting (Auxology 1.0). Statistical processing of the results was carried out using nonparametric methods.

Results: Preterm infants with AGA with a gestational age of more than 32 weeks had optimal growth rates consistent with population standards throughout the follow-up period. Preterm infants with SGA and gestational age >32 weeks reached the control group and population values by the age of 3 years: a median of 93 cm (89, 95), -0.03 SD (-0.08, 0.12).

Preterm infants with AGA with a gestational age of less than 32 weeks had growth rates that differed from population values from -0.3 to -1.1 SD. There was no clear trend to improve the growth rates by 5 years: a growth median of 103 cm (100; 106), -1.1 SD (-1.4, -0.9). Premature infants with SGA and gestational age less than 32 weeks had the most pronounced growth retardation: from -2.3 SD in 1 year to -1.5 SD at 5 years of age. Deficiency of growth more than -2 SD in different age periods had from 1/4 to half of children of this group. The strongest correlation of growth with gestational age was noted in the group of prematurity with SGA ($r = 0.4\text{-}0.8$, $p<0.05$).

Conclusions: Preterm infants with SGA and gestational age of less than 32 weeks have a high risk of growth retardation in the first 5 years of life and require in-depth examination to address the issue of hormone growth therapy.

P1-P152

Microalbuminuria and Glomerular Filtration Rate in SGA Born Young Adults

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Background: Following Barker's hypothesis on fetal growth retardation, low birth weight and being born small for gestational age (SGA) might be linked to fewer glomeruli which influences adult disease. Growth hormone (GH) treatment leads to a greater kidney length and total kidney volume, as well as a higher glomerular filtration rate (GFR). Microalbuminuria, defined as more than 20mg/L albumin in random urine sample, is a marker for renal diseases and is a risk factor for cardiovascular disease. Effect of GH-treatment, SGA birth and catch-up growth on renal albumin excretion are lacking.

Methods: Kidney function and blood pressure was assessed in 50 young adults born SGA, who received treatment during childhood (SGA-GH) and compared with that of 34 young adults with spontaneous catch-up growth after SGA birth (SGA-CU), 30 adolescents who remained short (SGA-S) and 50 adolescents born appropriate for gestational age (AGA) with a normal adult height. We measured urine albumin and creatinine levels and we measured creatinine levels in serum. We calculated GFR values and compared all values between the 4 groups.

Results: Mean age of the participants was 20.9 (1.8) years. Mean albumin levels in urine were 9.9 mg/L in SGA-GH, 6.1 mg/L in SGA-S, 6.6 mg/L in SGA-CU and 12.6 mg/L in AGA ($p=0.400$). Estimated GFR-values were 107.6 mL/min in SGA-GH, 111.4 mL/min in SGA-S, 108.9 mL/min in SGA-CU and 102.5 mL/min in AGA ($p=0.355$). Mean systolic blood pressure ($p=0.124$) and diastolic blood pressure ($p=0.701$) was similar in all groups and within the normal ranges. No significant correlation was found between change in height SDS from birth to adult height and kidney function parameters.

Conclusion: Our results show that none of the groups had microalbuminuria. Being born SGA and experiencing catch-up growth, spontaneous or due to GH-treatment, does not negatively influence kidney function and blood pressure in young adults.

P1-P153

Testing the Performance of a Preexisting Growth Prediction Model in a Cohort of Prepubertal Patients Born Small for Gestational age (SGA) Receiving GH Treatment in *PATRO* Children

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Aim and Background: Growth hormone (GH) treatment of short children born SGA and its effects on growth varies greatly between treated individuals. In the present study we tested the performance of a preexisting growth prediction model (Ranke et al.; JCE&M 2003 pp 125-131) to estimate 1st-year height velocity (HV) in a german subcohort of prepubertal children born SGA treated with GH (Omnitrope®).

Methods: 190 treatment-naïve prepubertal children born SGA (72 girls) were enrolled within the international post authorisation safety study PATRO children®. The model was validated by comparing predicted and observed HV in the first year of treatment with Omnitrope®.

Results: Baseline characteristics at start of GH treatment and predicted vs. observed 1-year growth rate as well as the index of responsiveness are given in the table. Mean predicted and observed 1-year HV were similar and the mean index of responsiveness was close to zero.

Conclusions: Our results indicate accurate performance of the growth prediction model. It may therefore be used for growth monitoring and individualization of GH therapy in children treated with the biosimilar Omnitrope.

Table 1. (for Abstract no P1-P153)

Parameter	Mean	SD	Median
Age at GH start	6.58	2.14	6.00
Height SDS baseline	–3.11	0.79	–2.95
GH dose at start (mg/kg/day)	0.032	0.006	0.033
1st-year Δ-height SDS	0.731	0.30	0.74
1st-year observed HV (cm/yr)	8.58	1.54	8.80
1st-year predicted HV (cm/yr)	8.61	0.73	8.78
Index of Responsiveness (IoR)	–0.024	1.089	–0.020

P1-P154

Early Onset GH Replacement in GH Deficiency: Is Neonatal Hypoglycemia Important for Long Term Follow-up?

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A small number of GH deficient patients can be recognized before age 3, and only few of them are diagnosed during work-up for hypoglycemia. Data comparing clinical and laboratory characteristics of hypoglycemic vs non-hypoglycemic population of children with early onset GH deficiency is scarce. The aim of this study is to assess long-term follow-up of growth hormone therapy in early onset GH deficiency, and compare pre-treatment and treatment related factors with respect to history of hypoglycemia.

Methods: Twenty-three children with early onset GH deficiency in whom GH treatment was initiated before 3 years of age were included. Patients were grouped according to history of hypoglycemia. We retrospectively analyzed pre-treatment clinical and laboratory parameters such as birthweight, initial growth factor and GH as well as other pituitary hormone levels, and longitudinal growth and weight indices of patients. Diagnosis of GH deficiency was based on decreased growth velocity and low peak GH level in two GH stimulation tests, or low GH in a critical sample during hypoglycemia in cases with neonatal hypoglycemia.

Results: Thirteen children (7 females) out of 23 (10 females) had history of hypoglycemia. Eighteen children (10 hypoglycemic) had combined pituitary hormone deficiencies. Birth weight, gestational age at birth, initial length Z-score, weight for length Z-score, growth velocity Z-score, IGF1 and peak cortisol levels were similar in the two groups. Hypoglycemic patients were diagnosed, and received GH and thyroid hormone replacements at an earlier age than non-hypoglycemic patients (p:0.02, <0.01, 0.02, respectively). Prolactin levels were lower in hypoglycemics than non-hypoglycemics (p:0.01). Initial mean length Z-score improved significantly in the course of GH replacement in the whole group (-3.51 at onset, and 0.6 at 5th year of treatment), however there was no significant difference between the two groups. Only 2 patients were obese at onset (1 hypoglycemic), during follow up 7 patients (6 hypoglycemic) developed obesity, suggesting an increased tendency for obesity in hypoglycemics in comparison to non-hypoglycemics (p:0.08). Weight for length/height Z-score increased at 36th month of treatment in the whole group (p:0.073), which was attributed to the hypoglycemics (p:0.04) rather than non-hypoglycemics (p:0.83).

Conclusion: GH deficient children with history of hypoglycemia are more prone to develop obesity in the face of a similar growth response to GH treatment. Further studies are needed to explain this finding.

P1-P155

Prevalence of Diabetes Among Children Treated with Growth Hormone in Israel

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Background: Growth hormone (GH) is a diabetogenic hormone.

Objective: To determine the long term risk for diabetes in a cohort of children treated with recombinant human (rhGH) in Israel, using data from the Israeli National Diabetes Register (INDR) for 2014 as a reference.

Methods and patients: Between the years 1988 and 2009, 2,513 children under the age of nineteen were approved for GH treatment. The patients were categorized to a low-risk category that included patients treated for isolated GH deficiency and small for gestational age and a high-risk category that included patients treated for multiple pituitary hormone deficiency, chronic renal failure, Turner syndrome and Prader-Willi syndrome. This cohort was cross linked with the Israeli National Diabetes Register for 2014 and prevalent cases with diabetes were identified. The expected number of patients with diabetes was calculated for each risk category using the diabetes prevalence rates in 2014 as a reference. Standardized prevalence ratios (SPRs) of diabetes were calculated for the age group 10-29 years. The calculations were repeated after excluding patients who had diabetes before the commencement of GH treatment.

Results: Diabetes was identified in 23 patients. In the low risk category there was no difference in the prevalence of diabetes compared to the general population (SPR 2.05, 95% CI 0.94-3.89). In the high risk category there was a significantly higher prevalence of diabetes (SPR 11.94, 95% CI 6.53-20.0) compared to the general population. After exclusion of people with pre-existing diabetes, the SPR in the all-risk category was slightly attenuated.

Conclusion: GH treatment in individuals with pre-existing risk factors for diabetes is associated with increased prevalence of diabetes; therefore their glucose should be closely monitored during and after the treatment.

P1-P156

The Effect of Growth Hormone Treatment in Children After Hematopoietic Stem Cell Transplantation

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Background: Hematopoietic stem cell transplantation (HSCT) has become more common in treating malignant and nonmalignant diseases in children. However, HSCT is associated with several late effects that can impair growth, like insufficient growth hormone (GH) secretion, hypogonadism and growth plate damage. Growth hormone treatment (GHRx) is offered but limited data are available on its effect on adult height.

Objective: To evaluate the effectiveness of GHRx after HSCT during childhood.

Patients and methods: In this single center retrospective study, 34 patients were included who had HSCT between 1988 and 2010, received GHRx ≥ 1 yr and had reached adult height (AH). Each patient was matched with two controls who did not receive GHRx based on: gender, indication for HSCT (malignancy, benign hematological or immune deficiency), age at HSCT and total body irradiation. Predicted AH (PAH) was calculated based on bone age at start of GHRx or at equivalent age in controls. Annual data on growth and puberty were collected until AH.

Results: Boys started GH at 12.6±2.5 yr when height was -1.8±1.1 SDS versus -0.8±1.4 in controls and PAH was -1.8±1.2 versus -0.6±1.6 in controls. After 3.7 yr GHRx (median) (range 1.7-9.2) they reached AH of -2.3±1.3 SDS versus -2.0±1.2 in controls. The difference between AH and PAH was significantly smaller in GH treated boys (AH-PAH -0.5±0.7 SDS) than in controls (-1.4±1.1 SDS, $p<0.001$). AH was 2.1 SDS below target height (TH) in both groups.

Girls started GH at 10.7±2.2 yr when height was -2.2±1.1 SDS versus -0.6±1.1 in controls and PAH was -2.6±1.2 versus -0.8±1.0 in controls. After 4.9 yr GHRx (median) (range 2.4-8.6) they reached AH of -2.1±1.4 SDS versus -1.1±0.8 in controls. The difference between AH and PAH was significantly different in GH treated girls (+0.5±0.6 SDS) compared to controls (-0.3 SDS±0.7, $p<0.001$). AH was below TH in both groups (-1.8 versus -1.2 SDS).

Conclusion: GHRx had a positive effect on AH as compared to PAH in children after HSCT. AH was close to PAH in treated boys and above PAH in girls whereas AH was lower than PAH in untreated children, especially in boys. However, in both groups AH was low compared to the general population and far below TH.

P1-P157

Easypod™ Connect Observational Study: The Italian Experience

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Objective: The Easypod Connect Observational Study (ECOS) is a prospective long-term observational study aimed at evaluating the level of adherence in patients receiving growth hormone via the easypod device. ECOS started in 2010 in 24 countries. The easypod auto-injector device enables accurate records of patients' adherence to recombinant human growth hormone (r-hGH) to be collected, providing real-world data for evaluation. We present three years prospective adherence data from the Italian cohort of ECOS patients naïve to treatment.

Patients and methods: the Italian cohort of naïve patients comprised 81 patients (41 boys and 40 girls aged 1-16 y, 74 GHD, 4 SGA, 3 Turner syndrome). All patients received hGH (Saizen®) via the easypod™ device.

Results: adherence data were available for all patients after 1 year, for 51 after 2 years and for 23 after 3 years. The median level of adherence was maintained >80% over 3 years. Median change in height SDS after 1 year was 0,41. This level of adherence was not correlated with parameters of growth outcome by Spearman's product-moment correlation likely due to adherence values being skewed towards high positive levels. Additional modelling is expected to provide further insights on correlations between adherence and outcomes.

Conclusions: The majority of patients starting GH treatment with easypod™ maintained adherence >80% up to 3 years. ECOS has produced accurate, robust, and real-time adherence data in patients receiving Saizen® via easypod™ and provided useful insights into growth response to Saizen® treatment. Using easypod™ and easypod™ connect, physicians can identify patients with inadequate adherence, and with poor response to treatment, and help them maximize the benefits of recombinant human GH treatment

*On behalf of the ECOS Italian Investigators: C. Angeletti, F. Antoniazzi, S. Bernasconi, G.M. Cardinale, M. Caruso-Nicoletti, L Cavallo, S. Cianfarani, G. Citro, F. De Luca, S. Della Casa, M. Di Pietro, P. Garofalo, C. Giordano, N.A. Greggio, M.R. Licenziati, M. Maghnie, M. Parpagnoli, L. Persani, S. Pesce, M. Sacco, M. Salerno, L. Tafi,

P1-P158

Patients and Caregivers Perspectives on a Mobile App That Tracks Adherence and Outcomes in Children with Growth Disorders Treated with Recombinant Human Growth Hormone (r-hGH)

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Healthcare professionals (HCPs) receive adherence information on patient Saizen® recombinant human growth hormone (r-hGH) treatment via data wirelessly transferred from the easypod™ electromechanical delivery device to the web-based eHealth platform easypod™ connect. In order to empower patients and caregivers with this information and to provide educational tools, the growlink™ mobile app is being developed.

Concepts for the growlink™ app were developed using an agile design process following a benchmarking review of growth apps and a literature assessment of clinical practice. Proposed features included adherence information, height and weight growth graphs with reference curves, an ability to customise, a 'gamification' aspect and separate versions for patients and caregivers. Two rounds of user focus groups in Birmingham and London evaluated the app concept designs. Based on the feedback of young patients and their caregivers in Round One (4 children, 9 caregivers of children mostly <10 years and 1 teenager), original and revised concepts were shown to older patients in Round Two; 5 teenagers (3 of the girls had Turners syndrome) and 5 caregivers of the teenagers.

The ability to see adherence data was liked by older patients and caregivers as it was felt useful for reviewing adherence before meeting their HCPs. Adherence data was not as interesting to younger patients and their caregivers as r-hGH medication was taken as part of a routine (eg. bedtime). There were some concerns that tracking adherence could lead to being judged by HCPs. Growth goals are advocated by HCPs and younger patients and their caregivers felt height and weight measures of growth were strongly motivating, although some caregivers voiced concerns that poor growth could be demoralising. Older patients and their caregivers felt that measuring weight could lead to self-esteem issues. Despite this, both user groups wanted to see clear growth graphs with reference curves. Caregivers of younger patients liked the use of images and measurements to show the patient journey over time. A customisable app was popular; however overt 'gamification' was not liked by patients or caregivers. Neither group wanted separate versions of the app.

A priori assumptions on app design features were challenged. At odds with assumptions, a similar sharing of values between caregivers and patients was revealed. Whilst HCPs strive for monitoring, patients and caregivers would prefer clear reference based motivating and non-judgemental messages over time. The user research gave valuable insights that were fed back into the ongoing pilot.

GH & IGFs P2

P2-P206

Identification of Three Novel *GLI2* Gene Variants Associated with Hypopituitarism

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GLI2 is a downstream transcription factor in Sonic Hedgehog signaling, acting early in ventral forebrain and pituitary development. Heterozygous *GLI2* mutations have been reported in patients with isolated or combined pituitary hormone deficiency (CPHD).

Objective: Study of genetic etiology of the hypopituitarism and identification of the genetic alteration in *GLI2* gene.

Methodology: Molecular study: Search for variants by NGS sequencing (Ion ProtonSystem, SureSelectXTCustom Agilent) in the coding region and the intronic flanking regions of a panel of genes associated with hypopituitarism and multiple hormonal deficiency. For the interpretation of variants the guidelines of the American College of Medical Genetics and Genomics were followed.

Results: We found three heterozygous *GLI2* variants not previously described in 3 patients :

Conclusion: We had find three different variants in *GLI2*, described for the first time, in three patients with different phenotypes of hypopituitarism.

Table 1. (for Abstract no P2-P206)

Patient	Phenotype	GLI2 gene mutation	Variant interpretation
1	Male with clinical and biochemical studies concordant with combined pituitary hormone deficiency (CPHD). Microgenisotomy.Postaxial polydactyly. Epilepsy and global developmental delay. Start of hormone replacement therapy in the first year of life. RNM: Absence of pituitary stalk, ectopic neurohypophysis.	NM_005270.4.c.3670C>T (p.Gln1224*) (chr2:121747160).	Pathogenic
2	Girl with clinical and biochemical studies concordant with CPHD. Diagnosis and start of treatment was late. RNM: Absence of pituitary stalk, ectopic neurohypophysis.	NM_0052270.4:C.1978G>A (p.Ala660Thr) (chr2:121743875)	Probably pathogenic
3	Male with clinical and biochemical studies concordant with GH deficiency. Cryptorchidism and umbilical hernia. Developmental delay. Start of GH therapy in the second year of life. RNM: Small pituitary gland, ectopic neurohypophysis.	NM_005270.4:c.2059G>A (p.Gly687Arg) (chr2:121743956)	Probably pathogenic

P2-P207

Clinical and Preliminary Molecular Description of a Cohort of Patients with Growth Retardation Due to Severe Primary IGF1 Deficiency (GROWPATI Study)

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Background: Severe primary insulin-growth factor-1 (IGF1) deficiency (SPIGF1D) is a rare cause of growth retardation. Diagnostic criteria include age- and sex-dependent low basal IGF1 levels (<2.5th percentile), height ≤ -3SDS, absence of growth hormone (GH) deficiency and of any secondary causes of growth failure.

Objectives: Phenotypic description, follow-up and molecular studies in a cohort of patients diagnosed with growth failure due to SPIGF1D.

Methods: The historical study cohort was composed by patients (n=2546) referred to Pediatric Endocrinology Department of Necker Children's University Hospital, in Paris, France between 2004 and 2009 (*Teissier et al, EJE, 2014*). A group of patients (n=30) had been identified with SPIGF1D. We extended this cohort and further included 15 more patients with SPIFGD. Patients were followed up to December 2017 and data is presented concerning growth rate, puberty, final height, when available. Molecular studies were performed based on candidate gene approach by Sanger sequencing from patients' DNA (blood samples).

Results: From our current cohort of 45 patients with SPIGF1D, 27 patients were born small for gestational age (SGA) and 18 patients were classified with idiopathic short stature (ISS). At inclusion all patients were prepubertal. Four patients were diagnosed with constitutional bone disease (skeletal dysplasia). One patient was diagnosed with hypochondroplasia due to *FGFR3* mutation. Laron syndrome was diagnosed in a girl with severe growth failure (height: -9SDS). A heterozygous mutation in *GHR* was identified in two unrelated children. Noonan syndrome was diagnosed in one patient, Silver-Russell syndrome in another. GH treatment was initiated for 27 patients, in a context of SGA or ISS. Increlex® (recombinant human IGF1, rhIGF1) was initiated for two patients, without any adverse effects observed so far. All patients have had a normal puberty onset, on-going for most of them. Three patients (two males, one female) have achieved their final height. Genetic studies are ongoing for the remaining patients.

Conclusion: Our study provides a detailed clinical description of a well-characterised cohort of patients with SPIGF1D and confirms the heterogeneous spectrum of the disease. Long-term follow-up, especially for final height is necessary. On-going genetic studies will provide more insights in the understanding of SPIGF1D.

P2-P208

A Novel, Synonymous, Heterozygous, Splicing Variant Affecting the Intracellular Domain Of the Growth Hormone Receptor: Causality for Mild Growth Impairment and IGF-I Deficiency in an Affected Patient?

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Introduction: Although the majority of Growth Hormone insensitivity syndrome (GHIS) cases are classical, the spectrum of clinical phenotypes has expanded to include „atypical" GHIS subjects with milder phenotypes due to very rare heterozygous *GHR* mutations with dominant negative effects.

Case description: A 13 year old pubertal boy was presented with short stature (−1.7SD) and delayed bone age (11 6/12). Final adult height was −1.8 SD, 3SD below his mid-parental height (+1.27SD). His serum IGF-I was low (16ng/ml; reference range; 179-540) with low IGFBP-3 (1.3mg/L; 3.1-9.5), and ALS (565mU/ml; 1500-3500). GH stimulation test was normal, and GHBP, increased (6300pmol/L; 240-3000).

Methods: The *GHR* gene analyzed was from genomic DNA. Primary fibroblasts were established to evaluate *GHR* cDNA.

Results: A novel synonymous heterozygous *GHR:c.945G>A* variant in exon 9 (encoding part of the intracellular domain of GHR) was identified. *GHR c.945G* is the last nucleotide in exon 9 and a substitution from G to A could alter the donor splice site at the junction of exon 9-intron 9. Analysis of the *GHR* cDNA undertaken revealed heterozygous excision of exon 9 sequences, consistent with *GHR c.945G>A* being a splicing defect. The loss of exon 9 generates a predicted truncated GHR protein identical to the dominant-negative heterozygous *c.945+1G>A* variant reported by Iida et al (JCEM, 2008).

Conclusion: We describe the first synonymous heterozygous *GHR* splicing variant in the intracellular domain of GHR associated with mild short stature and very low IGF-I, thus supporting the continuum of genotype, phenotype and biochemistry of GHIS.

P2-P209

A Novel Mutation of *Type I Insulin-like Growth Factor Receptor* (*IGF1R*) Gene in a Severe Short Stature Pedigree Identified by Targeted Next-generation Sequencing (NGS)

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Objective: To identify genetic mutations of a pedigree affected by severe short stature in Chinese populations for the first time.

Methods: Auxological and endocrinological profiles were measured. Targeted next-generation sequencing (NGS) analyses comprising 277 shorted stature-associated candidate genes and 19 related copy number variation (CNV) regions were used to identify gene mutations in the proband. Three web-based software programs (SIFT, PolyPhen-2 and Align-GVGD) were used to evaluate the functional significance of the mutation.

Results : We identified a novel heterozygous missense mutation in exon3 (c.926C>T, p.S309L) of IGF1R in the Chinese proband, inherited from his mother. The proband and his mother had severe prenatal and postnatal growth failure. After recombinant human GH therapy, the growth rate increased in the patient. The missense mutation might affect the structure of the protein and was scored as deleterious according to the Align GVGD.

Conclusion: Our results show a novel missense mutation in the IGF1R (c.926C>T, p. S309L) associated with severe short stature in Chinese populations for the first time. Targeted NGS provides a promising method for efficient diagnosis and genetic consultation of short stature children.

P2-P210

Severe Short Stature, Growth Hormone (GH) Deficiency, Hypospadias, and Microcephaly: New Insights into the Role of Chromosome 4 Long Arm Duplication

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Background: Duplication of the long arm of chromosome 4 has been described in more than 60 patients. The severity and specificity of associated symptoms depend on the size and location of the duplication, and which genes are involved.Reported features include developmental delay, intellectual disability, birth defects, hypotelorism, growth retardation, short neck, dysmorphism, and abnormalities to the extremities.

Objective: To report a two-year old child with complex chromosomal duplication involving the long arm of chromosome 4 and severe short stature due to GH deficiency.

Case history/Methods: We describe a case of a two-year old boy, born at 36 weeks of gestation. The patient was found to have the following: poor weigh gain, short stature (-3 SDS) microcephaly, hypospadias, and horseshoe shaped kidneys. Biochemical evaluation revealed low level of growth hormone after stimulation test 1.45 mcg/L (reference >7 mcg/l) and normal cortisol and thyroid hormone levels. His head circumference was 43.9cm (<3rd percentile) with normal CT head. Developmentally, he met the milestones of gross and fine motor activities and normal eye contact, with delayed speech. Urinary tract ultrasound showed horseshoe shaped kidneys. Genome wide oligonucleotide array-based comparative genomic hybridization (aCGH) analysis was performed with use of human genome CGH Microarray kit 44B(OGT technologies).

Results: aCGH analysis revealed a gain of approximately 38 MB in the long arm of chromosome 4 extending from cytogenetic band q28 and q32. Chromosomal analysis was performed to confirm the abnormal aCGH findings. G banding chromosome analysis of 11 metaphase cells from a peripheral blood sample revealed a duplication in the long arm of chromosome 4 at band q28.1 and q32.3. Several genes, MMAA (coding for methylmalonic aciduria), FGF2 (coding for fibroblast growth factor 2), NUDT6 (FGF2 antisense gene), NR3C2 (involved in minerlacorticoid regulation), and SFRP2 (Wnt signaling pathway) lay within the duplicated region seen in the patient. FGF2 is involved in limb development, angiogenesis, migration, and differentiation of neuronal cells and cardiogenic differentiation. Targeted overexpression of FGF2 isoforms in osteoblastic lineage cells in mice results in phenotypic changes,including dwarfism, rickets, hypophosphatemia.

Conclusion: Our patient carries a duplication of chromosome 4 with a cytogenetic band q28 and q32. The patient exhibited features related to growth hormone deficiency, short stature hypospadias, horseshoe kidney, and microcephaly. Our patient expands the spectrum of phenotypes associated with chromosome-4 long arm duplication and further work is on-going to undertand the phenotypic features in this patient.

P2-P211

Growth Hormone Treatment for Short Stature Associated with TRNT1 Deficiency: A Case Series

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Background: TRNT1 (CCA-adding transfer RNA nucleotidyl transferase) enzyme deficiency is a newly reported inborn error of metabolism caused by defective post-transcriptional modification of mitochondrial and cytosolic transfer RNAs (tRNAs). TRNT1 mutations cause a complex multisystem disease leading to manifestations in most organs. We here described the effect of growth hormone (GH) treatment on short stature in two siblings with TRNT1 deficiency.

Case presentation: The two siblings presented with developmental delay, anemia, elevated transaminases, recurrent infection, hearing loss, macrocephaly and severe failure to thrive. Both were initially diagnosed with SIFD (sideroblastic anemia, immunodeficiency, fever, developmental delay) and later confirmed to have TRNT1 mutation by whole exome sequencing.

Patient 1 is 6 years old female who initially presented to endocrine clinic at age 18 months of age for severe short stature and episodes of hypoglycemia. Her lab evaluation was only remarkable for low IGFI. Other pituitary evaluation and hypoglycemia workup were unrevealing. She was started on GH treatment at 18 months of age. Her hypoglycemia resolved and growth velocity is also improving. As of now, she has been on GH treatment for 3 and half years. Her height SDS has increased from pretreat - 4.22 to current - 3.22.

Patient 2 is the younger male sibling of patient 1. He has more severe phenotypes than patient 1's. He presented to endocrine clinic at 14 months of age also for severe short stature evaluation. His lab evaluation revealed low IGF I without other pituitary deficiency. He was started on GH treatment at 15 months of age and tolerated well. Since age of 20 months, he has been ill due to recurrent infection and severe anemia. As a result, his GH has been on hold.

Literature review: TRNT1 mutations cause a spectrum of disease ranging from a childhood-onset complex disease with manifestations in most organs to an adult-onset isolated retinitis pigmentosa presentation. The severity of the signs and symptoms vary widely. The clinical manifestations in children can include cyclical, aseptic febrile episodes, sideroblastic anaemia, B lymphocyte immunodeficiency, retinitis pigmentosa, hepatosplenomegaly, exocrine pancreatic insufficiency and renal tubulopathy, sensorineural deafness, cerebellar atrophy, brittle hair, partial villous atrophy and nephrocalcinosis. About 20 cases have been reported in the literature so far.

Conclusion: This is the first report of growth hormone treatment on short stature in the patients with TRNT1 deficiency. So far, the result of patient 1 appears to be encouraging although more long term data are needed.

P2-P212

Case Report: Novel Case of Short Stature and Co-Occurrence Of SHOX Gene Mutation and Fanconi Anemia

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Fanconi anemia (FA) is a rare congenital disorder caused by mutations in any of over 16 documented genes leading to chromosomal fragility.[i] Patients may present with physical manifestations including short stature or upper limb deformities[ii], hematologic manifestations including progressive pancytopenia[iii], or oncologic manifestations including solid tumorsiii. Short stature (>2 SD below mean) is a common finding in FA and thought to be multifactorial. Both endocrine abnormalities, including impaired spontaneous GH secretion and hypothyroidism, and specific genetic mutations IVS4, have been implicated and are associated with more severe height deficiencies.[iv],[v],[vi] Of note, a less se-

Table 1. (for Abstract no P2-P212)

Lab	Result
IGF-1	65 ng/ml
IGF-BP3	2 ug/mL
TSH	2.02 UIU/mL
Free T4	1.2 ng/dL
Complete Metabolic Panel	Normal
ESR	25 mm/hr
Celiac Screening	Negative

vere degree of short stature has been documented in FA patients without these abnormalities without a clear underlying cause.[v] We present a novel case study of a 12-year-old male with Fanconi Anemia diagnosed at age 4 and short stature who was later found to have a co-occurring SHOX whole gene deletion. Mutations or deletions of the SHOX gene, located in the pseudodominant region of the X and Y chromosomes, have been implicated as a cause of short stature in patients with idiopathic short stature (ISS), and a cause of short stature and limb abnormalities in patients with Leri-Weill dyschondrosteosis (LWD) and Turner Syndrome.[vii],[viii] Previous co-occurrence of SHOX gene mutation and Fanconi Anemia has not been documented. Abnormalities in the SHOX gene may be partially responsible for short stature in patients with FA.

Patient presented to us at 11.5yrs of age for evaluation of short stature. Has a history of Fanconi's anemia diagnosed at age of 4yrs, with poor weight gain and need for G-Tube feedings for 6 years. On examination patient was at -3.77 SD for height and -4.03 SD for weight, Tanner stage I, mild mesomelia, absent Madelung deformity, and otherwise normal examination. Biochemical evaluation was performed (Table 1), with low IGF-1 (-1.27SD) and whole gene deletion of SHOX gene. Bone age was delayed by 3 years. Growth hormone was initiated at 0.3mg/kg/week and has been tolerated well. We continue to monitor patient's growth and communicate frequently with hematology group following patient.

P2-P213

Different Genetic Causes of Short Stature in a Family

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Background: The most common endocrine cause of growth disorders in childhood is growth hormone deficiency (GHD). The rare monogenic forms of GHD are inherited as autosomal dominant or recessive traits and manifest as isolated deficiency or in combination with other hormone deficiencies. Here, we report on a three-year-old girl with a severe growth retardation (height 77cm, - 5,6 SDS). She is the only child of non-consanguineous parents from northern Iraq, who also showed short stature (mother's height: 126cm, father's height: 132cm).

Objective: We aimed to investigate the etiology of short stature in the family by using laboratory and genetic tests (Sanger and whole-exome sequencing).

Results: X-ray analysis of the left hand showed a retarded bone age (1.6 years). Basal serum Insulin Growth Factor-1 (IGF-1: < 25µg/L) and IGF Binding Protein-3 (IGFBP-3: < 0,5 µg/L) levels were abnormally low. Thyroid function tests and calcium, phosphate and urine analyses were within the normal range; however, 2-Plane cranial MRI showed an empty Sella. Next, we performed growth hormone (GH) provocation tests with arginine (maximum of GH-peak after 45min: 1,28 µg/L) and clonidine (maximum of GH-peak after 60min: 0,77µg/L). Both stimulation tests revealed a complete GH deficiency in combination with very low GH serum levels (< 3 µg/L). Because of the family history we performed genetic investigations. Sanger sequencing of *GH1* revealed a heterozygous mutation (c.291+1G>A) leading to aberrant splicing in our patient and her father that has already been described in other patients with autosomal dominant GHD (Ariyasu *et al.* 2013, Cogan *et al.* 1995). The mother does not carry this mutation; however, subsequent trio whole-exome sequencing identified a *de novo* heterozygous mutation in *COL1A2* (c.2565+1G>A) in the mother. This mutation is described to cause Osteogenesis imperfecta Type IV. The mutation in *GH1* was not detected by exome sequencing due to low coverage.

Conclusion: Our patient and her father have an isolated GHD Type II with a heterozygous mutation in *GH1* gene identified by Sanger Sequencing. Surprisingly this mutation could not be found by performing whole-exome sequencing which revealed the cause of short stature of the mother (OI Type IV). This case shows that a combination of a careful medical history, physical examination and new technologies like exome sequencing can help to make the right diagnosis.

P2-P214

Incidence of Cranial MRI Abnormalities in Patients with Isolated Growth Hormone Deficiency: 20 Years of Results

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Background: Patients with isolated growth hormone deficiency (GHD) will routinely have an MRI scan of the pituitary and brain to assess pituitary size and presence of any intracranial lesions. The result may change the threshold for monitoring for further hormone deficiencies. However the test may also detect unexpected or unrelated abnormalities

Aim: To review the incidence of normal and abnormal MRI scans in children with a diagnosis of isolated GHD.

Methods: The biochemistry and MRI reports of children with isolated GHD (peak GH <7ug/L) born in a UK tertiary centre be-

tween 1997 from 2017 were reviewed. All children with multiple pituitary hormone deficiencies, septo-optic-dysplasia spectrum, and those children with known malignancies were excluded. Extra-cranial abnormalities such as sinusitis and mucosal thickening were excluded.

Results: 81 children were diagnosed with isolated GHD. 72 children had MRI results available. Of these, 38 (53%) were reported as normal and 34 (47%) abnormal. The median age of diagnosis was 5.99 years (range: 0.62 to 18.69), with a median height SDS of -3.45 (-0.33 to -8.41) at diagnosis. The median GH level was 3.25ug/L. The rate of MRI abnormalities was similar in the group above and below the median GH level. Of those with MRI abnormalities: 12 showed a small or hypoplastic pituitary gland, 2 had a microadenoma and 1 a cyst. 9 had an abnormal infundibulum and in 6 the posterior pituitary gland was not visible. A total of 16 MRI scans showed additional cranial anomalies (Chiari malformation (n=4), arachnoid cysts (n=3), enlarged ventricles (n=1), small optic nerves (n=1), other (n=7)). 3 of the children with pituitary hypoplasia had a CM.

Conclusions: Nearly half the children with isolated GHD had an abnormal MRI scan. The most frequent abnormality is pituitary hypoplasia, followed by infundibulum and then posterior pituitary abnormalities. One fifth had additional cranial anomalies; with 4 (5.6%) having a Chiari malformation. Chiari malformation in GHD is an uncommon but recognised association, and patients with this condition may need additional monitoring if given growth hormone treatment.

P2-P215

Systematic Prospective Study of Eye Funduscopy Before and After Starting Treatment with Growth Hormone in 290 Patients

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Introduction: Idiopathic intracranial hypertension (IIH) is a rare entity in childhood. It is characterized by signs and symptoms of increased intracranial pressure with normal neurological examination (except for possible paresis of the sixth cranial nerve), cerebrospinal fluid study and neuroimaging. The association between HII and treatment with growth hormone (GH) was first described in 1993 by the Food and Drug Administration and it has later been demonstrated. Incidence varies between 0.025-0.03% of totality of treatments. It usually occurs a few weeks after the starting of treatment and its suspension reverses the symptomatology. The examination of eye funduscopy permits its diagnosis.

Material and Methods: Prospective descriptive study performed by pediatric ophthalmologist. Examination of eye funduscopy before and 3 months after treatment with GH in patients with short stature and the following diagnoses: GH deficiency (n = 238, 82%), of which idiopathic (IGHD) in 162 (55%) and associated with other diseases or comorbidities in 87 (30%), small for gestational age (n = 33, 11%), Prader-Willy syndrome (n = 3, 1%) and SHOX gene mutation (n = 5, 1.7%).

Results: 308 patients were included; 290 completed follow-up. 4 patients (1.3%) presented papilledema after GH onset: 2 patients with GH deficiency in association with poly-malformation syndrome, 1 patient with panhypopituitarism due to a central nervous system tumor and 1 patient with IGHD and previous history of HII.

Conclusion: In asymptomatic IGHD patients without history of HII, we do not consider it necessary to performeye funduscopy examination after starting treatment with growth hormone.

P2-P216

Incidence and Prevalence of Growth Hormone Deficiency in The Russian Federation – An Analysis of Two Registries

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Background: Growth hormone (GH) therapy for growth hormone deficient (GHD) children in Russia is fully state funded as part of the "Seven high expenditure diseases" (7HED) federal program. Thus, it is important to thoroughly understand the disorder, including its epidemiology. In Russia, there are two parallel functioning registries: the official federal medical statistics (OFMS) which provides purely statistical information and the 7HED registry which must contain a patient's data to make free treatment accessible.

Aim: To determine the prevalence and incidence of GHD in children and adults in Russia.

Materials and Methods: Statistical data analyzed: the OFMS and the 7HED registries for the year 2015, the official federal statistics of Russian population (age and gender) for the year 2015. Both medical registries collect data from the whole of the country.

Results: According to OFMS the prevalence of GHD among children is 1:6950. Prevalence of GHD in adults was shown to be 1:37300. The prevalence of GHD in the whole population is estimated at 1:20200 people. The 7HED registry shows similar, yet slightly different results: 1:6860 children (difference of 1,2%), 1:46300 adults (19,4%) and 1:21900 people (7,7%) in the whole population. According to the 7HED registry out of the 4132 children registered, 1173 were girls and 2959 were boys, which means a girls:boys ratio 1:2,52. The OFMS registry showed a child (age 0-14) to teen (age 15-17) ratio of 1:1,57.

The incidence of GHD for children varies between 1:40800 children per year (OFMS) and 1:48500 children per year (7HED).

In several regions of Russia, the prevalence/incidence of GHD among children turned out to be unusually high (1:1155 in total and 1:7867 per year) or low (1:30490 in total and no new cases at all in 2015) in comparison to the average. These discrepancies, including the differences between the OFMS and the 7HED registries call for a clinical and organizational audit.

Conclusion: Considering how dependent GH therapy outcome is on a timely diagnosis our suggestion was to widen the functional ability of the 7HED registry by adding clinical data, which would allow for a transformation of the registry into a fully functional tool for GHD patients monitoring and therapy quality control.

P2-P217

The BSPED National Growth Hormone (GH) Audit: Trends in Prescribing from 2013–2016

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Introduction: Prescribing of recombinant human growth hormone (GH) for growth failure in UK children is based on guidance from the National Institute of Clinical Excellence. In2013, the BSPED initiated this national audit of children/adolescents newly-prescribed GH to monitor trends in NHS prescribing practice. Here we have examined these trends from 2013 to 2016.

Patient population: All patients aged≤16.0years newly starting GH therapy in the UK.

Methods: Anonymised data provided by NHS consultants who initiate GH treatment was analysed for diagnostic indication and age at treatment start.

Results: Of 85 centres, 76 submitted data (89%). Table 1 shows number of patients starting GH for licensed (growth hormone deficiency (GHD), born small for gestational age (SGA), Turner syndrome (TS), Prader–Willi syndrome (PWS), chronic renal insufficiency (CRI) and SHOX deficiency). Off-license prescribing includes idiopathic short stature, genetic syndromes, chronic inflammatory conditions and low IGF1/GH resistance. Table 2 shows age treatment started.

Conclusion: Off-license prescribing has declined by half in this 4 year period. Compared to other indications, GH is initiated at a significantly younger age in children with PWS, followed by SGA. Reference: NICE 2010 TA188. Human growth hormone (somatropin) for the treatment of growth failure in children. https://www.nice.org.uk/guidance/ta188/chapter/1-Guidance

P2-P218

The Rationale and Design of TransCon GH

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Background: The fundamental challenge of developing a long-acting growth hormone (LAGH) is to create a more convenient growth hormone (GH) dosing profile while retaining the excellent safety, efficacy, and tolerability of daily GH. With GH receptors on virtually all cells, replacement therapy should achieve the same tissue distribution and effects of daily (and endogenous) GH while

Table 1. Number of patients (%) starting GH for each indication (P2-P217)

Year	GHD	Turner	PWS	CRI	SGA	SHOX	Off license	Total
2013	536(55)	85(9)	61(6)	35(4)	144(15)	10(1)	94(10)	966
2014	537(56)	104(11)	53(6)	24(3)	150(16)	20(2)	65(7)	944
2015	481(56)	85(10)	50(6)	22(3)	149(17)	15(2)	53(6)	856
2016	559(57)	98(10)	50(5)	23(2)	177(18)	25(3)	51(5)	983

Table 2. Median age (range) in years at starting GH treatment (P2-P217)

Year	GHD	Turner	PWS	CRI	SGA	SHOX	Off license
2013	8.5 (0.1–16)	8.4 (1.3–15.4)	2.6 (0.3–13.5)	9.8 (1.5–15.6)	6.1 (1.5–14.8)	8.8 (2.2–15)	8.6 (1.4–15.7)
2014	8.6 (0.1–16)	5.9 (2.5–16)	2.3 (0.3–13.9)	7.6 (1–12.2)	6.3 (1.7–15.3)	8.7 (2.5–14.7)	9.5 (2.4–15.8)
2015	8.7 (0.1–16)	7.4 (2.1–15.4)	1.9 (0.2–15.1)	10.7 (2.3–15.1)	6.1 (1.3–14.7)	9.7 (2.8–13.4)	9.1 (3.6–15.6)
2016	8.2 (0.1–15.9)	6.7 (1.8–15.9)	2.0 (0.2–11.7)	8.2 (1.8–15)	6.3 (1.8–15.6)	7.8 (1.6–14.6)	9.3 (1.8–15.3)
2013–2016	8.5 (0.1–16)	7.3 (1.3–16)*3	2.2 (0.2–15.1)*1	9.0 (1.0–15.6)	6.2 (1.3–15.6)*2	8.7 (1.6–15)	9.2 (1.4–15.8)

*1PWS younger than other groups (p<0.0001).
*2SGA younger than all except PWS (p<0.0001).
*3TS younger than GHD (p=0.035).

maintaining levels of GH and resulting IGF-1 within the physiologic range.

Methods: To create a LAGH that extends the GH half-life thereby allowing less frequent dosing, two basic approaches have been followed: (a) combine unmodified GH with a prolongation technology (a depot, crystal, or prodrug) or (b) modify GH in such a way (protein enlargement or albumin binding) that the GH analogue has a longer half-life. We reviewed the nearly 20 LAGHs that have reached various stages of clinical development and analyzed why a product delivering unmodified GH combined with an inert prolongation technology may be an appropriate and potentially optimal design for a successful LAGH.

Results: To date, only two LAGHs have gained the approval of either the Food and Drug Administration (FDA) or the European Medicines Agency (EMA); both released unmodified GH, thus presumably replicating distribution and pharmacological actions of daily GH. Other technologies have been applied to create LAGHs, including modifying GH (for example, protein enlargement or albumin binding) such that the resulting analogues possess a longer half-life. TransCon GH is a LAGH prodrug in which GH is transiently bound to an inert carrier. It was designed to achieve the same safety, efficacy, and tolerability as daily GH but with more convenient weekly dosing. In phase 2 trials of children and adults with growth hormone deficiency (GHD), similar safety, efficacy and tolerability to daily GH was shown as well as GH and IGF-1 levels within the physiologic range.

Conclusion: The only LAGHs that have succeeded in providing both accelerated height velocity as well as corrected increased truncal metabolism have been (besides daily GH) depot formulations, which release unmodified GH. Therefore, a viable LAGH would likely have to maintain the same tissue distribution as native GH, ie, a candidate based on unmodified GH.

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Baseline Demographics of the TransCon Growth Hormone Phase 3 heiGHt Trial

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Background: TransCon Growth Hormone (GH) is a novel sustained-release recombinant human GH (somatropin) prodrug in development for children with growth hormone deficiency (GHD). It is designed to release unmodified GH and intended to provide comparable efficacy, safety, tolerability, and immunogenicity to daily GH with once-weekly dosing.

Based on results from a phase 2 trial, which demonstrated comparable efficacy (annualized height velocity for TransCon 0.21 mg GH/kg/wk of 12.9 cm/yr vs. 11.6 cm/yr for the same dose of daily GH), the ongoing randomized phase 3 global heiGHt trial is designed to investigate the safety, tolerability, and efficacy of weekly TransCon GH versus standard daily GH over 52 weeks in 150 treatment-naive prepubertal children with GHD. Enrollment is nearing completion.

Methods: Subjects are randomized in a 2:1 ratio and receive either once-weekly TransCon GH 0.24 mg GH/kg/wk or dose-equivalent once-daily somatropin for 52 weeks. Key baseline demographic variables include age, gender, height SDS, IGF-1 SDS, peak stimulated GH, and bone age delay. Endpoints include efficacy (height SDS and changes in serum IGF-1 and IGFBP-3 levels), safety, and immunogenicity.

Results: We will present key baseline demographic variables. Beyond simply descriptive purposes, these data also have important implications as predictors for annualized height velocity (HV) based on published literature. Therefore, we will also evaluate baseline characteristics to better understand expected annualized HV of subjects while receiving GH treatment. A power calculation will be presented based on the final sample size of the heiGHt Trial.

Conclusion: Baseline variables can provide important insights about the study population and how well they will respond to GH therapy, as well as how representative the study population may be to the general population who may be eligible for treatment in the future. The results of the phase 2 TransCon GH trial, which included a daily GH as an active control, informed the phase 3 heiGHt Trial design, allowing the optimization of statistical power. The heiGHt Trial is well powered to demonstrate noninferiority between TransCon GH and daily GH, and its demographics are in the range of other pivotal GH trials.

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The ZOMATRIP Study: Four Year Combination Therapy of GH and GnRHa in Girls with a Short Predicted Adult Height During Early Puberty: Adult Height Outcome

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Background: A combination of growth hormone (GH) and a gonadotropin releasing hormone analogue (GnRH a) is hypothesized to improve adult height in children with a poor adult height prediction.

Study Design: In this multicenter study, 24 girls in early puberty (bone age ≤ 12.0 y),with a predicted adult height ≤ 151.0 cm and normal body proportions were treated with GH (Zomacton) 50 µg/kg/day and triptorelin (Gonapeptyl) 3.75 mg/month SC or IM (for 4 years. Adult height was defined as the height attained at a bone age of at least 16 y. Bone age was determined yearly by the Greulich and Pyle method and height predictions were made using the Bayley-Pinneau tables. Height standard deviation scores (SDS) were calculated using Flemish growth curves (Roelants 2009).

Results: Sixteen girls completed the study per protocol (PP). Reasons to drop out during the treatment phase were: doping concerns in sports (1), no wish to postpone puberty any further after 2.5 or 3 years (3), poor compliance (1), premature stop of GH injections (1). Two participants did not return for their adult height visit after stop of treatment.. Mean height SDS was -2.25 ± 0.73 at the start of treatment, rose to -1.36 ± 0.81 at the end of treatment and further increased to -1.10 ± 0.76 at adult height. Height (mean ± SD) increased from 131.3 ± 4.1 cm to 155.3 ± 4.7 cm at the end of the treatment period and to an adult height of 159.8 ± 4.8 cm. Adult height was attained at a median age of 18.5 y and surpassed the predicted height at the start of treatment by 12.0 ± 2.6 cm (range 4.7–19.7 cm).

Serious adverse events in the total group were : depression (2 y after treatment), pyelonephritis and a fracture of forefoot bones in a ballet dancer (possibly related to the treatment). Other adverse events were restricted to injection site reactions (pain, bruising, scarring) and common health problems for this age group.

Conclusion: A 4 year combination treatment of GH and triptorelin, started in early puberty, was safe and resulted in an adult height significantly above predicted adult height. This outcome must be weighed against the marked financial and psychological burden of the treatment.

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Growth Hormone Treatment in Children Born Small for Gestational age (SGA)

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Introduction: Growth failure is a common consequence in small for gestational age (SGA) children.

Patients and Methods: The growth patterns and serum insulin like growth factor 1 (IGF1) concentrations before and after the 1st year under growth hormone treatment of 32 short stature SGA born children have been evaluated. In addition, we investigated the insulin like growth factor 1 receptor (IGF1R) exon 2 as a hotspot for IGF1R genetic alterations. It is of note that no dysmorphic features were observed in this group of children.

Results: The tests for pituitary reserve were within normal ranges for all 32 patients. Growth hormone (GH) treatment (0.037mg/kg/day) was initiated at the mean age of 9.32±3.19 years. Growth velocity increased yearly from -1.80 SDS after the first year to -0.03 SDS at the sixth year of treatment. Their IGF1 serum concentrations before treatment were age and sex appropriate, while during treatment a significant increase was observed fitting in the upper third of the normal range: before the treatment IGF1 SDS was 0.84±1.78 after 1st year the concentrations increased to IGF1 SDS 0.94±2.23. No genetic alterations were found in the IGF1R exon 2 by PCR analysis.

Conclusions: Herein we present 32 short stature SGA children with no dysmorphic features treated with GH. They all had increased growth velocity and entered the normal growth range on their growth charts. No side-effects were observed. GH treatment in children with no genetic alterations on the IGF1R exon 2 is safe and efficient in treating SGA children with short stature.

Key words: small for gestational age, short stature, IGF1, insulin like growth factor 1 receptor, growth hormone treatment.

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Height Perception of Children with Growth Hormone Deficiency: Influencing Factors and Links to Psychosocial Functioning

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Objectives: The aims of this study were: (1) to evaluate the perception of children with Growth Hormone Deficiency (GHD) and their parents, regarding their current and future predicted height, as well as the modulating factors; (2) to investigate the relation between perceptions of height and psychosocial functioning in children with GHD.

Methods: The study group consists of 322 children/adolescents (219 boys) diagnosed with (isolated) GHD, treated with growth hormone. The mean age of patients was 13.1 years (SD=2.5years) and the mean duration of treatment was 3.4 years (SD=2.6 years). Patients, as well as one of their parents, were asked to complete the Greek version of the Quality of Life in Short Stature Youth (QoLISSY) questionnaire and the Silhouette Apperception Technique (SAT) questionnaire, as a routine component of their medical visit.

Associations between SAT and demographics were evaluated using chi-square test of independence. Whereas, the relation between SAT and QoLISSY questionnaire was evaluated using Mann-Whitney test.

Results: The majority of children/adolescents (71.6%) and their parents (82.5%) overestimated patient's current height. Similar results emerged for the future predicted height with children and parents overestimating it (91.5% and 64.6% respectively).

Younger children (p=0.036) and those whose father had a high educational level (p=0.021) perceived their present height with more accuracy. The same pattern was observed for parent perceptions. Parents of older patients (p=0.01) and those having a low educational level (p=0.032) overestimated youths' current height to a greater degree.

When predictions for adult height were examined, younger age of patients (p=0.037), medium socioeconomic status of the family

(p=0.042) and parents' short stature (0.012) were positively related with overprediction.

Parents overestimating children's current height, reported higher levels of Physical QoL (p=0.016), Social QoL (p=0.001) and Total QoL (p=0.005) for their children. They also had a more positive perception for their children's experience linked to GH treatment (p=0.039) and referred that their children worry less about their future related to their short stature (p=0.024).

Accurate predictions for adult height, on behalf of the parents, were related with higher scores for children's general beliefs about stature (p=0.049).

Conclusions: The results of the present study suggest that the majority of GH treated patients and their parents overestimate the child's current and predicted height. The relation between overestimation of height and better HrQoL poses the question whether increased perceived height leads to better psychosocial adaptation or if it simply consists a defense mechanism.

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Health Lifestyle and Obesity of Adult Patients With Congenital Isolated Growth Hormone Deficiency Treated in Childhood

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Background: Data on congenital isolated growth hormone deficiency (cIGHD), mostly due to consanguinity, treated in childhood and followed into adult age is very rare and on few patients.

Aim: To assess the clinical and social characteristics of adults with cIGHD who were treated in childhood and followed thereafter.

Subjects: Thirty nine patients with cIGHD from our clinic were followed into adult age (mean age 30.7 ± 13.3). All were treated by hGH in childhood. Starting age was 7 ± 4.2 y and duration was 2-18 y. Out of the cohort of 39 patients, ascertained detailed data was found for 32 patients.

Methods: Data was collected from medical records of our endocrine clinics.

The study was approved by the Hospital Ethics committee.

Results: Mean (± SD) height for the males is 160.2 ± 10.6 cm, for the females 146.4 ± 5.4 cm. Twenty two patients have an education of high school or higher and 2 are in special institutions. Most are employed in manual labor. All have full sexual development and 14 are married. After cessation of GH treatment and with advancing age all have progressive increase in adiposity to the degree of obesity as revealed by high skinfold thickness and missed by BMI. Twelve patients suffer from hyperlipidemia, 4 developed diabetes mellitus, and 5 have cardiovascular diseases. One patient died. None developed cancer.

Conclusion: Patients with congenital IGHD who do not receive early and regular replacement treatment are prone to lag in achieving normal height and suffer from educational and vocational handicaps. They are protected from cancer.

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Factors Influencing Health Related Quality of Life in Children/Adolescents With Growth Hormone Deficiency

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Objectives: To describe the Health Related Quality of life (HrQoL) of children/adolescents with Growth Hormone Deficiency (GHD) and to examine the effects of sociodemographic (i.e., patients' age, sex and family socioeconomic status) and clinical characteristics (i.e., degree of short stature and duration of treatment) on HrQoL from patients' and their parents' perspectives.

Associations between QoLISSY questionnaire and demographics were evaluated using Mann-Whitney or Kruskal-Wallis whenever applicable and spearman's rho correlation coefficient.

Methods: The study included 322 children/adolescents with mean age 13.1±2.5 years and one of their parents as proxy. All patients had a clinical diagnosis of GHD and were treated with GH. The mean duration of treatment was 3.4±2.6 years. In order to evaluate children's psychosocial functioning, children and parents, separately, completed the disease specific, Greek version, of the Quality of Life in Short Stature Youth (QoLISSY) questionnaire which refers to core dimensions of HrQoL (Physical, Social, Emotional), as well as Coping, height-related Beliefs, Treatment, concerns about the Future and Effects on parents.

Results: Regarding gender differences, results showed higher scores for coping efforts for girls (p=0.033) compared to boys. Parents of girls, referred that their children worry less about their future (p=0.042) than parents of boys.

Younger children self reported better coping efforts (p=0.012) and better experiences regarding GH therapy (p=0.012) than adolescents, whereas their parents rated their children lower in levels of Coping (p=0.003).

Higher socioeconomic status was positively correlated with children's HrQoL (p=0.049).

Regarding the degree of short stature, taller children/adolescents had better HrQoL, both self- and parent-reported, on the scales Physical QoL (pChildren=0.001, pParents=0.002), Social QoL (pChildren=0.001, pParents=0.009), Emotional QoL (pChildren=0.001), Effects on parents (pParents=0.027) and Total QoL (pChildren=0.001, pParents=0.007).

Older age at treatment initiation was associated with more limitations on children's perceived Total HrQoL (p=0.001) while longer duration of treatment was found to be associated with better self-report Total HrQoL (p=0.002) and with Beliefs (p=0.029) about stature. The parent report version analysis yielded comparable results.

Children rated themselves as having higher HrQoL as compared to their parents.

Conclusions: Patient-related factors such as gender, age, socioeconomic status and degree of short stature affect the psychosocial functioning of children with GHD. Furthermore, age at initiation and duration of GH treatment play an important role. Parents report worse levels of HrQoL as compared to their children, possibly due to increased anxiety and/or expectations regarding their children.

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Health-Related Quality of Life and Psychosocial Functioning in Young Adults Born SGA after GH/GnRHa Treatment

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Background: Being born small for gestational age (SGA) has a negative effect on health-related quality of life (HRQoL) and self-perception. This might be more negatively influenced by postponement of puberty using additional gonadotropin-releasing hormone analogue (GnRHa) treatment.

Methods: 154 adolescents born SGA participating in a large Dutch growth hormone (GH) trial (75 with 2 years of GnRHa-treatment) completed the TNO-AZL Adults Quality of Life questionnaire, Self-Perception Profile of Adolescents and Child/Adolescent Behaviour Checklist at adult height (AH) attainment. Scores in GH-treated adolescents with GnRHa-treatment (GH/GnRHa group) were compared with GH-treated adolescents without GnRHa treatment (GH\ group) and a reference population. In addition, we assessed correlations between HRQoL, self-perception, problem behaviour and adult height (AH).

Results: After a mean of 7.8 years of GH treatment, mean age (SD) at AH was 17.3 (1.3) and 16.7 (1.4)years in the GH/GnRHa and GH group, resp. HRQoL was similar between both groups, and also when compared to reference population, all categories but cognitive function were similar. Self-perception was +0.57 SDS for GH/GnRHa group and +0.68 SDS for GH group regarding behavioural attitude, which was significantly higher in both groups compared to reference population ($p<0.001$). No significant correlation was found between HRQoL, self-perception, problem behaviour and adult height.

Conclusion: Our study shows that 2 years of GnRHa treatment in addition to GH treatment has no negative effect on HRQoL, self-perception and problem behaviour in early adulthood, compared to a GH-treated group and a reference population.

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Adherence to Treatment in Growth Hormone Deficient and Small for Gestational Age Patients Naïve to Easypod™ in Mexico: Final Results of the Easypod™ Connect Observational Study (ECOS)

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Background: The easypod™ auto-injector is designed to make daily administration of recombinant human growth hormone (r-hGH) comfortable and easier to patients. Easypod™ device delivers pre-set doses of r-hGH (Saizen®) and stores a digital record of adherence to therapy that can be shared with healthcare providers for evaluation.

Objective: To assess adherence to r-hGH therapy delivered via the easypod™ device in easypod™-naïve patients according to the approved pediatric indications for Saizen® in Mexico: growth hormone deficiency (GHD) or born small for gestational age (SGA); as well as to evaluate the association of adherence with growth outcomes.

Methods: ECOS is a multicenter (24 countries), 5-year, longitudinal, observational study, which aims to evaluate country-specific adherence to r-hGH therapy prescribed via the easypod™ electromechanical auto-injector. Herein we present the subanalysis for the Mexican population included in ECOS (NCT01555528). The primary endpoint was the recorded adherence at yearly intervals. Secondary endpoints were height velocity, height velocity standard deviation scores (SDS), height, height SDS, as well as IGF-1 concentrations after each year of treatment. Demographic, auxological and diagnostic data were obtained from medical notes, with adherence data obtained directly from the patients' easypod™ records. Adherence was calculated as the number of days with injections received divided by the number of days with injections planned and expressed as percentage. Correlations between adherence and growth outcomes were calculated using Spearman's product-moment correlation.

Results: This study included 193 Mexican patients, among whom 147 were easypod™-naïve (mean age: 9.96±3.41 years, 56.8% boys, mean height at baseline: 124.88±18.95): 118 with GHD, 24 SGA and 5 with Turner syndrome. A total of 105 (71.4%) patients were also GH-naïve. Overall median adherence was >90% over the first year of treatment and >80% over 4 years. Adherence was not different by r-hGH indication or between GH-naïve or experienced patients. At 1-year follow-up, mean change in height was 8.78±2.20 cm, whereas mean height velocity was 8.80±1.94 cm per year. In all, 84.7% patients had normal IGF-1 concentrations

at 1-year follow-up. Adherence associated with change in height (r=0.254, P=0.003), change in height SDS (r=0.239, P=0.005), height velocity (r=0.183, P=0.03) and height velocity SDS (r=0.194, P=0.03).

Conclusion: Adherence rates with the easypod™ device are high and maintained over time in GHD and SGA easypod™-naïve Mexican patients. This system could assist physicians in practical monitoring of adherence to r-hGH treatment.

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Growth Pattern and Final Height Outcome in Children With Septo-Optic Dysplasia and Isolated Hypopituitarism treated with rhGH in a Single Centre

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Aim: To identify the distinctive features of GH Deficiency (GHD) and to assess the response to GH treatment (rhGH) in children with Septo-Optic-dysplasia (SOD) and Multiple Pituitary Hormone Deficiencies (MPHD).

Methods: Retrospective longitudinal single centre study of children with SOD (n:171) and MPHD (n:53). GHD was diagnosed in patients with growth failure by an insufficient GH response (≤6.7 μg/l) to provocation (Insulin Induced Hypoglycaemia or Glucagon) combined with low IGF1/IGFBP3. Neurosecretory GH dysfunction was diagnosed in children with low IGF1/IGFBP3, poor growth velocity (GV), structural Hypothalamo-Pituitary (H-P) abnormalities and abnormal nocturnal GH production characterised by fewer than 3 GH peaks > 6.7 ng/L on overnight profile (20' sampling for 12 hours).

Results: Within the SOD cohort, 132/171 (77.2%) had some degree of hypopituitarism. 11/132(8.3%) had preserved GH function (age range: 0.52-15.46 years), whilst only 2/53(3.8%) MPHD were GH sufficient (ages: 0.57, 0.62 years). Of the patients with GHD, 9/121(7.4%) SOD and 3/51(5.9%) MPHD were born SGA. Despite being started on lower rhGH doses (25.61 ± 7.61 vs 29.12 ± 9.29 μg/kg/day; p=0.012), SOD had similar GV and IGF1 SDS after one and two years of treatment and similar delta between mid-parental height and height at the onset of puberty, as compared with MPHD. In MPHD only, there was a direct correlation between the starting rhGH dose and GV SDS after 2 years of treatment (r=0.475, p=0.003). Although not reaching statistical significance due to the small numbers (18 SOD and 6 MPHD), the final height SDS was lower in MPHD compared to SOD (-1.73 ± 1.80 vs -0.82 ± 1.66 SDS), whilst the delta between mid-parental height and final height was similar between groups (-1.12 ± 1.74 vs -0.77 ± 1.90 SDS). Neurosecretory GH dysfunction was diagnosed in 5/122(4.1%) SOD (but none of MPHD) (age at diagnosis: 2.55-14.64 years). All 5 had small anterior pituitary, two had posterior pituitary absence, one had pituitary stalk interruption syndrome.

Conclusions: Although GHD is the most frequent deficiency in children with SOD and MPHD, it may not always be present at diagnosis. When compared with MPHD, SOD patients with GHD display similar growth responses and final height outcomes, despite the use of lower GH doses. In SOD with structural H-P abnormalities and normal GH responses to provocation, but with low growth rates and growth factor concentrations, an abnormality of the GH secretory pattern should be considered.

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Reliability of Clonidine Testing for the Diagnosis of Growth Hormone Deficiency in Children and Adolescents

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Introduction: The diagnosis of growth hormone deficiency (GHD) is currently based on clinical, auxological, biochemical, and neuro-radiological investigation. Provocative tests of GH secretion using physiological/pharmacological stimuli are required to confirm GHD. The clonidine test (CT) is widely used to assess GH secretory status.

In this retrospective study we analyzed the reliability of CT and the effect of puberty in a large number of children with short stature who had been evaluated for suspected GHD.

Subjects and methods: Data were collected from 327 children and adolescents with short stature, and/or poor growth velocity, (204 boys and 123 girls, age 10.04±3.35 SD) followed in four Italian Pediatric Endocrine Units between 2005 and 2013. All children underwent CT as the first GH stimulation test after exclusion of other known causes for their short stature. All children with a GH peak ≥7 μg/L, normal growth velocity for age, and no other recognizable cause for their shortness were considered as non-GHD. Steroid priming was never used in any of the subjects.

Children were subdivided into two groups based on pubertal stage according to Tanner (group 1, pre-pubertal Tanner 1, n=223; group 2, pubertal Tanner 2-5, n=104) and into two groups according to diagnosis (GHD vs non-GHD). We then analyzed separately prepubertal vs pubertal GHD children (n=64 and 23, respectively) and prepubertal vs pubertal non-GHD children (n=154 vs 81, respectively).

Results: In 70 prepubertal children and 28 pubertal children the GH peak after CT was <7 μg/L. GHD was confirmed in 87 (37 organic, 50 idiopathic). The remaining 11 (6 pre-pubertal and 5 pubertal) who failed CT, had normal GH responses to a second stimulation test independently of the pubertal status (p=0.66). Mean BMI-SDS in these children was similar to that of the children

with GH peak ≥7 μg/L, and none was obese. Overall, the prevalence of false positives was 3.3%.

Mean peak GH after CT was similar between prepubertal and pubertal GHD and non-GHD children. Mean IGF-I-SDS was significantly higher in pubertal vs prepubertal non-GHD subjects while there was no difference between prepubertal and pubertal GHD patients.

Conclusions: This study demonstrates that using a validated cut-off of 7 μg/L CT is reliable in the diagnosis of GHD in children and adolescents and that steroid priming is probably not required.

The oral CT is a reliable and safe GH releasing agent in both prepubertal and pubertal children.

P2-P229

Area Under the Curve Of Growth Hormone, an Additional Tool in Assessing Stimulation Test Results

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Introduction: Growth hormone (GH) deficiency is diagnosed through the combination of clinical observation and low GH upon stimulation, in two separate stimulation tests. Normal response is considered as a single rise of GH above the local cutoff point which is used, and differs between countries and range between 7-10 mcg/L. The aim of our study was to assess whether a calculation of area under the curve (AUC) of GH can be used as an additional tool in the diagnosis of GH deficiency, and to find the level of AUC which correlates best with a GH peak of 7.5, which is considered normal in our country.

Methods: Patients who underwent GH stimulation tests which were performed in our clinic during a 3 year period were analyzed and an AUC was calculated for each test. Correlation between AUC and peak GH was calculated using pearson correlation coefficient, and using linear regression an AUC level was found which correlates with a peak GH of 7.5.

This level was used as an AUC cutoff for the diagnosis of GHD and false negative rates were calculated, using the traditional peak GH method compared to the AUC of GH during the test.

Results: 751 GH stimulation tests were performed. 527 clonidine, 150 glucagon, 74 arginine tests. A strong correlation was found between AUC and peak GH in all 3 tests (0.88, 0.87, 0.89 respectively). The AUC which correlated with a peak GH level of 7.5 in the 3 tests was 513.6, 532.5, and 398 mcg/L/min respectively.

Using these levels as cutoffs for the diagnosis of GHD we found false negative rates using the peak GH level as high as 10.9%, 23.8% and 23.5% in the above 3 tests respectively. False positive rates were 12.1%, 20%, 9.6% respectively. When limiting the analysis to a group with borderline peak GH of 7.5-10 mcg/L the false negative rates rose to 24%, 38%, 20% respectively.

Discussion: The decision to treat children with daily injections of GH for many years is based on a single peak of GH during a supra physiologic test, which at times does not correlate with multiple other samples taken during that and a second test. Calculating an AUC could serve as an alternative or additional information in the diagnostic workup. When GH levels are borderline 7.5-10 higher rates of false negative tests are seen and AUC calculation may be of special benefit.

P2-P230

Evaluation of Spontaneous Nocturnal GH Secretion: Noe Versus Two Consecutive Nights

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Introduction: GH deficiency may be evaluated by spontaneous nocturnal GH secretion. Usually one night is examined. Since sleep may be disturbed by a new environment, a night to accustom is required by some investigators, which is questioned by others. Thus, we examined spontaneous nocturnal GH secretion during 2 consecutive nights.

Methods: 49 girls and 56 boys with suspicion of GH deficiency were examined between 10 pm and 8 am during 2 consecutive nights. Blood was taken every 20 min. via i.v. catheter, sleep was recorded by the study nurse and GH was determined by ECLIA.

Results: 26 Patients had reduced GH secretion in both nights, all of them had at least more than 6,5h continuous sleep. 29 had a reduced GH in one of the nights, 10 in the first and 19 in the second, so that no GH deficiency was noted. Sleep was slightly lower in the 1st than in the 2nd night (7,12h vs. 7,33h). The longest sleeping period was also higher in the 2nd night (6,21 vs 6,55h) Likewise, mean GH as well as peak GH concentration was higher in the 2nd night (4,45 vs 4,82 ng/ml and 15 vs 15,19 ng/ml). Statistically, there was a tendency towards longer sleep and higher GH secretion ($p< 0,1$) and a significant higher mean GH secretion in the 2nd night ($p <0,035$).

Discussion: Evaluation of GH deficiency via assessment of spontaneous GH secretion should comprise of 2 consecutive nights instead of one to avoid overestimation of GH deficiency.

P2-P231

Relationship Between Growth Velocity and Change of Serum Insulin-like Growth Factor-1 (IGF-1), Serum IGF Binding Protein-3 (IGFBP-3) Concentrations, and IGFBP-3 Promoter Polymorphism during Gonadotropin-Releasing Hormone Agonist (GnRHa) Treatment

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Purpose: This study aims to investigate the effect of GnRHa on GH-IGF-1 axis and to evaluate if -202 A/C IGFBP-3 promoter polymorphism affects the growth velocity during treatment on girls with central precocious puberty (CPP).

Methods: Data was collected from 97 girls, diagnosed under 9 year of age and treated by GnRHa for at least 1 year in Kangdong Sacred Heart Hospital between 2014-2015. Their body height, weight, Δ Height standard deviation score (SDS), serum IGF-1 and IGFBP-3 concentrations and bone age were measured at the start and after a year of GnRHa treatment. -202 A/C IGFBP-3 promoter polymorphism were analyzed. Possible correlations between the variables were calculated.

Results: During the treatment, height SDS, IGF-1 SDS, IGFBP-3 SDS and IGF-1/IGFBP-3 ratio significantly decreased. There were significant correlations between serum IGF-1 concentration and Δ Height SDS (r=0.405, *p*=0.000), and between serum IGFBP-3 concentration and Δ Height SDS (r=0.228, *p*=0.025). C allele had significant correlation with serum IGFBP-3 concentration (p=0.004) but had no significant correlation with Δ Height SDS (p=0.947). IGF-1 decreased in C allele group after the treatment (p=0.049), and IGFBP-3 decreased regardless of allele group after the treatment (AA p=0.012, AC&CC p=0.001).

Conclusion: The results suggest that the growth velocity during GnRHa treatment may be related to serum IGF-1 and IGFBP-3 concentrations thus GnRHa may affect GH-IGF-1 axis.

P2-P232

The Predictive Role of IGF-1 on Irradiation-Dependent Growth Hormone Deficiency (GHD) in Childhood Cancer Survivors (CCS)

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Background: Conflicting outcomes have been reported about the role of low IGF1 levels in predicting irradiation-dependent GHD in CCS. IGF1 <-2SD had a sensitivity between 28 and 47% in different studies, but these results were drawn from small samples of patients or from mixed cohorts including patients with GHD due to different aetiologies.

Objective: Our aim was to analyse the screening role of low IGF1 levels in CCS at risk of developing GHD (GH peak after stimulation test<7μg/L) after radiotherapy involving the hypothalamic-pituitary area (HPA).

Method: We performed a retrospective analysis on 158 survivors of childhood brain tumours or leukaemia started on GH replacement treatment between 2003 and 2017 in our centre.

Results: 141/158 patients received either cranial, craniospinal or total body irradiation (TBI), with or without surgery and/or chemotherapy. To describe the specific detrimental role of irradiation on GH secretion, we identified 117 irradiated patients diagnosed with tumours not directly involving the HPA and who did not undergo surgery in the HPA. In this group, IGF1 levels <-2SD had a sensitivity of 31.9%. However, in 27/117 patients with severe childhood GHD (GH peak <3μg/L), IGF1 levels <-2SD were statistically more frequent (p-value 0.0023) and had a higher sensitivity (45.6%). Among 14/117 leukaemic patients exposed to TBI without cranial boost, IGF1 <-2SD had a sensitivity of 7.1%, statistically lower than subjects with brain tumours treated with higher radiation doses. 38/117 patients underwent a reassessment of GH status at final height, and GH peak <3μg/L was statistically more frequent both in patients with IGF1 <-2SD at diagnosis of childhood GHD (p-value: 0.0026) and in subjects with IGF1 <-2SD at final height (p-value=0.006). IGF1 <-2SD at final height had a sensitivity of 35.0% and a specificity of 100% in patients with a GH peak <3μg/L. Finally, pre-treatment IGF1 values showed a weak but statistically significant negative correlation with the outcome of GH replacement therapy expressed as Δheight SDS between final height and height at diagnosis (Spearmann's rho: -0.31, p-value: 0.041) but no correlation with the number of pituitary hormones in those with multiple pituitary deficiencies.

Conclusions: Our study confirmed that IGF1<-2SD has a low sensitivity at predicting irradiation-induced GH deficiency. Lower IGF1 levels in childhood are associated with more severe GHD both at childhood and adulthood assessment and correlate with a better response to GH treatment at final height.

P2-P233

Effects of zinc, Magnesium and Vitamin B6 (ZMA) Supplementation on Serum IGF-I, IGFBP-3 and Testosterone Concentrations in Young Athletes

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Background: The GH-IGF system plays an important role in strength gain. Some studies suggest that Zinc, Magnesium and Pyridoxine (ZMA) supplementation could increase GH/IGF and testosterone levels in young subjects. This hypothetical increase could lead to significant changes in body composition. ZMA is a very popular supplement, easily found in specialty stores, and it is presumed to increase GH, IGF-I and testosterone levels. However, studies are divergent regarding its efficacy.

Aim: The present study aimed to verify the effects of physical training associated with 8-week ZMA supplementation on the IGF-I, IGFBP-3 and testosterone levels in young males.

Methods: Eighteen healthy male amateur American football players aged 18 to 25 years with at least 1 year experience in this sport modality were included in the study and followed during 8 weeks of training. The training consisted of a 90 min-conditioning session based on strength and aerobic exercises twice a week and specific tactic training also twice a week in different days. Energy intake and diet composition were determined by nutritionist. It was a double-blind study and the subjects were divided into two groups: ZMA and placebo groups according to the supplementation received. Anthropometric evaluation and blood sampling, for serum IGF-I, IGFBP-3 and testosterone determination, were performed at two different moments: at the beginning (M1) and after 8 weeks of supplementation (M2).

Results: Serum IGF-I and IGFBP-3 concentrations were higher at M2 in both groups. The increase was similar in the ZMA and in the placebo group. Testosterone concentrations were also higher at M2 than at M1 in a similar degree in both groups. The changes

in anthropometric parameters that indicate lean mass gain or body fat mass reduction were similar in both groups.

Conclusion: The findings suggest that extra doses of the micronutrients present in the ZMA do not bring any additional benefits, either in the body composition or in the hormonal levels in subjects under adequate diet. Testosterone increase could partially explain the change in IGF-I and IGFBP-3.

P2-P234

High Protein Nutritional Supplementation Increases Serum IGF-I Concentrations in Short Children with Low IGF-I

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Background: Milk supplementation increases serum IGF-I concentrations in healthy children and the effect is attributed to elevation of insulin and/or direct effects of milk proteins. Low serum IGF-I concentrations are common among children with short stature and may be associated with GH deficiency but poor nutrition/malabsorption may also contribute. Effects of nutritional supplementation on serum IGF-I is poorly studied in short children.

Aim: To investigate whether 7 days high protein nutritional supplementation increases serum IGF-I levels in short prepubertal children with low IGF-I and whether an increase is more pronounced in children with nutritional deficiency.

Methods: Short (height SDS < - 2 SDS), prepubertal 3-13 year-old children with serum IGF-I concentrations < - 1 SDS were given a milk based protein supplementation of 18g/10 kg body weight and day during 7 days. Food consumption was assessed (3-day food record) and IGF-I and other hormones were measured at baseline and at the end of the intervention.

Results: 14 of 17 patients finished the 7 days intervention. Protein intake increased from 2.97 ± 0.58 to 4.45 ± 0.68 g/kgxday (P< 0.001) while fat energy percentage decreased (p=0.005). Intake of total or weight based energy and carbohydrate energy percentage were unchanged. Children increased their mean body weight by 0.39 ± 0.29 kg (P<0.001) and mean BMI SDS increased from -0.94 ± 0.74 to -0.70 ± 0.76 (P<0.001). Gender and age corrected serum IGF-I concentrations increased from -1.16 ± 0.3 SDS to -0.86 ± 0.49 SDS (P=0.015) corresponding to an increase of 11.1 ± 14.7 % (P=0.017). Insulin release was increased as suggested by suppression of SHBG (160 ± 23.2 versus 136 ± 35.4; P<0.008). Serum IGFBP-3 concentrations did not change (0.39 ± 0,94 versus 0.26 ± 0.76 SDS, P = 0.37). Markers of nutritional state at baseline or changes during the intervention (weight SDS, BMI SDS, 3-day energy or protein intake and IGF-I/IGFBP-3 ratio) did not correlate. Neither did these variables correlate with IGF-I changes apart from weight SDS at baseline that tended to correlate (r=-0.51, p=0.063).

Conclusion: Protein intake is important for serum IGF-I concentrations even in short children with low IGF-I and may have a therapeutic potential by affecting height long term. The short term IGF-I response to a high protein nutritional supplementation may be of clinical relevance as a marker of nutritional deficiency while other commonly used nutritional markers did not correlate.

P2-P235

Hormonal Predictors of Growth Hormone Therapy Effectiveness in Children with Short Stature – Evidence from Neural Prediction Model for Final Height

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Prediction of growth hormone (GH) therapy effectiveness in children with short stature is an important issue for optimizing its course. Recently, our research group has published prediction models derived with neural networks. The main predictors of final height (FH) in our model were: patient's height SDS at therapy onset, pre-treatment change of height SDS (HSDS V_0) and pre-treatment IGF-I and IGFBP-3 secretion but not the results of GH stimulation tests; the increases of IGF-I and IGFBP-3 concentrations in 1st year GH therapy were also significant variables.

The aim of present study is to analyze the influence of IGF-I and IGFBP-3 secretion before and during GH therapy on FH in children with wide range of GH secretion.

Analysis comprised 133 children (89 boys) with short stature (GH deficiency or idiopathic short stature), treated with GH up to FH. In all children 20 auxological and hormonal parameters was assessed before treatment, in 1st year of therapy and at FH (for details see: Smyczynska U et al. doi.org/10.1530/EC-17-0277). According to their FH, the patients were classified into 3 groups: below 3 centile (<3c), between 3 and 10 centile (3-10c) and over 10 centile (>10c). In all the patients concentrations of IGF-I and IGFBP-3 were measured before treatment and in 1st year of therapy. The index of difference between IGF-I SDS increase and IGFBP-3 SDS increase in 1st year of treatment (DIGF difference) was calculated.

At therapy onset IGF-I SDS was higher in <3c group (-1.55±1.07) and 3-10c group (-1.60±1.10) than in >10c group (-2.10±1.09), while IGFBP-3 SDS was lower in <3c group (-0.67±0.72) than in groups 3-10c (-0.37±0.96) and >10c (-0.40±1.04). In 1st year of treatment there were no significant difference in both IGF-I SDS and IGFBP-3 SDS between all the groups. The increase of IGF-I SDS was significantly (p<0.05) higher in group >10c (2.72±0.94) than in groups <3c (2.18±0.97) and 3-10c (2.13±0.92), similarly ΔIGF difference was significantly higher in >10c (1.87±1.18) than in both <3c (1.15±0.63) and 3-10c (1.27±0.82).

Pre-treatment IGF-I and IGFBP-3 secretion and their increase during the initial phase of GH therapy are important predictors of the attained FH. Neural models are useful for the identification of variables that should be subjected to further analysis.

P2-P236

Artificial Neural Networks for Prediction Final Height in Children with Growth Hormone Deficiency

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Background: Mathematical models predicting final height (FH) and its standard deviation score (SDS) in children with growth hormone deficiency is an important tool for clinicians to manage treatment process. Previously developed models do not have enough accuracy or are not good enough for practical use.

Objective and hypotheses: We used 4 binary and 7 continuous predictors available at the time of diagnosis and start of therapy and developed multiple linear regression (MLR) models and artificial neural networks (ANN).

Method: The sample included 121 patients of Endocrinology Research Center (Moscow, Russia) who were under observation in 1978-2016 and reached the final height. All patients were treated by rhGH in daily dose of 0,033 mg/kg at least for 3 years. The input variables obtained at therapy onset include 4 binary and 7 continuous.

FH SDS was calculated using Auxology software.

Statistica software v.13 (StatSoft, Inc., USA) was used for statistical analysis and ANN development. Different topologies were tested including linear and Bayesian networks, radial basis functions and 3- and 4-layer perceptrons. RMSE and explained variance R^2 (%) were the main characteristics of models' quality.

Results: MLR models had poor quality. The best ANN predicting FH has RMSE 4.41 cm and explains 75.9% of variance, and 11 predictors are used. The best ANN for predicting FH SDS explains 42.4% of variance and has RMSE 0.601 SDS, and 11 predictors are used. It seems promising to increase the sample and improve the ANN models.

Conclusions: ANN demonstrated to be the efficient approach to mathematical modeling for clinical purposes.

The ability to predict the individual effectiveness of growth hormone replacement therapy is of great importance. Based on patient's features the endocrinologists are able to manage regime and drug doses. The models provide personalized approach to treatment of patients with GH-deficiency. ANN allows making dose of rhGH and regimen of injection individually adjusted and contribute to improved overall outcomes. ANN can also be useful for evaluating effectiveness of the therapy in patient subgroups and for demonstrating factors determining FH. Prediction models may also reduce the drug costs for GH treatment.

P2-P237

Predictors of Poor Response to Growth Hormone Therapy in Children with Short Stature – Evidence from Neural Prediction Model for Final Height

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Prediction of poor response to growth hormone (GH) therapy in children with short stature is an important issue for personalized approach to treatment. Recently, our research group has published prediction models derived with neural networks. The main predictors of final height (FH) in our model were: patient's height SDS at therapy onset (H_0SDS) and pre-treatment IGF-I and IGFBP-3 concentrations but not the results of GH stimulation tests; pre-treatment growth rate was also a significant variable.

The aim of present study is to analyze the main predictors of poor and good growth response to GH therapy in children with wide range of GH secretion.

Analysis comprised 133 children (89 boys, 44 girls) with short stature, 101 with GH deficiency (GHD) and 32 with idiopathic short stature (ISS), treated with GH up to FH. In all children 20 auxological and hormonal parameters were assessed before treatment, in 1st year of therapy and at FH (for details see: Smyczynska U et al. doi.org/10.1530/EC-17-0277). According to the increase of FH SDS with respect to H_0SDS below or over 1.0 SD, the patients were classified as poor and good responders, respectively. As all but one poor responders were GH-deficient, further comparison between GHD and ISS was performed only for good responders.

Both groups had similar H_0SDS but in poor responders it was significantly higher than in good responders (-1.29±0.79 vs. -1.75±0.78, p=0.03) while corrected by target height (TH) SDS; pre-treatment growth rate (HSDS V_0) was significantly better in poor than in good responders (-0.09±0.20 vs. -0.25±0.21, p=0.002). Poor responders had insignificantly higher IGF-I SDS than good responders before treatment (-1.17±0.96 vs. -2.07±1.07, p=0.06) and in 1st year of therapy (1.04±0.93 vs. 0.52±1.12), however IGF-I increase was lower in poor than in good responders (2.21±0.95 vs. 2.59±0.97). There were no similar differences for IGFBP-3. The only significant difference between GHD and ISS was that in GH secretion.

More severe deficit of height with respect to TH, decrease of height SDS before treatment and more severe IGF-I deficiency were the main predictors of good response to GH therapy, with no difference between GHD and ISS. In poor responders decreased IGF-I sensitivity should be taken into account. Neural models are useful for identification of variables that should be subjected to further analysis.

P2-P238

Growth Hormone Therapy and its Challenges in GH deficient Cases in a Multinational Population-a Sneak-Peek

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Objectives: To identify growth hormone deficiency (GHD) in cases referred for short stature in a multi-national population and evaluate the acceptance, adherence and side effects of GH therapy in these GH deficient cases.

Materials and methods: Retrospective analysis was done on all the cases referred for short stature to Pediatric endocrine facility of our hospital from January 2016 to January 2017. GHD was diagnosed on the basis of a GH response <10 μg/L documented by 2 GH provocation tests (clonidine followed by glucagon) in suspected GHD cases. The patient was started on GH treatment after detailed counseling at initial dose of 25 - 35 μg/kg/day. Patients were monitored 3 to 6 monthly and also evaluated for adherence. The determination of the growth response to GH therapy was considered the most important parameter for response. Regular IGF-1, glucose metabolic parameters, thyroid and adrenal functions monitoring was done.

Results: Out of total 356 cases worked up for short stature,68 underwent GH stimulation test. 37 were identified as GH deficient. 26 had Isolated GH deficiency and 11 had Multiple Pituitary hormone defects MPHD(most common-Thyroid followed by hypogonadism & adrenal). The age range was 2.9 years to 15.1 years with a mean age of10.6 years. 27 were males & 10 were females. Maximum number of cases were Emiratis-9 followed by Indians-7, Pakistanis-6, Jordan-4, Egypt-3 & the rest were other nationalities. Average peak GH levels post stimulation was 5.6 ng/ ml (range 1.2 to 9.5ng/ml). MRI Pituitary was reported as normal in 22, small size for age in 10, Pituitary microadenoma in 3 & as empty sella in 2 cases. Out of 33 patients (89%) started on GH therapy, 22(66%) were good responders whereas 7 responded poorly (21%) and response could not be assessed in 4(12%). Factors affecting response were age, pubertal status and adherence. Reduced insulin sensitivity (6) was the most common side effect followed by hyperlipidemia (2) & blurring of vision (1). 7 patients (24%) unmasked their thyroid and adrenal insufficiency during course of therapy.

Conclusion: Acceptance and adherence of long term GH treatment needs proper motivation and counseling particularly in multi-cultural milieu. Close monitoring and constant support system is vital for success of GH therapy.

GH & IGFs P3

P3-P192

Good Growth Response to Growth Hormone Therapy in Short Children with Normal Growth Hormone Secretion

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The availability of biosynthetic growth hormone (GH) ensures that children who are deficient can have replacement therapy, but it also has created the opportunity to treat children who are short but do not have a deficiency. Non-GH deficient short stature, without treatment, the height outcomes in most studies have failed to reach mid-parental target height. GH therapy resulted in mixed height outcomes; some reached genetic target height whereas others failed.

The aim of this study was to report the outcome of the included cases with initial height below - 2 SD score, normal stimulated GH levels (>10 μg/L), and treatment with biosynthetic GH for at least one year.

That was retrospective study included patients with the inclusion criteria for one year attending pediatric endocrine clinic in Sidra Medicine, Doha,Qatar from January 2017 till January 2018.

Results showed twenty children, 15 males and 5 females aged 4.3 to 13.8 years with mean peak GH of 15.58 ± 6.95 μg/L received GH for duration of 2.49 ± 1.61 years with the average GH dose 0.04 mg/kg/day. The mean Mid Parental Height Standard Deviation Score (MPHSDS) was - 1.23 ± 0.57 SD.

The pubertal stage at presentation was 15 Tanner 1 and 3 Tanner 2 and 2 at tanner 3 increased average 1.3 in 2.5 years. There was no bone age delay with bone age difference of - 0.13±0.67 years. The mean HSDS at start of treatment was -2.33 ±0.41 and after one

Table 1. (for Abstract no P3-P192)

	Start of treatment	On lat visit	Differences
Age in years			
Mean	9.88	12.36*	2.49
SD	2.62	2.27	1.61
IGF-I ug/L			
Mean	143.4	407.1*	263.7
SD	57.4	162.4	105
HtSDS			
Mean	–2.34	–1.57*	0.77
SD	0.41	0.55	0.14
Pubertal stage			
Mean	1.35	2.7*	1.35
SD	0.65	1.35	0.7

* $p < 0.05$

year of treatment was -1.83 ±0.48 with 0.5 SD change and at the last visit was -1.56 ±0.54 with 0.75 SD change. The average deviation from MPHSDS was -1.08 SD at start versus -0.3 SD at the last visit. IGF-1 levels SD changed from -0.9 ± 0.6 to be 0.1 ± 0.2 SD. The increment in HSDS was positively correlated with the increment in IGF-1 levels (P = 0.018 and r = 0.6).

Conclusion: Growth hormone therapy benefits short children with normal growth hormone secretion achieve normal HSDS and approach MPHSDS. The IGF-1 increment correlates with the HSDS increment.

P3-P193

Growth Hormone Deficiency in Two Children with Williams-Beuren Syndrome. The Long-Term Response to Growth Hormone (GH) Therapy

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Background: Pre- and postnatal growth retardation of unknown pathogenesis is a common clinical feature in patients with Williams-Beuren syndrome (WBS). However, growth hormone deficiency (GHD) has not been considered a major cause of growth retardation.

Case reports: We report 2 female patients with confirmed WBS who had defective GH secretion in response to two provocative tests and low IGF-I level and their growth response to GH therapy for 9 years. The first patient was investigated at the age of 7 years with HtSDS = -3, BMISDS = 0.8 and bone age = 7 years, Peak GH response to 2 provocative tests (Clonidine and glucagon) was 6.5 and 5.9 ng/dl respectively, IGFSDS = -2.2. She was started on HGH 0.05 mg/kg daily for 9 years with a significant increase in IGF-I. She attained normal pubertal development and pubertal growth spurt. Her final adult height = 155 cm (HtSDS= -2) and weight = 52 kg. The second female patient had undergone surgical repair for supra-valvular aortic stenosis at 6 months of age. She was investigated at the age of 5 years because of her HtSDS = -2.8, BMI = 10 kg/m2 and IGF-ISDS = -2.7 and bone age = 5 years. She underwent two provocative tests which showed subnormal peak GH response (5.6 and 7 ng/dl). She was started on GH 0.05 mg/kg daily with good increment in IGF-I. At the age of 11 years she started her pubertal development and at the age of 12 years her height = 135.5 cm (HtSDS = -2) and BMI = 12 kg/m2 and her bone age = 12 years.

Discussion: The growth pattern of children with WBS is characterized by prenatal growth deficiency, failure to thrive in infancy (70%), poor weight gain and linear growth in the first four years; a rate of linear growth that is 75% of normal in childhood; and a brief pubertal growth spurt. The mean adult height is below the third centile. These two patients with defective GH-IGF-I axis showed a good response to long-term GH therapy with a stature gain = 1 SD and normal pubertal growth spurt. The pathogenesis of GHD in our patient is unclear.

Conclusion: GH deficiency might contribute to the growth failure in some patients with WBS and in such cases, HGH therapy will most likely improve final height.

P3-P194

Growth Hormone Treatment: Does Timing Matter?

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Introduction: Treatment with recombinant growth hormone (rGH) is safe and has greatly improved the approach of children and adolescents with growth hormone deficiency (GHD) and other growth disorders. Some studies show that most of the height gain associated with GH treatment occurs in prepubertal years. The aim of our study was to evaluate the effect of age at start of the treatment on final height in children with isolated or GHD in a Portuguese cohort.

Methods/design: We performed a retrospective and comparative study of 92 patients who completed treatment with rGH. The parameters evaluated included sex, diagnosis, mid-parental height (MPH), height at the beginning and end of treatment and duration of treatment during pre-puberty/early puberty. Girls with <10 years and boys with <11 years (group 1; n= 50 patients) were compared to girls with ≥ 10 years and boys with ≥11 (group 2, n= 42 patients). Statistical analysis was performed using paired and independent t-test samples; results are presented as mean±SD.

Results: Most patients had isolated GHD (n=66; 72%) and were male (n=60; 65%). Mean age at the start of treatment was 9.8±3.5 years and mean duration of treatment was 6.2±3.9 years (group 1 - 9.3±3.9 *vs* group 2 - 3.69.3±1.4; p<0.001). Patients in group 1 had more pre-pubertal years of treatment (6.2±3.1 *vs* 0.97±0.4 years; p<0.001).

At the start of treatment, mean height standard deviation score (HSDS) was higher in group 1 [-2.7 ±1.7 SDS *versus* -2.9 ±0.8 SDS); p<0.001]. Final HSDS was also greater in group 1 (-1±1.2 SDS *vs* -1.5±0.7 SDS; p=0.001], as was DHSDS (+2.1±1.7 SDS *vs* +1.38±0.8 SDS; p=0.015). The majority of patients attained MPH, although there was a non-statistically difference between the two groups (-1.1±9cm in group 1 *vs* -5.6±7cm in group 2). Eighty percent of patients achieved a final height between -2 and +2 SDS.

Discussion: Our results show that in this cohort of treated Portuguese children with GHD, younger age at the start of treatment was associated with improved final height and underscores the need for early diagnosis and therapy.

P3-P195

Support for Patients Treated with Growth Hormone to Reach their Growth Potential: Addressing Adherence Barriers Through Personalised Behavioural Patient-support Programmes

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Background: Recombinant human growth hormone (r-hGH) treatment can optimise growth potential; however, optimum outcomes are not always achieved owing to several reasons, including poor adherence. This analysis sought to operationalize psychosocial drivers of non-adherence in GH patients, using the three-component, evidence-based capability, opportunity and motivation behavioural framework (COM-b). The framework allows for matching of specific interventions to help modify behaviours, and the interaction between the components can help to explain why patients do not engage with a recommended behavioural change. This evidence-based approach may enhance patient-support programmes (PSPs) for people treated with Saizen® who monitor their treatment with the easypod Connect platform.

Methods: A narrative review of the literature was conducted to determine drivers of non-adherence in people prescribed r-hGH treatment. Six overarching drivers were identified that could potentially be modified through behavioural intervention in both the patient and caregiver populations, as appropriate: disease and treatment coherence; emotional burden; treatment-related anxiety; self-administration; teenage years; and transition to adult/self-care. The drivers were then mapped across the disease and treatment journey to determine when support needs may fluctuate. These insights were used to guide recommendations to enhance the PSPs to provide content and techniques that will facilitate adherence and support overall disease management, delivered directly to patients and caregivers.

Support design recommendations: Three high-level support recommendations were made:

1. A personalisation questionnaire to identify individual needs and tailor support for each person.
2. Tailored reminder and support messaging delivered electronically, prioritised by behavioural topic (e.g. emotional burden).
3. PSP-nurse-coaching modules, focussed on core behavioural drivers and including evidence-based behaviour-change techniques.

Current stage of work: The personalisation questionnaire, tailored reminder and support messages, and nurse-coaching modules will be implemented within the Saizen PSP program. This program already includes other eHealth solutions, such as the growlink app, the easypod Connect platform and program-nurse support services.

P3-P196

Main Discrepancies Between Predicted and Observed Growth Responses with iGRO in Children Treated with GHr in Spain

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Introduction: Growth prediction algorithms (i.e. iGRO), provide an estimate of a patients´ likely growth in the first year, and subsequent years, of GH treatment at a given dose, taking into account the patient´s combination of physical characteristics. Comparing a patient´s actual growth with their predicted growth after the first year of GH treatment, it is possible to determine whether the patient is responding to GH as expected (Index of responsiveness; IoR) and hence any appropriate action may be taken.

Objective: The aim of this study is to analyze the frequency and type of discrepancies between predicted and observed growth responses with IGRO in children treated with GH in Spain during the first year of treatment.

Methods: Cross-sectional descriptive study including prepubertal patients (children with growth hormone deficiency (GHD), Turner Syndrome or Small for gestational age (SGA) patients) who started GH treatment between 2011 and 2016 and received the treatment during 12 months. Eighty patients data were analyzed.

Results: 80 patients have been included in the study. 59.2% were SGA, 32% had GHD and 8.6% had Turner Syndrome. 86.5% of patients had an IoR above -1.28 SDS (ranging between -1.25 to 3.81 SDS), reason why they were considered good responders at standard doses of GH. The eleven patients who did not respond (IoR range between -4.00 and-1.35 SDS) were all compliant except one (less than a dose missed per week). Nine had other concomitant pathologies (CNS tumor in full remission, a midline malformation, Steinert´s dystrophy, two patients had malnutrition and three patients had pituitary hypoplasia associated to other pituitary deficits). The suboptimal response of the remainder patient could be related to the administration of an infraterapeutical dose.

Conclusions: Variations in responsiveness to GH may be influenced by multiple factors such as inappropriate diagnosis, the presence of other systemic disorders, and lack of compliance with treatment or impaired sensitivity to GH. The discrepancies between predicted height by iGRO and observed growth after a year of GH treatment were low in our series.

P3-P197

Adherence and Long-Term Outcomes of Therapy in Pediatric Subjects in Greece using Easypod™ Electromechanical Device for Growth Hormone Treatment: The Phase IV Multicentre Easypod™ Connect Observational Study (ECOS)

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The Easypod™ Connect Observational Study (ECOS) was the first global study of easypod™, currently the only electronic injection device for recombinant human growth hormone (r-hGH; Saizen®). ECOS reported accurate and robust real-time adherence data in a large cohort of patients. In this analysis, we assess the adherence of r-hGH administered via easypod™ in a cohort of Greek patients from ECOS (EMR200104-520, NCT01363674).

Patients aged 2-18 years, treated with r-hGH administered via easypod™ for ≥6 months and ≤3 years, with a documented start date, and no gaps in the injection data for >1 week, were included. The primary objective was to assess the level of adherence in patients receiving r-hGH via easypod™ (proportion of days with injection received/days with injections planned; adherence was defined as ≥85%). Growth outcomes (change in height, change in height standard deviation score [SDS], height velocity and height velocity SDS), correlation between adherence and growth outcomes (Spearman product moment), and the impact of adherence on IGF-I concentrations, were assessed as secondary objectives. Adherence data were downloaded from the easypod™ device; demographic, auxological and diagnostic data were taken from medical notes. All analyses were descriptive.

Overall, 180 patients were enrolled and 88 were included in the complete analysis set; 78 with growth hormone deficiency, 4 small for gestational age, 3 with Turner syndrome and 3 with no diagnosis (median age was 11 years, 37.5% were female and 62.5% were male), 82 patients were GH-naïve. After 1 year of treatment, median adherence was 95.5% (N=84). When analyzed over 6-month intervals, median adherence remained at approximately 90% for up to 48 months although there was no correlation between adherence and growth outcomes at 1 year. A median increase in height of 7.25cm was reported after 1 year of treatment. The majority of patients had normal IGF-I concentrations (55 of 62 patients [88.7%]); 4 (6.5%) had abnormally low concentrations and 3 (4.8%) had abnormally high concentrations. Similar adherence levels and growth outcomes were observed in GH-naïve patients. Of the eight serious adverse events reported, six were considered unrelated to the study drug. No new safety findings were identified.

Treatment with r-hGH administered via easypod™ led to high adherence rates in this representative population, in agreement with the results from the global analyses of ECOS. Treatment efficacy and normalization of IGF-I concentrations were noted after 1 year. Correlation could not be detected as adherence was high with low variance.

P3-P198

Growth Hormone Deficiency in Neurofibromatosis: Report of Four Cases

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Introduction: Short stature is frequently associated to neurofibromatosis (NF). In these patients this condition is often caused by growth hormone (GH) deficiency. We describe four boys affected by NF type 1 and GH deficiency treated with GH replacement therapy.

Case Report: GH deficiency was diagnosed in four patients with NF type 1, who were referred to our Pediatric Endocrinology Unit for short stature.

Patient 1 started GH replacement therapy at the CA of 11.3 years, height was -2.5 SDS, target height (TH) -1.5 SD. Tanner stage 1, bone age (BA) 8.5 years. After 1 year on GH replacement therapy, height improved to -1.9 SD, Tanner stage 2, BA 9.5 years. After 2 years height was -1.7 SDS, Tanner stage 3, BA 12.5 years. The brain MRI didn't show any variations during follow-up.

Patient 2 started GH replacement therapy at the CA of 11 years. He was prepubertal, height was -2.3 SDS, target height -0.8 SDS, BA 10 years. During the first 6 months on GH treatment growth rate improved from 4 cm/years to 6 cm/years, even thought calculated over a period of only 6 months. No adverse events were reported.

Patient 3 started replacement therapy at the CA of 9.5 years. He was prepubertal, height was -2.7 SDS, TH -1.2 SDS and BA 7.5 yrs. After three months on GH treatment height increased from -2.7 SDS to -2.5 SDS.

Patient 4 started GH replacement therapy at the CA of 8.8 years, height was -2.2 SDS, TH -1.1 SDS, BA 7 yrs. After three months on GH replacement therapy height increased from -2.2 SDS to -2.0 SDS.

Conclusions: Evaluation of GH secretion in children with NF-1 and short stature, in the absence of other identifiable causes of short stature, is necessary because GH therapy may significantly improve their growth rate. GH therapy has proven to be safe in NF patients and it is not associated with increased risk of malignancy.

P3-P199

Extremely Low Body Mass Index Negatively Impact the Response to Growth Hormone Treatment in Children with Growth Hormone Deficiency

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Introduction: The nutritional status of a child is essential for the overall development and in particular for the statural growth. It was previously reported that growth hormone (GH) administration in children with growth hormone deficiency (GHD) could have a beneficial effect on body mass index (BMI) in both underweight and overweight children, suggesting a complex interplay between nutrition and growth.

Therefore, the aim of the study was to analyze the influence of BMI on the response to GH treatment in children with GHD and the evolution of BMI under treatment.

Material and methods: We performed a retrospective study which included 154 children with GHD (69,5% boys, 30.5% girls) with a mean age at diagnosis of 8.39±3.6 years, treated for 3.16 years with GH. Standard deviation score (SDS) for BMI was calculated at 6, 12, 24 months of treatment and at the last evaluation. Patients were divided in groups according to SDS for BMI: ≤ -2SD (group 1, n=27) and > -2SD (group 2, n=127). Statural growth was evaluated by SDS for height and gain in height SDS. Comparisons between groups were performed by Mann-Whitney-U test. Evolution of BMI SDS during treatment was analyzed with paired student t-test.

Results: at the beginning of the treatment the mean height SDS was -3.14 SD and mean BMI was -1.06 SD. Patients in group 1 had significantly lower gain in height SDS at 6 (p=0.002), 12 (p=0.002) and 24 months (p=0.027) in comparison to children in group 2. Also, at the final evaluation the mean gain in height SDS/year of treatment was lower in group 1 (p=0.011). We also noticed that BMI SDS gradually improved during the treatment period (- 1.33 SD at the start of treatment, - 1.27 SD at 6 months, -1.15 at 12 months, -0.89 at 24 months, -0.41 SD at the final evaluation, p<0.05 versus baseline).

In conclusion, our study showed that extremely low BMI can negatively impact the response to GH treatment in children with GHD. However, GH administration was associated with a gradual improvement in BMI SDS during treatment.

P3-P200

Small for Gestational Age (SGA) Patients with Premature Treatment Discontinuation: Their Journey in French Real-life Settings

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Objective: Premature GH treatment discontinuation of SGA is usually linked to safety or ineffectiveness. However, this population is poorly addressed compared to those with final adult height (FAH). Authors investigated the journey of SGA prematurely discontinued Norditropin® treatment in a French real-life.

Methods: Observational prospective ongoing study: 291 Norditropin®-treated SGA. Annual FU up to FAH. Descriptive analyses made on the criteria addressed and compared prematurely discontinued with the study completers: target height, age at treatment initiation, GH dose at inclusion, treatment duration, % of patients discontinued temporarily minimum once, Δ height between inclusion and treatment stop, height at last visit, % of patients >-2 SDS, last GH dose, age at last visit.

Results: 90 patients reached FAH, including 51 naïve (56.6%); 69 (23.71%) discontinued prematurely, including 37 naïve (53.6%); 23 lost to FU; 109 ongoing.

Significant difference was observed for the following mean values in prematurely discontinued versus completers, respectively (years):

- Age at treatment initiation: 8.9 [8.0; 9.7] vs. 9.5 [5.4 ; 11.2] (p=0.0579)
- Age at last visit: 13.1 [9.3; 15.2] vs 15.4 [14.4; 16.4] (p=<0.0001)
- Treatment duration: 3.0 [2.1; 3.9] vs 4.8 [3.7; 6.2]. (p=<0.0001)

First year of FU the Δ height of prematurely discontinued was comparable with completers. Second year growth slows considerably and continues to decline. Fourth year 42% continue treatment versus 83% among study completers.

Height at last visit was -1.6 [-2.2; -1.1] for study completers and -1.8 [-2.4; -1.3] for prematurely discontinued (p=0.1252).

The most common reason for premature treatment discontinuation was related to adverse event or questioning on safety of GH treatment for 13 patients, poor adherence and treatment fatigue concerned 11 patients, 8 subjects were satisfied with obtained stature.

Table 1. Height gain SDS between each visit, mean values (for Abstract no P3-P200)

FU	Inclusion-V2	V1-V2	V2-V3	V3-V4
Completers N=90	0.50 [0.38; 0.61] (N=86)	0.27 [0.21; 0.34] (N=87)	0.15 [0.08; 0.22] (N=84)	0.03 [-0.02; 0.09] (N=75)
Premature discontinuation N=69	0.40 [0.32; 0.48] (N=59)	0.17 [0.08; 0.25] (N=63)	0.07 [-0.01; 0.16] (N=52)	0.00 [-0.09; 0.10] (N=29)

One year between two visits.

Conclusion: French real-life data show that around one fifth of SGA patients treated with GH stopped treatment prematurely at a median the third year with the main reasons being safety issues, poor adherence and satisfaction of obtained height. An increased understanding of reasons for premature treatment discontinuation is needed. The link between first year height gain and good long-term statural response should be investigated further.

P3-P201

Effects on Near-Adult Height and Safety of Recombinant Human Growth Hormone in Growth Hormone Deficiency and Turner Syndrome patients: results from the LG Growth Study

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Objectives: This study was performed to evaluate effectiveness on near-adult height (NAH) and safety of recombinant human growth hormone (rhGH) (Eutropin® Inj., Eutropin®Plus Inj., Eutropin®AQ Inj., LG Chem, Ltd.) treatment in children with growth hormone deficiency (GHD) and Turner syndrome (TS).

Methods: The LG Growth Study (LGS) is a multicenter, long-term, observational study designed to evaluate the long-term effectiveness and safety of rhGH treatment (NCT01604395). The data on NAH (height at ≥18 years of age, or height velocity <2 cm/year at ≥16 years for boys or ≥15 years for girls) and safety of rhGH were analyzed.

Results: This study included 51 GHD patients and 57 TS patients. At the start of treatment, the mean age of the patients with GHD and TS was 12.2 ± 3.0 and 10.8 ± 3.2 years, respectively. Bone age (BA) of GHD and TS was 10.5 ± 3.1 and 9.7 ± 2.8 years, respectively. The median initial rhGH dose was 0.2 and 0.3 mg/kg/week, respectively. The mean baseline height SDS (HtSDS) for GHD and TS patients was -2.80 ± 1.45 and -3.51 ± 0.84, respectively. The midparental height (MPH) SDS was -1.09 ± 0.88 and -0.56 ± 0.83, and a difference between baseline HtSDS and MPH SDS was -1.97 ± 1.32 (95% CI: -2.44 to -1.51) and -2.86 ± 0.95 (95% CI: -3.17 to -2.55), respectively. The mean age at the measurement of NAH for GHD and TS patients was 18.4 ± 2.6 and 17.6 ± 1.6 years, respectively. Duration of treatment was 4.9 ± 2.7 and 5.3 ± 2.5 years, respectively. There was no change of dose during the treatment period. The mean HtSDS for GHD and TS patients was -1.29 ± 1.62 and -2.36 ± 0.92 at NAH, and a difference between NAH SDS and MPH SDS were -0.22 ± 1.03 (95% CI: -0.56 to 0.11) and -1.72 ± 0.80 (95% CI: -1.96 to -1.49), respectively. Adverse events (AEs) were reported in 20 GHD patients (39.2%) and 28 TS patients (49.1%). The most common AEs were upper respiratory tract infection (9.3%) and headache (7.4%). Serious adverse drug reactions Craniopharyngioma was recurred in two patients with GHD (3.9%) during rhGH treatment.

Conclusions: In this study, rhGH treatment increased the HtSDS and reduced the gap between HtSDS and MPH SDS at NAH in both patients with GHD and TS.

P3-P202

Final Adult Height After Growth Hormone Treatment in Patients with Turner Syndrome

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This study aimed to evaluate final adult height after recombinant growth hormone (GH) treatment in girls with Turner syndrome (TS) and elucidate the contributing factors to growth response. (Seventy-four patients with Turner syndrome who were treated with GH and reached adult height and 18 patients without treatment were enrolled in this study. To determine final height gain, we assessed the difference between the final height standard deviation score (SDS) and height SDS at the initiation of treatment. In addition, the difference between the final height and predicted adult height at the initiation of treatment was assessed. GH therapy was initiated at a mean age of 8.91±3.71 years in TS patients. The mean duration of GH therapy was 6.42±3.03 years. The mean height at the initiation of treatment was 116.54±16.66 cm, and height SDS was -3.73±1.48. Patients who underwent GH treatment reached an adult height of 152.08±4.67 cm, and final height SDS was -1.96±1.50. The difference between final adult height and predicted adult height was 6.20 ± 1.20 cm. Final height SDS was found to have a significantly positive correlation with height SDS at the initiation of treatment (P<0.001) and mid-parental height SDS (P<0.001). In addition, the final height was influenced by confounding variables including the duration of GH therapy, chronological age at the initiation of treatment and karyotype. Height SDS gain was found to have a significantly positive correlation with height SDS at the initiation of treatment (P<0.001), chronological age at the initiation of treatment (P<0.007) and the duration of GH therapy (P<0.015). Our findings demonstrate that GH therapy seems effective in improving final height SDS and height SDS gain in TS patients, and that early intervention of GH administration in patients with TS seems to be necessary for final height gain.

P3-P203

Results of Mecasermin Treatment in Pediatric Patients Evaluated for Severe and Partial Primary Deficiency of IGF-1

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Background: Severe primary deficiency of insulin-like growth factor-1 (IGFD) being characterized by growth failure and short stature in children, constitutes an indication to recombinant human IGF-1 (mecasermin) treatment. It is defined by serum insulin-like-growth factor-1 (IGF-1) levels less than or equal to 2.5 th percentile, height less than or equal to -3SDS, normal growth hormone (GH) secretion and exlusion of secondary causes of IGFD.

Objective: Our objective was to present results and possible side effects of mecasermin treatment in pediatric patients evaluated for severe and partial primary deficiency of IGF-1 at a pediatric endocrinology unit in Poland.

Methods: We present 5 patients (4 male and 1 female) (aged: 7 to 16 years) treated in our unit with mecasermin between 2010 and 2018. The patients were qualified for replacement therapy by performing physical examination with stature measurement and running laboratory and radiological tests according to the protocol. The presence of IGFD was confirmed by IGF-1 generation test. We performed genetic tests involving IGF-1 – GH pathway in William Harvey Research Institute, Barts and the London School of Medicine. Initial doses of mecasermine 0.04 mg/kg twice a day were given.

Results: In Patient 1 (delta 71 ng/ml) height velocity equaled 7.8 cm/year in the first, 8.2 cm/year in the second and 8.9 cm/year in the recent, eighth year of treatment. In Patient 2 (delta 58 ng/ml) height velocity equaled 6.5 cm/year in the first, 6.3 cm/year in the second and 4.5 cm/year in the recent, sixth year of treatment. In Patient 3 (delta 66 ng/ml) height velocity equaled 5.7 cm/year in the first year of treatment. Then therapy was discontinued. In Patient 4 (delta 16 ng/ml) height velocity equaled 6 cm/year in the first, 6.1 cm/year in the second and 6.9 cm/year in the recent, third year of treatment. In Patient 5 (delta 12.8 ng/ml) height velocity equaled 7.6 cm/year in the first, recent year of treatment. We observed only one complication in the form of hypoglycemia in Patient 4.

Conclusions: Therapy with mecasermin in case of partial IGFD provides comparable satisfactory results to severe IGFD treatment.

P3-P204

Children Born Small for Gestational Age Treated with Growth Hormone: Evolutionary Aspects

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Introduction: Short stature is defined as stature less than -2 standars deviations (SD) for a person's age and sex of the reference population. Short for gestational age children (SGA) represent 20% of all children with short stature. 10% of these can not catch-up and remains their height below -2 SD. Growth hormone (GH) treatment is a recognized therapy for SGA children authorized in Europe at 4 years old.

There are studies that support that younger children are more responsive to therapy. For this reason we have carried out a review of the SGA children treated with GH in our hospital.

Methods: Retrospective descriptive study of SGA children treated with GH from 2010 to 2017. We aimed to assess the anthropometric data at the beginning and after one year of treatment.

Results: The review includes 81 patients (58% males). 12.3% were multiple- gestations and 33.3% premature. The mean birth weight was -1.95 SD and the length -2.80 SD. 92.5% of the children had a birth length less than - 2 SD, 58% a weight less than - 2 SD, and in 49.8% both measures were below -2 SD.

The mean age at the beginning of treatment was 6.08 years with a height of -2.91 SD and a height velocity of -1.65 SD. After one year of therapy we observed an increase in both parameters: -2.09 and 3.25 respectively and approximately 54% of the patients reached a height greater than -2 SD (80% of them under 6 years).

We observed a significant relationship between younger children and better treatment response (referred to: difference of SD after one year of treatment, height velocity and adult height prediction).

The average GH dose initially was 0.038 mg/kg/day. We couldn't prove relationship between GH dose and higher height velocity.

We couldn't prove relationship between increased delayed bone age and a greater response to treatment.

Regarding the insulin resistance parameters, an average basal insulin increase of 4.48 to 8.63 was observed without an increase in glycaemia or hemoglobin A1C levels.

Conclusions:

1. GH therapy is effective in SGA children with an increase of almost 1 SD after one year of treatment, increase in height velocity and adult height prediction.
2. Increases basal insulin levels but does not alter the other analytical parameters.
3. A greater treatment response is observed in younger children.
4. The greater delay in bone age is not related to a greater treatment response.

P3-P205

"Small for Gestational Age (SGA) Patients in Real Life French Clinical Practice: What Is the Difference Between Good and Poor Responders to GH Treatment"

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Objective: Age and height at treatment start, target height, GH dose, and first year treatment response are among known criteria of GH deficiency (GHD) good responders (final adult height [FAH] >-2 standard deviation score [SDS]) to GH treatment (GHT). The

authors investigated whether the same criteria are applicable to SGA patients based on real-life ongoing French registry data.

Methods: 291 SGA children treated with Norditropin® were included, 183 were naïve. Naïve completers were stratified in poor and good responders according to FAH ≤-2SDS or >-2SDS, respectively. The following criteria were addressed and compared: height and weight at birth, target height, age, height and GH dose at treatment initiation, growth velocity (GV) year before GHT, Δ height and GV in the first year of treatment, GH cumulative dose and treatment duration. Analysis was descriptive; Student t-test was used to compare mean quantitative data (SD) [min; max] (*p* value) and Fischer test for the proportion of qualitative data. [Confidence interval 95%] was also calculated.

Results: To date, 51 naïve patients have completed the study, 31 were good responders and 20 poor responders.

A significant difference or positive trend was observed for the following mean values in good versus poor responders:

- Height at treatment start (SDS): -2.7 (0.5), [-2.8; -2.5] vs. -3.2 (0.4), [-3.4; -3.0] (*p*=0.0006)
- Age at treatment start (years): 10.0 (2.5), [9.1; 11.0] vs. 11.4 (2.2), [10.4; 12.5] (*p*=0.0490)
- GV 1 year before treatment (SDS):- 0.01 (2.1), [-1.1; 1.1] vs. -1.8 (1.8), ([-3.1; -0.4] (*p*=0.0446)
- Target height (SDS); -1.3 (-1.3), [-1.6; -1.0] vs. -0.8 (1.0), [-1.3; -0.4] (*p*=0.0857)
- GV the first year of treatment (SDS): 2.33 (1.98), [1.59; 3.07] vs. 1.35 (1.77), [0.52; 2.17] (*p*=0.0780)
- Δ height ≥+0.5 SDS (% patients): 66.7%, [48.8%; 80.8%] vs. 40%, [21.9%; 61.3%] (*p*=0.0845)

Good responders were taller and younger at the beginning of treatment with better GV the previous year of treatment. GV in the first year of treatment had a superior positive trend compared to poor responders.

Conclusion: French observational registry data show that some GHD criteria of good response could be applicable to SGA patients treated with Norditropin® and useful for clinical practice. Nevertheless, the observational design of the study and the small sample size of patients could limit the power of analysis. Further investigations with more patients completed the study are needed as well as other observational studies.

P3-P206

Body Mass Index (BMI) in Patients with Growth Hormone Deficiency (GHD) at Diagnosis, One Year and Two Years After Treatment with Growth Hormone (GH)

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Introduction: Growth velocity is reduced in patients with GH deficiency and this may result in an increase in Body Mass Index (BMI). Treatment performed with Growth Hormone (GH) while accelerating growth velocity, might reduce BMI. The objective of this study was to evaluate BMI in patients with GHD at diagnosis, 1y and 2y after started treatment with GH and to compare if there is difference between the BMI of the patients with and without pituitary abnormalities.

Methods: Were analyzed medical records of patients with GHD, sex, chronological age (CA) at diagnosis, height and weight to obtained BMI (BMI-SDS) at diagnosis, 1y and 2y after started treatment of GH, and reports of MRI and/or CT scans of patients at age 3 to 16y among 1995 to 2016 at Pediatric Endocrinology Ambulatory at Regional University of Blumenau. It was approved by the Ethics Committee.

Results: 141 patients were evaluated, 82 male, pituitary abnormalities were found in 42, CA at diagnosis were 10.14y (mean). The accentuated lean group presented significant differences between BMI-SDS at diagnosis and the second year of treatment (-4.21 to -2.89, p<0.05). The lean group showed a significant difference between BMI-SDS at diagnosis and the first year of treatment (-2.4 to -1.94, p<0.05) but not with the 2ndy of treatment. In patients with overweight/obesity at diagnosis, the BMI-SDS decreased significantly in the 1st year (1.38 to 1.12, p<0.05) and then rose again (1.3) until 2nd y. The patients with normal BMI-SDS at diagnosis remained normal at 2nd y of treatment. No differences were found in BMI-SDS when compared patients with and without pituitary abnormalities during 2y of treatment.

Conclusion: In this sample BMI-SDS increased in patients with very low BMI, decreased in patients with high BMI and remained constant in eutrophic patients during treatment with GH. Although height gain in overweight/obese patients with GHD should have feed control during GH treatment in this patients. No differences were found in BMI-SDS when compared patients with and without pituitary abnormalities.

P3-P207

Erythropoietin and Granulocyte Macrophage Colony Stimulating Factor Levels in Growth Hormone Deficient Children after 1 year of Growth Hormone Therapy

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Background/Aims: An increase in growth rate in children suffering from growth hormone deficiency (GHD) subjected to recombinant growth hormone treatment (rGHT) was shown to be accompanied by acceleration of metabolic processes that may stimulate hematopoiesis. Therefore, the aim of the present study was to examine the effects of one year rGHT on erythropoietin (EPO) and Granulocyte Macrophage Colony Stimulating Factor (GM-CSF) levels in GHD children.

Methods: Eleven treatment-naïve prepubertal GHD children were included in the study (aged 3 to 9 years old, median 5.7 years). The study protocol included blood tests in three time points: at baseline, after 3 month of rGHT and after 1 year of rGHT. Parameters analyzed included: IGF-1 and IGFBP-3 levels, red blood cell (RBC) count, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) and EPO and GM-CSF levels.

Results: As expected, over the whole period of rGHT treatment we observed a significant increase in all anthropometric parameters. IGF-1 and IGFBP-3 values and RBC count also increased. Three months into rGHT we observed an slight increase in EPO and GM-CSF levels (median 17.8 mU/ml and 3.3 pg/ml, respectively), which was however statistically insignificant. Further, by the end of rGHT both parameters did not differ significantly from their initial values (for EPO median 14.7 & 10.9 mU/ml and for GM-CSF median 2.2 & 1.6 pg/ml, respectively). Also, we did not observe any correlation between EPO, GM-CSF levels and other measured blood parameters.

Conclusions: This work demonstrates that one year rGHT in GHD children does not lead to an increase of hematopoiesis-stimulating factors EPO and GM-SCF, suggesting that haematopoesis is not increased during the treatment period.

Keywords: growth hormone deficiency; children; erythropoietin; granulocyte macrophage colony stimulating factor

P3-P208

Cost-effectiveness of Growth Hormone Therapy in Children in Russia

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Background: Growth hormone deficiency (GHD) in children is a rare condition, which requires pathogenic therapy. In Russia GH treatment (GHT) is part of a federal program called "Seven high expenditure diseases" (7HED) and is fully state funded. In the rare cases when a GHD child cannot be treated with GH, financial and medical support for the child and its family is provided by the state. It is therefore important to understand the cost-effectiveness of GHT for children in Russia.

Aim: to determine the cost-effectiveness of GHT for GHD children in Russia as part of the 7HED federal program.

Methods: Data of 50 GHD children from four different regions of Russia was analyzed. All children were treated with GH within the 7HED program. Treatment duration of at least 6 years was an inclusion criterion. The amount of GH used and treatment costs (GH therapy and monitoring) were studied. Incremental costs were determined between GHT of a GHD child and a program with no pathogenic treatment, but a state-funded financial and medical support instead.

Results: The median treatment costs of a GHD child (dosage 0,033 mg/kg/day) during a period of 6,95 years were 6,26 [4,91; 7,87] thousand (th.) Euro or 0,91 th. Euro per child per year. With monitoring included the costs were calculated to be 6,76 per child during 6,95 years or 0,99 th. Euro per child/year of which 7,05% were monitoring costs.

An analysis of the alternative program showed that the total costs of financial and medical support amounted to 17,95 th. Euro per child per 6,95 years or 2,58 th. Euro per child/year, of which 1,2% were monitoring costs.

Therefore, the incremental costs between a standard GH treatment program with medical monitoring included and a program with no GH treatment, but financial support and medical monitoring are 11,11 th. Euro per child per 6,95 years or 1,59 th. Euro per child/year.

Conclusion: This work has shown that the Russian federal „Seven high expenditure diseases" program is cost-effective for GH treatment of GHD children.

P3-P209

Vitamin D Status in Children with Isolated Idiopathic Growth Hormone Deficiency (GHD) in North and Central Greece

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Background: Vitamin D status in children with isolated GHD has been analyzed in few studies with controversial results. The aim of the study was to assess vitamin D status in children with idiopathic GHD in North and Central Greece.

Materials and methods: 128 children (M/F: 76/61, mean age 9,5 (SD±3,5years) with isolated GHD were compared with 65 controls (M/F: 46/3, mean age 9,3 (SD±3,2years). Children were divided into four groups according to the season of evaluation: the winter (Dec-Feb: 44 children), the summer (Jun-Aug: 51 children), the spring (Mar- May: 59 children) and the autumn group (Sep-Nov: 26 children). Height, weight, BMI and BMI z-score were evaluated at the time of 25(OH)D3 serum levels measurement. Serum 25(OH)D3 levels <30 ng/mL and 20 ng/mL were defined as vitamin D insufficiency and deficiency, respectively.

Results: 79 children (36,9 %) were vitamin D insufficient, 70 (32,7 %) deficient and only 44 (20,6%) were between normal range. Lower vitamin D levels were found in the winter group than in the summer group (20.8±6.42 vs 27.11±11.97ng/ml; p=0.004). No difference was found in vitamin D status between GHD children and controls. No difference was also found in VitD levels between GHD children from North and Central Greece (23,3±8,8 vs 25,5±11,64ng/ml; p=0,35) despite the season of evaluation. No correlation between vitamin D, BMI z-score and GH max levels was also found.

Conclusions: Our data demonstrated a very high prevalence of hypovitaminosis D in Greek GHD children, regardless the region. Vitamin D status in children with idiopathic GH deficiency was similar to healthy children. Vitamin D assessment should therefore be considered routinely in GHD children even at sunny Mediterranean countries.

P3-P210

A Pilot Study for Comparing Efficacy and Safety of the CinnaTropin® to the Reference Recombinant Human Growth Hormone in Children with Isolated Growth Hormone Deficiency and Multiple Pituitary Hormone Deficiency

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Background: CinnaTropin® (CinnaGen, Iran) is a recombinant human growth hormone manufactured in Iran. Herein, we compared the efficacy and safety of the CinnaTropin® with the corresponding reference (Nordilet® Norditropin, Novo Nordisk, Denmark) in children with idiopathic growth hormone deficiency (IGHD) and multiple pituitary hormone deficiency (MPHD).

Methods: This was a randomized, open-label and cross-over study. Eligible patients (aged 4-16 years) were randomized to receive CinnaTropin® or Nordilet® for three months. Each patient was then crossed over to the other arm to receive the other product for further three months. The Efficacy of the treatment was assessed in terms of height, height standard deviation score (HSDS), height velocity (HV), and HVSDS. The Safety was also studied through evaluating incidence of adverse events by physical examination, patient complaints, and laboratory parameters during the treatment period.

Results: Thirty patients participated and completed the study. The mean age of participants was 8.80 ± 2.19 in the CinnaTropin® and 9.01 ± 1.78 years in the Nordilet® group. The mean ± SD of height velocity for three months of treatment was 6.57±2.42 and 7.50±2.16 (P=0.12), HSDS was 0.06±0.13 and 0.11±0.12 (P= 0.13), HVSDS was 0.45 ± 2.85 and 1.83 ± 3.15 (P=0.09) for the CinnaTropin® and the Nordilet® groups, respectively for each item. The incidence of adverse events was similar between the studied groups.

Conclusions: Our obtained findings indicate that CinnaTropin® has comparable efficacy and safety profile in comparison with the corresponding reference product (Nordilet®) in both children and adolescents with IGHD and MPHD.

P3-P211

Study of the Effectiveness of Growth Hormone in Children Born Small for Gestational Age in an Area of Northwestern Spain and Its Associated Factors

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Introduction: Recombinant growth hormone (GH) is an effective treatment for short children who are born small for gestational age(SGA). Short children SGA who fail catch-up growth by 4 years of age are candidates for GH treatment, at a dose of 35-70 µg/kg/day. Factors associated with response to GH treatment during the initial 2-3 years of therapy include age and height standard deviation scores at the start of therapy, midparental height, and GH dose. It is important to know the effectiveness of the treatment in our geographical area and compare the clinical and analytical results with those of other populations.

Objective: The aim is to study the predisposing factors of good response in SGA children treated with rhGH in our community, as well as its possible adverse effects.

Methods: Information from the application protocols for growth hormone treatment has been collected of our geographical area (Northwest Spain) for a period of 10 years.

It has been made a descriptive and analytical statistical study using SPSS 20.0. Tests used T-Student and Pearson correlation.

Results: Valid data of 180 patients (52.2% males; 47.8% females) have been obtained. All of them met the standars required by the European Medicines Agency.

Background: 12.8% multiple pregnancy; 18.3% associated perinatal pathology; 10.6% associated non-perinatal pathology. Birth information: weight -1.88 SDS; length -2.83 SDS.

Information at the beginning of treatment: age 7.39±2.6 years; height -3.16SDS; growth rate at start -1.74SDS. 96.1% started treatment before the onset of puberty.

Information at one year of treatment: height -2.34SDS; rate of growth +3.03SDS. Information at second year of treatment: growth rate +1.48SDS

The average treatment dose was 0.036 mg/kg/day. No adverse events were reported.

Conclusions: Our results agree with other published series and these are representative of our population. We observe an age of late onset of treatment, however, with an adequate response in growth correlated with the genetic height, the height at the beginning, the age of onset and the growth rate at the beginning of the treatment.

Its important to optimize the treatment to achieve catch-up growth to a normal height in early childhood, maintain a normal height gain, and achieve an adult height within the normal target range.

Although a high dose of up to 0.067 mg/kg/day is relatively safe, adequate response to lower doses should be considered in the light of long-term comorbidities in these patients.

P3-P212

Height Velocity and Height Gain in the First Year of Growth Hormone (GH) Treatment: Predictive Factors of Good Statural Response in Small for Gestational Age (SGA) Patients

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Objective: Bang et al. showed that Δ height and growth velocity (GV) the first year of treatment could be predictive factors of statural response in SGA (n=54). Poor responders showed GV <1SDS (55%) and Δ height <0.5SDS (45%). Moreover, Ortego et al. seems to confirm the suitability interest of KIGS mathematical model in a retrospective SGA cohort (n=103) showing that the percentage of good responders in the first year varies between 46.6% (Δ height ≥0.5SDS) and 81.6% (GV≥1SDS).

The authors questioned if these predictive factors for the final adult height (FAH)>-2SDS could be applicable in the French SGA cohort.

Methods: Observational ongoing study of 291 SGA children treated with Norditropin® included 183 naïve patients. Naïve completers (n=51) were stratified to poor and good responders according to FAH ≤-2SDS or >-2SDS, respectively. Logistic regression model for prediction of FAH (≤-2SDS/>-2SDS) considered the Δ height or GV in the first year of treatment. The value of the area under the curve (AUC) defines the strength of the model to distinguish poor from good responders considering the value of explanatory variable (Δ height or GV): low predictive model if AUC<0.7; moderate predictive model if 0.7≥AUC<0.9; excellent predictive model if AUC=1.

Results: Δ height in the first year. The best prediction of good response (AUC=63.3%) was obtained by stratifying the variable in these classes: ≤0.5/>0.5 SDS (odds ratio [OR]=3, confidence interval [CI]=0.93; 9.70, p=0.0665).

The concordance of observed and predictive FAH for good responders concerns 67% of patients.

The best prediction of good response (AUC=65.8%) was obtained by stratifying the variable in classes: ≤0.75/>0.75 SDS (OR=5.32, CI=1.35; 20.98, p=0.017).

The concordance of observed and predictive FAH for good responders concerns 86.6% of patients.

Table 1. The error rate of wrong categorisation of patients is 36% (for Abstract no P3-P212)

	Predictive values	
Observed values	<-2SDS	>-2SDS
<-2SDS	12	8
>-2SDS	10	20

One patient with missing data. GV in the first year.

Table 2. The error rate of wrong categorisation of patients is 30%. (for Abstract no P3-P212)

	Predictive values	
Observed values	<-2SDS	>-2SDS
<-2SDS	12	8
>-2SDS	10	20

One patient with missing data.

Conclusion: The strength of this predictive model has not been confirmed perhaps due to small sample size. Nevertheless, there were some interesting observations for good responders.

Further investigations are needed because this type of model might help in managing short stature patients.

P3-P213

Role of Insulin Like Growth Factors on the Growth Parameters in Children with Acquired Hypothyroidism: An Analysis

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Introduction: Growth retardation as clinical manifestation among children with acquired hypothyroidism is observed later in the course of the illness. Thyroid hormones along with insulin like growth factors (IGF) have important role in somatic and skeletal growth. Studies addressing role of IGF's towards growth retardation in children with acquired hypothyroidism are limited.

Objective: To evaluate effect of Insulin like growth factors in children with acquired hypothyroidism on growth parameters.

Methods: 27 children with acquired hypothyroidism, 8-18 years old recruited for evaluation after obtaining Institutional ethics clearance& informed consent. Height, weight, body mass index (BMI) recorded& analyzed on new IAP growth charts. Those with Growth hormone or multiple pituitary hormone deficiency and altered liver functions were excluded. Fasting samples for thyroid profile (T3, T4& TSH), IGF-1&IGFBP-3 collected. Thyroid profile analysed by electro-chemiluminiscence, IGF-1, IGFBP-3 by enzyme linked immunoassay DRG Kit. Statistical analysis done using software version SPSS 17.0.

Results: 27 children (8 males, 19 females) had mean age of 13.77±3.09 years, height 138±15.4 cm (-2.53SD), weight 35.89±11.67 kg (-1.09SD) and BMI 18.25±3.26 (-0.34SD). Stunting observed in 15/27(55.5%) (<-2SD). Mean T3,T4 were normal. Mean TSH- 19.81±30.7μIU/ml was raised with significant negative correlation with height (r=0.56, p=0.035). Mean levels of IGF-1 significantly lower than the age and sex matched normal population- 206.5±1.13ng/ml, but IGFBP-3 was normal 4493±2375.67 ng/ml. Height had positive correlation with IGF-1 (r=0.36) but not with IGFBP-3. Significant positive correlation of IGFBP-3 was observed with weight (r=0.479, p=0.011) and BMI (r= 0.538,

p=0.004). TSH had negative correlation with IGF-1 (r= -0.085), but no correlation observed with IGFBP-3.

Conclusion: Stunting observed in 55% children with acquired hypothyroidism. Significantly reduced IGF-1 levels along with abnormal TSH correlated positively with the height deficit in our cohort of acquired hypothyroid children. Though, IGFBP-3 was associated with increased weight& BMI. No correlation of IGFBP-3 observed with height or thyroid profile. Thus, IGF1 is associated with height deficit in children with acquired hypothyroidism.

P3-P214

Two Siblings with Short Stature

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2 siblings were referred for evaluation fo short stature and failure to thrive. Both were born of 3rd degree consanguinity, first and second in birth order. the first sibling was 2 1/2 year old at time of referral and had birthweight of 3.1 kg and had gross motor delay. Present height was 65 cm (SDS -6.2 SD)and weight was 6kg (<3rd centile) Second sibling was 1.5 years old, with gross motor delay with height of 57 cm (SDS -6.5 SD) and weight was 4.3 kg (<3rd centile). Mid-parentalheight was 153.4 cm. Head circumference was 45 cm in older sibling and 44 cm in younger sibling, both less than 2 SD for age. Intelligence was normal in both siblings. Both siblings had doll like facies with mid facial hypoplasia, frontal bossing and micrognathia and no other midline defects. There was also also no evidence of hypoglycemia. Routine investigations were normal and bone age was 2 years. Blood glucose levels were normal. IGF-1 was very low (<25 ng/ml) in both siblings. Basal Growth Hormone was 61.85 ng/ml in the first sibling and 50 ng/ml in the second sibling. Genetic analysis revealed a homozygous deletion in Exon 7 of GH Receptor Gene in both children but the parents were unaffected. The parents were apprised about the need for treatment with IGF-1 and have applied for a grant from the government.

The mutation identified in this case appears to be a novel mutation with no similar deletions in Exon 7 being reported in published literature. A similar case had been detected in West India with genetic analysis done at the same centre, but was not reported. Most mutations in GH insensitivity arise from EXON 3 OF GH receptor. This case report illustrates the fact that ethnic differences might lead to novel mutations in distinct population sub-groups and case finding needs to be targeted to reveal further new mutations in the GH receptor.

P3-P215

RHGH Replacement Therapy and Side- Effects: A Retrospective Study of 10 Years

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Treatment with Recombinant Human Growth Hormone (rhGH) has been of significant value in promoting quality of life in children with GH deficiency. However, it has been associated with several side-effects in the literature, including hypothyroidism, usually transient during the replacement therapy.

The aim of this study was to evaluate the side effects of hGH replacement therapy, among children who were followed up at the Pediatric Endocrinology Outpatients Unit of our hospital during the years 2008-2017.

A total of 160 children were referred to the Pediatric Endocrinology Outpatients Unit during a period of ten years, due to short stature. Following clinical examination, necessary laboratory and imaging studies, growth hormone deficiency was diagnosed and treatment with rhGH was initiated. The effects of the treatment on thyroid function, glucose metabolism and IGF-1 levels were assessed.

HGH replacement therapy was administered to 160 patients (61.9% males). Three of them were diagnosed with Turner syndrome and one with Prader-Willi syndrome. Median follow-up time was 5.24 years, with no statistical difference between males and females. Treatment with rhGH was initiated at a mean age of 8.23 years and completed at 13.47 years on average. During the replacement therapy, thyroid dysfunction was recorded in 105 of 160 children (65.5%). A decrease in T4 levels of about 1.12mg/dl and in TSH levels of about 0.4U/ml was observed. Fourteen of the study patients (8.8%) required replacement therapy with L-T4, whereas the remaining children presented a transient borderline disorder which was restored following completion of therapy with rhGH. A total of 111 children (69.3%) presented a slight elevation in HbA1c level (0.34% on average), while 13 patients did not present any changes and 36 presented a decrease in HbA1c. The vast majority of our patients (95.75%) responded to the treatment demonstrating elevated IGF-1 levels (by 3.5 times on average).

Concluding, thyroid function as well as glucose metabolism may be significantly deranged during replacement therapy with rhGH. Thyroid function disorders should be closely monitored due to the potential negative effects on growth rate. Latent central thyroid dysfunction disclosed by administration of rhGH remains a challenging research area.

P3-P216

Efficacy and Safety of Recombinant Human Growth Hormone in Treating Chinese Children with Idiopathic Short Stature

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This study aims to investigate the efficacy and safety of recombinant human growth hormone (rhGH) in the treatment of idiopathic short stature (ISS).

Methods: The data of 200 ISS children, who were treated with rhGH from January 2008 to December 2016, were collected and retrospectively analyzed. The data of height, bone age, blood glucose, insulin, thyroid function and IGF-1 were collected, and annual growth rate (AGR), height standard deviation score (HtSDS) and related factors that affect AGR were statistically analyzed.

Results: (1) AGR and HtSDS changes: As the time of treatment increased, the growth rate decreased year by year. The growth rate in the second year was significantly lower than that in the first year (P<0.0001), and the growth rate in the fourth year was significantly lower than that in the third year (P<0.05). HtSDS gradually increased from the first year to the third year, and became significantly higher than that in the year before the treatment (P<0.01). The difference in the increase in HtSDS between the fourth year and third year was not statistically significant (P>0.05). (2) The influence factors of AGR included age at initial treatment, IGF-1 level during treatment and AGR in the year before treatment. (3) The most common side effects during treatment included transient hyperglycemia and temporary hyperinsulinemia, and these returned to normal after the treatment was stopped. Some patients presented with accelerated bone age growth after two years of treatment (annual growth of bone age ΔBA was >2 years), compared with children without accelerated bone age growth, and the difference between BA and CA (BA-CA) was significantly reduced at the beginning of the treatment (P<0.01).

Conclusion: RhGH has a good growth promoting effect on ISS children. A variety of factors may affect the growth rate, and related adverse reactions should be monitored during the treatment.

P3-P217

Comparison the Recombinant Human Growth Hormone (rhGH) Treatment in Children with Idiopathic Short Stature (ISS) and Growth Hormone Deficiency (GHD)

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Background: The efficacy and safety of rhGH treatment on ISS and GHD were not reported in Chinese children. In this study, we aimed to compare the efficacy and safety of rhGH therapy in ISS and GHD.

Methods: The clinical data in children with ISS and GHD who were treated with rhGH for more than one year from 2005 to 2016 were retrospectively analyzed. Growth velocity(GV), HtSDS, IGF-1 SDS, BMI and the incidence of fasting hyperglycemia, fasting hyperinsulinmia and hypothyroidism were recorded and compared.

Results: 150 ISS and 153 GHD children who received rhGH treatment more than one year were enrolled. Two groups had no significant differences in the age of treatment, bone age, height and BMI. GV in GHD was higher than ISS group but there was no significant difference in GV between the two groups (P> 0.05). HtSDS at the beginning of treatment and half year of treatment were significantly lower than the ISS group(P <0.05). The incidence of hypothyroidism in GHD group was significantly higher than that in ISS group (13.72% vs 6.0%, P <0.05). The incidence of hyperinsulinmia in ISS group was significantly higher than that in ISS group 15.33% vs 7.84%, P<0.05).

Conclusion: rhGH has a similar effect on the growth of ISS and GHD. Children with ISS are more likely to develop fasting hyperinsulinmia, and children with GHD are more likely to have hypothyroidism.

P3-P218

Bone Age Maturation During the Three Years of Growth Hormone Treatment in Patients with Idiopathic Growth Hormone Deficiency and Idiopathic Short Stature: Analysis of Data from LG Growth Study

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Background: Although the beneficial effects of growth hormone (GH) treatment on statural growth are well known, the impacts on skeletal maturation are not fully understood. In the current study, we aimed to investigate the progression of bone age (BA) in children with idiopathic GH deficiency (iGHD) and idiopathic short stature (ISS) based on a LG Growth Study (LGS). We also evaluated the progression rate of BA relative to chronologic age (CA) between iGHD and ISS and to find their associated factors

Methods: A total of 93 children (79 with iGHD and 17 with ISS) were analyzed from LGS. All patients included in the study were being treated with recombinant human GH (Eutropin) and their BA was assessed using the Greulich and Pyle method at baseline and every year during first three years of GH therapy.

Results: The means of chronological age (CA) was 7.77 ± 2.77 years in iGDH groups and 8.17 ± 2.97 years in ISS group at start of GH treatment. In iGHD groups, the means of height SDS and difference between BA and CA (BA-CA) was -2.45 ± 0.66 and -1.96 ± 0.96 years in iGHD group and -2.60 ± 0.62 and -2.04 ± 1.25 years in ISS group, respectively. In the iGHD group, the BA-CA at the first, second, and third years of treatment was significantly decreased with GH treatment compared to that of at start of treatment which

was -1.74 ± 1.05 years, -1.48 ± 1.02 years, and -1.24 ± 1.21 years, respectively. The BA-CA The progression rate of BA was similar every year in iGHD group. In the ISS group, BA-CA at the first, second, and third years of treatment was -1.74 ± 1.05 years, -1.48 ± 1.02 years, and -1.24 ± 1.21 years, respectively. The BA-CA at the second, and third years of treatment decreased significantly whereas the BA-CA at the first year did not decrease significantly. In ISS group, the progression rate of BA decreased significantly and there was no statistical significance. In the GHD group, 65 children were in BA-CA ≥1 year at the start of treatment whereas 46 children were in BA-CA ≥1 year at the third year of treatment.

Conclusion: The progression rate of BA during GH treatment is significant although clinically acceptable. Clinicians should be considered when efficacy of GH treatment is evaluated.

P3-P398

Recombinant Growth Hormone Therapy in Prepubertal Children with Idiopathic Short Stature in Korea : A Phase III Randomized Trial

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Several studies have evaluated the effects of growth hormone (GH) on auxological and biochemical parameters in children with non-GH-deficient, idiopathic short stature (ISS). This study evaluated the efficacy and safety of Growtropin^{R}-II (recombinant human GH) in Korean patients with ISS.

This was a 1-year, open-label, multicenter, phase III randomized trial of Growtropin-II in Korean patients with ISS. In total, 70 prepubertal subjects (39 males, 31 females) between 4 and 12 years of age were included in the study. All patients were naive to GH treatment.

Annual height velocity was significantly higher in the treatment group (10.68 ± 1.95 cm/year) than the control group (5.72 ± 1.72, p<0.001). Increases in height and weight standar deviation scores (SDSs) at 26 weeks were 0.63 ± 0.16 and 0.64 ± 0.46, repectively, for the treatment group, and 0.06 ± 0.15 and 0.06 ± 0.28, respectively, for the control group (p<0.001). Serum insulin-like growth factor(IGF-1) and insulin-like growth factor binding protein-3(IGFBP-3) increased significantly in the treatment group at week 26 compared to baseline. However, the SDS for body mass index(BMI) at 26 weeks did not change significantly in either group. Growtropin^{R}-II was well tolerated and safe over 1 year of treatment.

One-year GH treatment for prepubertal children with ISS demonstrated increased annualized velocity, height and weight SDSs, and IGF-1 and IGFBP-3 levels, with a favorable safety profile. Further evaluations are needed to determine the optimal dose, final adult height, and long-term effects of ISS treatment.

Growth & Syndromes P1

P1-P159

Does X-Chromosome Gene Dosage Determine Growth and Phenotypic Features in Turner Syndrome with 45,X/46,XX Mosaicism on Standard karyotyping? A Cross-Sectional Analysis of the French National Rare Disease Network Database

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Background: Turner Syndrome (TS) with a 45,X phenotype is generally more severe than TS with mosaicism, but the potential role of the degree of mosaicism in modulating TS phenotype has never been investigated. We assessed the impact of various degrees of 45,X/ 46,XX mosaicism on phenotypic features in a cohort of TS patients.

Method: We analysed a cohort of TS with 45,X/ 46,XX mosaicism (percentage mosaicism from peripheral blood lymphocytes,

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Table 1. (for Abstract no P1-P159)

	Patients 45,X/46,XX patients (*n*=183)		
	45X <10% (*n*=28)	45X : 10-30% (*n*=72)	45X ≥ 31% (*n*=83)
Birth weight (SDS)	-0.42 (-0.96; 0.56)	-0.51 (-1.12; 0.12)	-0.77 (-1.65; 0.11)
Birth length (SDS)	-0.42 (-1.49; 0.43)	-0.72 (-1.38; 0.22)	-0.93(-1.75; -0.14)
Congenital heart malformation	11%	13%	9%
Congenital kidney malformation	0%	11%	22%*
Median age (y) before GH treatment	11	9.8	9.6
Height deficit (SDS) with respect to target height before GH treatment	1.44 (0.89; 2.37)	2.08 (1.40; 2.39)	2.33 (1.52; 2.89)
Spontaneous onset of puberty	17%	15%	16%
Median age (y) at last evaluation	13.6	16.4	16.0
Hearing impairment	10%	21%	28%
Hashimoto thyroiditis	7%	20%	33%
Overweight/obese	7%	10%	23%*

*p<0.03; **p<0.01.

known in n = 183/221 cases), in a national observational multicentre study (n = 1536). Data were collected retrospectively from medical records and analysed according to the degree of mosaicism, classified as low (<10%), moderate (10-30%) or high (>30%). The genetic analyses carried out included standard karyotype analyses of more than 20 cells or fluorescence *in situ* hybridization on about 100 cells.

Results: A trend towards association with the degree of mosaicism was observed for birth weight SDS, birth length SDS and height deficit with respect to target height SDS before growth hormone treatment, the patients with lower levels of mosaicism being less likely to be affected. High levels of mosaicism were associated with a higher frequency of malformations of the kidneys (p<0.01) but not of the heart. During adolescence, mosaicism levels were higher in patients who were overweight/obese (p<0.03), and hearing impairment and Hashimoto thyroiditis were more frequent in patients with higher levels of mosaicism. Spontaneous puberty was not associated with the degree of mosaicism.

Conclusions: In TS patients with 45,X/ 46,XX mosaicism, high levels of mosaicism seem to be associated with a more severe phenotype. Further studies of larger cohorts are required to improve our understanding of these associations.

P1-P161

Analysis of Osteoblats Precursors in Girls with Turner Syndrome

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Background and Aim: Subjects with Turner Syndrome (TS) show low cortical bone mineral density (BMD), osteoporosis and risk of fractures. Previously, we demonstrated the enhanced spontaneous osteoclastogenesis in girls and young women with TS before and after pubertal induction with hormonal replacement therapy (HRT). The bone resorption observed in girls before puberty induction seems to be supported by the high FSH serum levels observed at prepubertal stage, while in young women on continuous HRT the effects on osteoclasts seem to be mediated mostly by high RANKL levels.

We aimed to investigate if osteoblast differentiation/activity could also be impaired in girls with TS.

Method: Markers of bone remodelling were measured in sera of 10 girls with TS (median age 5.2 ± 1.2) and 10 age matched controls. Bone mineral density was evaluated by DEXA. The percentage of circulating osteoblast precursors CD34+/CD45-/Osteocalcin (OCN)+ cells was evaluated by flow cytometry.

Results: Lumbar spine BMD-Z-score was reduced in 50% TS patients, together with levels of 25-OH Vitamin D. In sera of TS patients we also detected a significant slight increase of the levels of the osteoblastogenesis inhibitor sclerostin compared with the

controls (28.45 ± 9.43 *vs* 20.99 ± 9.31, p<0.01 respectively). Consistently, we also detected a significant low percentage of circulating osteoblast precursors CD34+/CD45-/Osteocalcin (OCN)+ cells in TS patients with respect to the controls (1.1 ±. 0.2 vs 3.5 ± 0.5 p<0.01, respectively). The percentage of circulating osteoblast precursors positively correlated with the reduced lumbar spine BMD-Z-score (r=0.42, p<0.01) and with the low levels of 25-OH Vitamin D (r=0.45, p<0.01)

Conclusions: In TS patients the low percentage of circulating osteoblast precursors CD34+/CD45-/Osteocalcin (OCN)+ cells together with the high levels of sclerostin sustain the involvement of osteoblasts in the impaired bone remodeling associated to TS.

P1-P162

Comparing the Cumulative Dose of Growth Hormone Therapy Using Body Weight-based Dosing versus Body Surface Area-Based Dosing in Children with Turner Syndrome—Data from the ANSWER Study

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Background and Objective: The American Norditropin Studies: Web-Enabled Research (ANSWER) Program is a long-term, US-based, non-interventional study designed to collect information on the effectiveness and safety of Norditropin® growth hormone (GH). From June 2002 to September 2016, 20,204 pediatric patients were enrolled by their treating physicians, including 1,003 patients with Turner syndrome (TS). This analysis compares cumulative GH doses when adjusting GH dosage based on body weight (BW; actual dosing) vs body surface area (BSA; theoretical dosing calculated from average BSA and average dose).

Methods: Patient information was entered by participating physicians using a web-based tool. A total of 577 eligible TS patients were GH-naïve at study entry. The theoretical BSA-based dose of 1.46 mg/day was derived from observed dose vs BSA data that best corresponded with an ideal body weight (BSA=1 m^2).

Results: Patients with TS (n=577) had a mean (SD) baseline height standard deviation score (SDS) of -2.52 (1.02), baseline weight SDS of -1.16 (1.45), and baseline insulin-like growth factor-I (IGF-I) SDS of -0.66 (1.72); mean (SD) and median start age for GH treatment were 9.25 (3.95) and 9.56 years, respectively. At baseline, 338 patients (59%) were aged <10 years, and 239 (41%) were ≥10 years; spontaneous puberty (Tanner stage ≥ 2) was reported for 23 patients. After starting GH treatment, mean IGF-I SDS increased from baseline (-0.66) to year 1 (+1.11), and then remained similar during further treatment follow-up. The ratio of BW-based vs theoretical BSA-based GH dose (1.46 mg/day) was <1 before age 10 years and >1 after age 10 years. Compared with BSA-based dosing, mean GH dose with BW-based dosing was lower before age 10 years, but higher after age 10 years.

Conclusions: GH dosing based on a hybrid method in which the GH dose is BW-based before age 10 years and BSA-based after age 10 years may result in a lower cumulative dose than BW-based GH dosing alone. Conclusions regarding the effectiveness of BSA-based dosing could not be derived from these retrospective data, as all BSA-based doses were theoretical; however, demonstrating the effectiveness of a hybrid dosing method may support a rationale for optimized and individualized GH dosing and could have the potential to lower the cost of therapy. Further research is warranted to explore the benefits of a hybrid dosing method and whether this approach results in height outcomes similar to those of BW-based dosing.

P1-P163

The Association between Growth Hormone dose and Short-term Height Outcomes in a Large Cohort of Paediatric Patients With Turner syndrome: Real-World Data from the NordiNet® International Outcome Study (IOS) and ANSWER Program

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Objectives: The recently updated clinical practice guidelines for Turner syndrome (TS) recommend a growth hormone (GH) dose of 45–50 μg/kg/day, increasing to 68 μg/kg/day in case adult height potential is substantially compromised (1). Real-world data on the modifiable factors impacting near-adult height in GH-treated TS patients are limited, but short-term responsiveness to GH has been suggested as one factor (2). We, therefore, analysed the impact of GH dose on short-term height outcomes in a large cohort of paediatric patients with TS.

Methods: Two complementary, non-interventional, multicentre studies, NordiNet® IOS (NCT00960128) and the ANSWER Program (NCT01009905), evaluated the long-term effectiveness and safety of Norditropin® (somatropin; Novo Nordisk A/S, Denmark) as prescribed by treating physicians in a real-world clinical setting. Data from 1125 TS patients were included in the analysis. Changes in height standard deviation score (ΔHSDS) and association with GH dose were evaluated using a repeated measures mixed model, adjusting for factors previously shown to impact height gain: age at treatment start as well as baseline and target HSDS.

Results: Baseline characteristics [mean (SD)]: age at treatment start (years), 8.60 (3.83); height (cm), 114.76 (19.75); HSDS, −2.61

(0.92); target HSDS, −0.18 (0.97); insulin-like growth factor-I standard deviation score, −0.84 (1.48); bone age/chronological age ratio, 0.87 (0.15). Mean GH dose (μg/kg/day) was 45.21 (11.00) at baseline, and 46.52 (9.70) and 45.83 (9.77) for years 1 and 2, respectively. Mean increase in height from baseline (cm) was 8.46 (2.53) at year 1 and 15.12 (3.66) at year 2. Statistical analysis showed that a GH dose of <50 μg/kg/day was associated with a significantly lower increase in HSDS versus a dose of ≥50 μg/kg/day (p=0.0407). Mean estimated ΔHSDS (SD) were: patients receiving <50 μg/kg/day: 0.51 (0.12) at year 1 and 0.78 (0.11) at year 2; patients receiving ≥50 μg/kg/day: 0.59 (0.11) at year 1 and 0.85 (0.13) at year 2.

Conclusions: These data suggest that higher GH doses are associated with greater short-term height gain in patients with TS. The results support the importance of dose optimisation in this patient population. Although a safety evaluation was outside the scope of this analysis, no new safety signals were identified in this patient cohort.

References

1. Gravholt CH *et al. Eur J Endocrinol* 2017;177:G1–G70.
2. Ranke MB *et al. Pediatr Res* 2007;61:105–110.

Table 1. (for Abstract no P1-P164)

Age	1 yr	5 yrs	12 yrs	16, 17 yrs
Number	32	30	16	31
HSDS	-1.82 (-3.99,-0.08)	-0.76 (-4.16,2.25)*	-0.59 (-4.27,1.59)	-2.66 (-4.27,-0.64)**
BMISDS	-0.83 (-3.27,1.85)	2.51 (-2.36,5.63)*	1.94 (-0.13,4.3)	2.52 (-1.5,4.18)

* p<0.0001 vs age 1; ** p<0.0001 vs age 5 and age 12.

P1-P164

Changing Patterns of Growth in Prader-Willi Syndrome

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Introduction/Aim: Children with Prader-Willi syndrome (PWS) show alterations in infantile, childhood and pubertal growth. Growth Hormone (GH) therapy is recommended due to reported improvements in height velocity (HV) and body composition. The aim was to describe the patterns of growth in PWS and the influence of both changes in clinical practice and GH therapy.

Methods: Height SDS (HSDS), BMISDS and HVSDS of children attending a dedicated PWS clinic, 2000-2017, were analysed. To identify changes in growth we compared growth parameters between 2000-2012 and 2013-2017. In 21 children who received GH (median age at GH start 4.92yrs (2.27,8.1), consecutive measurements were available at -1, 0, +1 and +2 years from GH start.

Results: Overall, 60 children (31F/29M) were included. Three phases of growth after the age of 1 year were identified: 1-5yrs, with acceleration in both HSDS (r, 0.310, p,<0.0001) and BMISDS (r, 0.602, p,<0.0001); 6-12yrs, with stabilisation in both HSDS (r, 0.063, p, 0.417) and BMISDS (r, -0.154, p, 0.087); and 13-18yrs, with deceleration in HSDS (r, -0.383, p,<0.0001) and unchanged BMISDS (r, 0.015, p, 0.896).

At age 5, children in 2013-2017 (n,12) had higher HSDS [median,-0.08 (-1.74,1.54) vs -1.04 (-4.16,0.5)] than those in 2000-2012 (n,18) (p,0.03). At age 12, children in 2013-2017 (n,5) had higher HSDS [median, 1.13 (-0.62,1.59) vs -1.35 (-4.27,0.23)] (p,0.027) and lower BMISDS [median, 1.05 (-0.13,2.14) vs 2.44 (0.13,4.3)] (p,0.032) than those in 2000-2012 (n,11). After 2 years on GH, median HSDS improved from -1.43 (-4.59,0.95) to -0.11 (-3.53,1.57) (p,<0.0001) and median HVSDS from 0.62 (-5.9,4.17) to 2.8 (-2.2,5.2) (p,0.027). BMISDS was unchanged.

Conclusion: We were able to delineate 3 distinct phases of growth in PWS: early childhood (1-5yrs), late childhood (6-12yrs) and adolescence (13-18yrs). Changes in our clinical practice have led to improvements in both height and BMI. GH therapy was associated with an increase in height and stabilisation of BMI.

P1-P165

Sleep-Disordered Breathing in Children with Prader-willi Syndrome in Relation To Growth Hormone Therapy Onset

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Context: Prader-Willi syndrome (PWS) is a multisystemic complex genetic disorder. Individuals with PWS are at risk to develop sleep-disordered breathing, including obstructive and central sleep apnea syndromes. PWS patients commonly receive Growth hormone (GH) treatment. Concerns have been raised following reports of sudden death shortly after GH initiation. During recent years GH treatment was increasingly initiated earlier – commencing treatment already during the first year of life. To date, no data are available on whether age at treatment initiation is associated with sleep apnea development.

Objective: We investigated occurrence and severity of sleep apnea in PWS children after treatment initiation and sought for differences between patients treated within or after their first year of life.

Design and Setting: This was a retrospective and longitudinal study with data obtained from 2007 to 2017.

Patients and Methods: We analyzed polygraphic registrations (PGs) of 62 children (aged 0-2.5 years at baseline), diagnosed with PWS. 21 children (group A) started GH therapy within and 41 children (group B) after their first year of life. Polygraphic and auxological data was acquired before treatment (t0), at 3 months (t1), 6 months (t2), 10 months (t3), 1.2 years (t4), 2.2 years (t5)

and 3.2 years (t6) after GH onset. To test any differences in prevalence and incidence, main outcome measures included obstructive apnea hypopnea index (OAHI), severity of obstructive sleep apnea (OSA), central apnea index (CAI), oxygen desaturation index (ODI), mean and minimal peripheral blood oxygen saturation.

Results: We observed no significant differences in OAHI, CAI, ODI and peripheral oxygen saturation in relation with treatment onset. Prevalence of pathological OSA (≥1.5) increased significantly from 25.0% to 33.3% at t1 in group A ($p<0.05$). However, prevalence did not differ between groups at any time point. The percentage of patients with severe OSA rose from 2.5 (t0) to 4.9 (t1) only in group B ($p<0.05$). We found a decrease in the ODI from 4.0 to 3.1, 2.7, 2.9 at t1, t2 and t4 in group A, respectively ($p<0.05$). Group B showed a decrease in the ODI from 3.6 at baseline to 1.6 at t8 ($p<0.05$).

Conclusions: Development of OSA in PWS children appears to be independent of GH treatment onset. Thus, GH treatment may be initiated early in life. However polygraphic screening should be sustained regularly, especially within the first year after treatment initiation.

P1-P166

Safety and Effectiveness of Growth Hormone Treatment in Patients With Prader-Willi Syndrome under 2 years of Age in a Reference Hospital

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Introduction: Growth hormone (GH) treatment was approved in 2000 for patients with Prader-Willi syndrome (PWS). The main reason for its use was the improvement in body composition. As a result of 2 fatal episodes, it was decided to initiate it from 2 years of age arbitrarily. Average age of real start: 4-6years. GH per se is not a risk factor for mortality in PWS. The 2013 guideline recommends to star it as soon as possible, preferably under 2 years of age, when obesity is established.

The main objective of our study is to test the safety and effectiveness of GH treatment in patients with PWS less than 2 years of age (registered in Clinical Trial Govcode: NCT02205450).

Materials and methods: Longitudinal observational study (EPA-PS) during 2 years of 13 patients with PWS who started treatment with GH under 2 years of age.

Results: we analyzed the data of 13 patients (8 boys and 5 girls) with genetic diagnosis of PWS (64.3% deletion, 35.7% maternal uniparental disomy). The average age of onset of GH was 12.3 months (range of 9-20 months). There were no fatal adverse effects. One patient had a serious adverse effect not attributable to GH (published in Am J Case Rep 2017 Gastric Dilatation). We observed a significant decrease in the subscapular and triceps folds ($p<0.0001$), an increase in height and a decrease trend in body mass index. Regarding psychomotor level, the median age start walking and speaking was 19.47 and 16.93 months, respectively, (clearly lower in those who started GH <15 months and before of classically described).

Conclusions: GH treatment is safe in PWS patients under two years of age and significantly improves their body composition. Those who started GH before 15 months started to walk sooner.

P1-P167

Improved Mental and Motor Development During 3 Years of GH Treatment in Very Young Children With Prader-Willi Syndrome

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Context: Infants and toddlers with Prader-Willi Syndrome (PWS) have a mental and motor developmental delay. Short-term data suggest a positive effect of growth hormone (GH) on mental and motor development in infants and children with PWS. There are, however, no longer-term results about the effects of GH treatment on mental and motor development.

Objective: To investigate the longer-term effects of GH on psychomotor development in infants and toddlers with PWS and the effect of age at start of GH treatment on psychomotor development.

Methods: Prospective cohort study in 63 young children with PWS. All patients were naïve to GH treatment at time of enrolment and started GH in a dose of 1 mg/m^2/day (≈0.035 mg/kg/day). Main outcome measures were mental and motor developmental age assessed with Bayleys Scales of Infant Development II (BSID-II) and expressed as % of the expected development (100%).

Results: Thirthy-five boys and 28 girls participated in the evaluation of psychomotor development. GH treatment was started at a median (IQR) age of 1.0 year (0.7-1.6). During 3 years of GH, mean (SEM) mental development increased from 58.1% (2.8) at baseline to 79.6% (3.7), and motor development from 41.9% (2.9) to 78.2% (3.9; both $p<0.01$). In spite of this improvement, the average mental and motor development after 3 years of GH was still significantly lower compared to healthy references (both $p<0.001$). A lower baseline psychomotor development and a younger age at start of GH treatment were associated with a higher increase in mental and motor development (all $p<0.01$).

Conclusion: Mental and motor development increased significantly during 3 years of GH treatment, reducing the gap between infants with PWS and healthy peers. Infants with a lower baseline psychomotor development advanced more than infants with a higher baseline psychomotor development. Currently, the increased awareness of PWS and the improved genetic tests have made it possible to diagnose PWS during early infancy. As starting GH treatment at a younger age results in a better psychomotor development, we nowadays start GH treatment in very young infants with PWS.

P1-P168

GH response to GHRH and Arginine in Previously GH-Treated Young Adults with Prader-Willi Syndrome

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Context: Some of the features of subjects with Prader-Willi syndrome (PWS) resemble those seen in subjects with growth hormone deficiency (GHD). Children with PWS are treated with long-term growth hormone (GH), which has substantially changed their phenotype. Currently, young adults with PWS have to stop GH treatment after attainment of adult height when they do not have adult GHD. Limited information is available about the prevalence of adult GHD in patients with PWS.

Objective: To investigate GH secretion and serum IGF-I and IGFBP-3 levels in a large group of young adults with PWS, who were GH-treated during childhood.

Methods: Cross-sectional study in 57 young adults with PWS. Main outcome measures were serum IGF-I and IGFBP-3 levels and GH peak during a combined GHRH-Arginine test. The influence of BMI, body composition and genetic subtype were assessed.

Results: Twenty-five males and 32 females with PWS participated in the current study. Mean (SD) age and adult height were 18.2 (2.1) years and -1.2 (0.9) SDS, respectively. Mean (SD) BMI SDS was 1.0 (1.3) and median (IQR) fat mass percentage (FM%) 41.5% (38.2 to 44.9).

Serum IGF-I was <-2 SDS in 12% of patients and IGFBP-3 was within the normal range in all participants. Mean (SD) GH peak was 21.5 ug/l (11.7; ~ 64.5 mU/l) and below 9 ug/l in 14% of patients. Only 1 patient (2%) fulfilled the diagnostic criteria for adult GHD, also when BMI-related criteria were used. Higher BMI and FM% were significantly associated with a lower GH peak and there was no significant difference between patients with a deletion or a mUPD.

Conclusion: In a large group of previously GH-treated patients with PWS, peak GH levels during a GHRH-Arginine test were low in 14% of patients. Only 2% of patients fulfilled the criteria for adult GHD. As GH treatment has positive effects on body composition and health profile in adults with PWS, there is a need for the registration of GH treatment for adults with PWS, regardless of serum IGF-I/GH levels.

P1-P169

A Novel Type of Pubertal Height, Weight, and BMI Reference, Aligned for Onset of Puberty

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Context: Specific references for height, weight and BMI that consider the maturation tempo for onset of puberty are lacking worldwide.

Aim: to fill the gap, by developing specific pubertal references for $height_{SDS}$, $weight_{SDS}$ and $BMI_{SDS,}$ all aligned for the individual onset of puberty

Method: *Reference population*: a subgroup of $GrowUp_{1990}$Gothenburg cohort of 1572 (763 girls) healthy children born at term around 1990 in Sweden of non-smoking mothers, with as mean 24 measures of weight and height from birth to adult height. *QEPS-model[1,2]*: For each individual, a QEPS-function estimated height curve was obtained and onset of puberty defined as AgeP5, age of 5% of the specific P-function growth. This was used for aligning the onset of puberty of the individuals in the reference population used for the pubertal references for total height, specific-pubertal height (P-function) and non-specific-pubertal (QES-functions) height references. This alignment was also used for the *LMS method* developed total weight and total BMI references.

Results: For both girls and boys we present onset-of-puberty-aligned references for 1) total $height_{SDS}$, specific-pubertal $height_{SDS}$ and non-specific-pubertal $height_{SDS}$ (Figure left panel); for 2) total $weight_{SDS}$ (Figure mid panel); and for 3) BMI_{SDS} (Figure right panel). The height reference was updated for the positive secular trend in height that is still ongoing in Sweden. In contrast, the weight and BMI references were developed to be similar to the weight status in Swedish children from before the obesity epidemic, ie as the previous references obtained from $GrowUp_{1974}$Gothenburg cohort.

Conclusion: A paradigm shift for monitoring growth and weight status during puberty is now possible by using this innovative type of references for pubertal height, weight and BMI, all aligned-for-onset-of-puberty and thereby for the first time considering the individual timing of puberty. It opens up new possibilities to monitor growth and weight status during puberty: in the clinic for the individual child and in research for groups of children in order to estimate the change obtained for every time-period defined from onset until end of puberty. By using these tools, new knowledge will be obtained for both detection of diseases and for individualizing their treatment during the puberty.

Figure Girls: *Left panel*: onset-of-puberty-aligned height: from top total-$height_{SDS}$, non-specific-$height_{SDS}$, specific-pubertal-$height_{SDS}$; *Middle panel*: onset-of-puberty-aligned-$weight_{SDS;}$ *Right panel*: onset-of-puberty-aligned-$BMI_{SDS.}$ Mean (solid lines), 1,2,3SDS-lines (dotted lines)

References

1. Nierop et al. J Theor Biol, 2016:406:143.
2. Holmgren et al. BMC Pediatr,2017:17:107.

P1-P170

Evaluating Cut-offs for Automatic Growth Screening in Swedish Children – Using The Finnish Growth Monitoring Algorithm

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Background: Growth charts provide excellent help to the pediatric team in identifying abnormal growth patterns. However, the evaluation is highly dependent on the skills of the clinician. A computerized automatic screening system will add quality and patient safety in finding children with disorders affecting growth. Such screening system has been developed and tested in Finland and resulted in earlier detection of growth disorders[1-3].

Aim: To examine the proportion of Swedish children that will be identified as growing abnormally using the Finnish algorithms for growth monitoring when using present Swedish reference values[4].

Material: The study population was selected from the GrowUp$_{1974}$Gothenburg cohort of 5111 final grade school children who were born in Sweden around 1974[4]. The 2432 children who had longitudinal measurements around school entry, i.e. at age 5-8 years, and information about their father´s and mother´s heights, were included in the analysis. The mean age of these children were 5.9 years (SD 0.47) with foregoing measurement at 4.5 years (SD=0.58).

Methods: Height measures were analyzed using 3 screening algorithms and 99.5 % screening specificity[1,2]: (1) against population-based height references using height$_{SDS}$ ≤ -2.8070; (2) for distance from target height$_{SDS}$ (calculated from parental heights) ≤ -2.8070; and (3) for Δheight$_{SDS}$ ≤ -2.8070, i.e. difference between selected height$_{SDS}$ and foregoing measurement.

Results: The Finnish algorithms identified 20 children (0.8 %) using height$_{SDS}$. 67 children (2.8 %) were identified by Δheight$_{SDS}$. 26 children were identified by the difference from mid parental height$_{SDS}$ (1.1 %). Combining the selection criteria identified 74 children (3.0 %).

Conclusion: In total, 74 (3.0 %) out of 2432 Swedish children were identified as being short, growing slowly or being short in relation to mid parental height at school start at age 5-8 years, applying 99.5 % specificity of the Finnish algorithm[1,2]. Using the Finnish algorithms for growth screening applied on the Swedish reference identifies a larger population for referral than what has been published from Finland[1].

References

1. Sankilampi U, et al. JAMA. 2013 Sep 11;310(10):1071-2.
2. Saari A et al. J Clin Endocrinol Metab. 2012. 97: E2125-32.
3. Saari A et al. JAMA Pediatr. 2015 Mar;169(3):e1525).
4. Albertsson-Wikland K et al. Acta Paediatr 2002, 91:739-754).

P1-P171

Prospective Study of Growth in Swedish Children Treated with Modified Ketogenic Diet

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Purpose: Modified ketogenic diet (MKD) is one treatment option for intractable epilepsy and metabolic conditions such as glucose transporter type 1 deficiency syndrome (GLUT1-DS) and pyruvate dehydrogenase complex (PDC) deficiency. MKD is a less restrictive diet than the classical ketogenic diet (KD) and thus more tolerable. Some studies indicate that prolonged KD treatment can negatively affect linear growth in children. Long-term data is missing regarding the effects of MKD treatment in children. This study was designed to prospectively assess growth in children treated with MKD for 24 months.

Methods: The included patients (n=38; 21 girls, 17 boys) had a mean±SD age of 6.1±4.8 years at MKD initiation. Underlying etiologies were genetic epilepsy (n=6), GLUT1-DS (n=7), PDC deficiency (n=9), cortical malformation (n=3), mitochondriopathy (n=2), tuberous sclerosis complex (n=2), encephalitis (n=2), stroke (n=2), Aicardi syndrome (n=1) and of unknown etiology (n=4). Thirty patients had seizures prior to MKD. Body weight, height and laboratory tests were assessed at baseline, 6, 12 and 24 months.

Results: After 24 months, 29 patients remained on MKD and 57% responded to the diet with >50% seizure reduction. Weight SDS and height SDS were stable over 24 months (P=0.054 and 0.10 respectively), i.e., weight SDS median (min-max) -0.4 (-2.5 to 3.5) at baseline and 0.2 (-1.8 to 2.1) after 24 months; and corresponding values for height SDS -0.4 (-4.0 to 2.5) to -0.3 (-2.9 to 1.4). BMI SDS increased from 0.2 (-3.3 to 4.5) to 0.7 (-0.9 to 2.6) after 24 months, P<0.005. The median plasma 3-hydroxybutyric acid levels increased from 0.05 mmol/L to 2.35 mmol/L (0.42-5.20 mmol/L) after 6 months, P<0.0001, but remained stable thereafter, i.e., 2.30 mmol/L (0.18-4.90 mmol/L) after 12 months and 2.30 mmol/L (0.16-4.90 mmol/L) at 24 months. Median pH was 7.38 (7.23-7.51) at baseline and 7.39 (7.34-7.45) after 24 months, P=0.45.

At baseline, median IGF-I SDS was -0.15, which decreased to -0.85 after 6 months and to -1.0 at 12 months. From 12 to 24 months IGF-I SDS increased to 0.05. Median IGFBP3 SDS at baseline was 1.0 and was stable after 6 months, then decreased at 12 months to 0.1. From 12 to 24 months IGFBP3 SDS increased to 0.6.

Conclusions: MKD is as effective as KD with respect to seizure reduction. This first prospective longitudinal study demonstrates no negative impact on growth for MKD treatment in children.

P1-P172

Early Gut Microbiota and Childhood Growth

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Introduction: Physical growth according to genetic potential is a hallmark of childhood health [1]. Childhood growth is complex and the physiological processes involved in promoting healthy growth are not fully understood, including the gut microbiota. The gut microbiota matures from birth towards adulthood, and this process might be affected by several factors, including mode of delivery, food intake and antibiotic treatment. The bacterial gut microbiota is observed to be more immature in stunted and malnourished children [2], and furthermore, rapidly matured bacterial gut microbiota at 6 months is related to greater obesity risk at 18 months of age [3]. As for the gut mycobiota (fungal microbiota), the addition of dry yeasts (*Saccharomyces cerevisiae,* Baker's yeast) into livestock feeds increases the feed intake and daily weight gain of young ruminants. This finding indicates that the gut mycobiota could affect human childhood growth, too. In this prospective cohort, we are studying whether the gut microbiota maturation the first two years relates to growth velocity up to 8 years of age.

Method: In a prospective cohort, we followed 298 healthy offspring from birth until eight years of age and collected the anthropometric data (height and weight) in this period. We collected offspring stool samples at 10 days, 3 months, 1 year and 2 years and quantified the fungal and bacterial abundances of all the samples (qPCR) and identified the bacterial and fungal species by Illumina sequencing. We have used statistical mixed model analyses that account for repeated anthropometric data.

Results: Preliminarily, we found that increased fungal DNA concentration at two years was associated to increased height growth in childhood (β=0.12 (p=0.038)).

Discussion: In this work in progress, we will explore whether bacterial and fungal abundances and species of the early microbiota are associated to childhood growth. If childhood growth velocity is affected by the early gut microbiota, this could provide new insights into healthy and deviant childhood growth and childhood health, which could open for novel therapy.

1 Kliegman RL. Nelson Textbook of Pediatrics. Growth, development and behavior Elsevier, 2016.

2 Subramanian S, Huq S, Yatsunenko T, Haque R, Mahfuz M, Alam MA, *et al.* Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature 2014;**510**:417-21.

3 Dogra S, Sakwinska O, Soh SE, Ngom-Bru C, Bruck WM, Berger B, *et al.* Dynamics of infant gut microbiota are influenced by delivery mode and gestational duration and are associated with subsequent adiposity. mBio 2015;**6**.

P1-P173

Clinical and Radiological Manifestations in a Large Swedish Family with a Pathogenic Heterozygous *ACAN* Variant

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Objectives: Heterozygous mutations in the aggrecan gene (*ACAN*) are associated with idiopathic short stature, with or without advanced bone age (BA), osteochondritis dissecans (OCD) and early onset of severe osteoarthritis (OA). Variable features also include midface hypoplasia, brachydactyly, short thumbs and intervertebral disc degenerative disease.

Methods: We reviewed 173 radiographs in 22 individuals (8F:14M), (3shoulders,10hands,

10wrists, 17spines, 10pelvis, 31hips, 79knees, 5 lower-legs, 4ankles, 4feet).

Furthermore 2 computed tomography scans (1hip;1knee), and 5 magnetic resonance scans (2hips;3knees). All included individuals belong to a five generation Swedish family with short stature, OCD, and early onset OA (MIM#165800), caused by a pathogenic sequence variant, p.V2303M, in the C-type lectin domain of *ACAN*.

Results: In the group of children (n=6; age ≤15yo; 3F:3M), six had moderately advanced BA (range:6-17.5months). There was no clear sign of a metaphyseal or epiphyseal dysplasia, but subtle defects of the distal radial growth plate were present in four children. There were 3 males with OCD in the knees and one of them also presented OCD of the hip, scoliosis and schmorl's nodes of intervertebral discs. Actually he went through a derotation osteotomy in both hips and later a proximal tibia osteotomy and distal fibula osteotomy.

Among 16 adult patients (5F:11M), 16 had OCD (7elbows,4 hips,13 knees, 5 patellas), 13 developed early onset (>40y) OA, (1shoulder, 5elbows, 3 spines, 1 metatarsophalangeal joint, 6 hips, 12 knees, 1 patella). Radiological manifestations of the spine were detected in 4 patients and included 1 scoliosis, 1 spina bifida occulta, 1 platyspondyly, 1 schmorl's nodes, and 3 with lowering of the intervertebral discs.

Moreover 8 adult patients (3F:5M) have been operated, 4 patients had hip replacement (1F:3M;3bilateral;1unilateral) and 5 knee arthroplasties (2F:3M; 3bilateral;2unilateral) in particular 5 patients had tibia osteotomy of which one had combined tibia and fibula osteotomy. We measured all phalanges of eight adult hand x-rays and found no brachydactyly.

Conclusions: The pathogenic heterozygous p.V2303M variant in the *ACAN* gene causes mildly disproportionate short stature with early-onset OA and intervertebral disc degeneration often requiring multiple orthopedic interventions. Radiologic findings, included moderately advanced BA, OCD in knees, hips, and elbows as well as OA in 13 individuals. Further studies are needed to identify preventive measures that may slow the progression of OA and intervertebral disc disease and to determine the role of rhGH to improve final height.

P1-P174

Identification of *ADAMTS6* as a Novel Candidate Gene for Idiopathic Short Stature with Advanced Bone Maturation

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Aggrecan (*ACAN*) is the major proteoglycan in the articular cartilage, critical for the structure and function of growth plate cartilage.

Case Report: 11-year-old (y) boy admitted at 1.8 y of chronological age (CA), due to poor growth rate Height (H): 76cm (-2.75 SDS). Initial physical examination: mild dysmorphic features and prepubertal external genitalia (two scrotal testes, 1 cc volume each). Neurologic maturation was normal. Initial bone age (BA) was estimated at 3.3 y

Routine and hormonal laboratory evaluations were normal.

He was initially considered as a rare case of idiopathic short stature with advanced BA.

No spontaneous catch up growth was observed during the first 4 years of follow up

Given the clinical evidence an *ACAN* gene mutation was considered and studied by whole exome sequencing but no deleterious variants were found.

Nevertheless, we identified a potential candidate gene: *ADAMTS6 (*Gene ID: 11174) with 2 heterozygous variants in the same allele, c.[2424T>G;2425C>T], p.[Asn808Lys;Leu809Phe]. These variants were predicted to be damaging by all *in silico* prediction tools, and were not found in any database. Segregation was confirmed by Sanger sequencing, revealing that his mother and sister were also heterozygous for these variants.

At 7.5y of CA with a BA slightly advanced (8.5y), H: 107.9cm (-3.03 SDS) even though a normal serum GH levels response to pharmacological arginine/clonidine stimulatory test was found, rhGH treatment (0.33 mg/Kg/day) was started.

Moreover, at 10.5 y of CA, clinical evaluation showed increase of testicular volume (TV) (4/4 cc) and Tanner Stage (TS): G1, PH 1. Four months later, early and accelerated pubertal progression was observed (H: 127.4cm (-1.77 SDS, rhGH treatment maximal ΔHSDS:+1.26, TV: 8/8 cc, TS: G3, PH: 3). Hormonal studies confirmed onset of puberty. According to present knowledge, there is no explanation to justify why the patient presented early onset of puberty and accelerated pubertal development. We speculate that *ADAMTS6* mutation might be involved in the regulation of the early onset of puberty and accelerated pubertal tempo.

Since aggrecan protein is involved in the regulation of developmental neural plasticity, we propose that the interaction between ADAMTS6 and aggrecan protein might be involved in the mechanism of early onset of puberty and accelerated pubertal tempo.

Finally we propose *ADAMTS6* as a candidate gene for idiopathic short stature and recommend further investigation to confirm this hypothesis.

P1-P175

Dual Function of the Retinoic Acid Catabolizing Enzyme CYP26C1 – Underlying Idiopathic Short Stature and Modifying Disease Severity in SHOX Deficiency

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Short stature is diagnosed when height is significantly below the average of the general population for that person´s age and sex. To elucidate the factors that modify disease severity/penetrance in short stature, we have studied a three-generation family with SHOX deficiency. We have found that the retinoic acid degrading enzyme CYP26C1 is a modifier for SHOX deficiency phenotypes towards the more severe clinical manifestations (Leri-Weill dyschondrosteosis) and confirmed these findings in independent cases.

Here, we asked whether damaging variants in *CYP26C1* alone could lead to short stature. We performed exome and Sanger sequencing to analyze 856 individuals with short stature where SHOX deficiency was previously excluded. Three different damaging missense variants and one splicing variant were identified in six independent individuals. The functional significance of the identified variants was tested *in vitro* (splicing defect) or *in vivo* (missense mutations) using Zebrafish as a model. The identified CYP26C1 variants affected the catabolic activity of *CYP26C1* in human primary chondrocytes and zebrafish embryos. Together, the genetic and functional data reported here indicate that *CYP26C1* represents a novel gene underlying growth disorders with dual function: damaging variants in *CYP26C1* in the absence of *SHOX* mutations can lead to short stature and damaging variants in *CYP26C1* modify SHOX deficiency phenotypic outcomes through the retinoic acid signaling pathway.

P1-P176

Growth Plate Disorders Are the Main Cause of Severe Familiar Short Stature in Children Classified and Treated with Growth Hormone as SGA or GHD

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Introduction: Familiar short stature (FSS) is a common variant of growth with heterogeneous etiology. Children with FSS are often excluded from further check-up and treatment. However, significant number of children with FSS comply even with the European criteria for growth hormone (GH) therapy – patients with SHOX-deficiency, growth hormone deficiency (GHD) or these born short for gestational age (SGA). The aim of the study was to identify genetic etiology of short stature in children from families with severe FSS treated with GH and classified as SGA and/or GHD.

Materials and methods: Out of 555 children treated with GH for GHD and/or SGA, 32 (5.8 %) had severe FSS defined as live-minimum height ≤-2.5 SD in both patient and his/her shorter parent. These were included into further study. Twenty-one were born SGA, 24 had GHD (median of GH level after stimulation 6.7 ug/l). In four, genetic etiology was already known (*ACAN* variants in 2 families, *NF1* in 1 family, *PTPN11* in 1 family). In remaining 28 patients (20 boys, median age 10.2 years, median age at start of GH therapy 7 years) no genetic cause of short stature was elucidated prior the study. Genetic analysis was performed using whole exome sequencing and the obtained results were further evaluated using ACMG standards and guidelines.

Results: A causative gene variant was identified in 17/32 (53 %) children of the study cohort. Of these, 9/17 carried gene variants affecting growth plate (*COL2A1* in 2 families, *COL11A1* in 2 families, *ACAN* in 2 families, *FLNB*, *FGFR3* and *IGF1R* in single families). Interestingly, 89 % of them (8/9) were born SGA. In 3/17, products of the disrupted genes affected IGF-associated proteins (*IGFALS* 2 families, *HGMA2* 1 family). In remaining 5/17 probands, the growth failure was caused by miscellaneous etiologies (genes *THRH*, *MBTPS2, GSHR, NF1, PTPN11*). Some variants fully explained the phenotype in proband and his/her family, others definitely contributed to the proband's short stature but did not explain all features of complex phenotypes within the families.

Conclusion: In children from families with severe FSS who are classified as SGA and/or GHD, genetic etiology of short stature is heterogeneous. Interestingly, genes affecting the structure and function of the growth plate play an important role.

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P1-P177

Genetic Investigation of Children with Syndromic Prenatal Onset Short Stature

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Background: Patients born small for gestational age (SGA) with additional syndromic features to short stature are likely to present with genetic causes.

Aim: To perform a clinical and genetic-molecular investigation of a group of syndromic SGA patients without catch-up growth.

Methods: We selected 118 patients born SGA [birth weight and/or length standard deviation score (SDS) ≤-2 for gestational age] without catch-up growth at the age of 2 or above [height SDS ≤-2] and dysmorphic features, developmental delay and/or intellectual disability. These patients were evaluated clinically, laboratory and radiologically by professionals with expertise in dysmorphology. Among these syndromic patients, they were reclassified as known or unknown syndromic short stature, according to the establishment of the clinical diagnosis by routine exams and clinical evaluation. Molecular evaluation was performed according to the clinical diagnosis. Unknown syndromic short stature patients were submitted for molecular karyotyping (aCGH/SNPa) and/or whole exome sequencing (WES).

Results: Fifty-three (44.9%) patients had a clinical diagnosis of a specific genetic syndrome and 78.7% confirmed the initial diagnosis by target genetic tests. These patients were diagnosed as Silver-Russell (n=9), Achondroplasia (n=6), Hypochondroplasia (n=4), Bloom (n=3), Noonan (n=2), Floating-Harbor (n=2), Leri-Weill dyschondrosteosis (n=2), Langer dysplasia (n=2), Cornelia de Lange (n=2) and other syndromes (Seckel, Laron, CHARGE, Osteogeneses imperfecta, Spondyloepimetaphyseal dysplasia; each one, n=1). Ten patients did not confirm the initial diagnoses by target analyses. Sixty-five patients were classified as unknown syndromic short stature based on the clinical data. Forty-three under-

went aCGH/SNPa screening and 12 (27.9%) patients had pathogenic CNVs. Twenty-six patients were submitted to WES and 13 (50%) had pathogenic/possibly pathogenic variants in genes already associated with growth disturbance: *ANKRD11* (n=3); *COL2A1* (n=2); *SRCAP* (n=2); *BRCA1; POC1A*; *IGF1R; PTPN11; KIF11* and *PCNA* (each one, n=1). These genes were associated with rare syndromic conditions associated with growth impairment. All identified SNVs are extremely rare or absent in public database, were predicted to be deleterious and segregated with the phenotype.

Conclusion: The rarity, variability and clinical heterogeneity of syndromic short stature makes establishing a clinical diagnosis difficult. Our genetic evaluation protocol established the definitive diagnosis in 52.5% (62/118) of a group of patients with syndromic short stature. Of these patients, 40.3% (25/62) had no initial clinical diagnosis. A clinical diagnostic paradigm with a systematic phenotype evaluation, targeted genetic testing and exome sequencing increases the diagnostic rate of syndromic short stature patients.

P1-P178

Identification of Three Novel Mutations in 10 Pediatric Patients with Unexplained Syndromic Short Stature Identified by Targeted Exome Sequencing in Korea

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Objectives: Owing to the tremendous advances in next-generation sequencing technology, numerous monogenic causes of growth disorders have been identified. Identifying novel rare genetic causes of short stature (SS) is quite challenging. In 2017, we reported a mutation analysis of 15 patients with undiagnosed syndromic SS or overgrowth. In this study, 6 mutations in another 10 Korean patients with unexplained syndromic SS are reported. The aim of this study is to identify underlying genetic causes of unexplained SS.

Methods: Ten pediatric patients with profound SS, mean height of −2.5 SD score (SDS), and a normal growth velocity, some of whom had additional dysmorphic features, were subjected to targeted exome sequencing (TES) study using the Next Seq platform and a TruSight One panel.

Results: Among the 10 patients with unexplained SS, 6 different disorders were identified, and the diagnostic yield was 60%. In the patients with SS, Coffin-Lowry syndrome (CLS) with a novel missense mutation inherited from mother, Cleidocranial dysplasia, Acid-bile subunit deficiency (ALSD) with a novel compound heterozygous mutation, Coffin-Siris syndrome (CSS) with a novel nonsense mutation, X-linked creatine transporter deficiency with speech delay, and Acromesomelic dysplasia, Maroteaux type (AMDM) were identified.

Conclusions: TES led to the diagnosis of a monogenic disorder in six of the 10 individuals, including cases with three novel mutations. This study shows that TES is a very promising tool for the identification of pathogenic mutations in patients with unexplained syndromic short stature.

P1-P179

Beckwith Wiedemann Syndrome: First International Consensus Regarding Diagnosis and Clinical Management

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Beckwith Wiedemann syndrome (BWS) is a rare overgrowth disorder characterised by macroglossia, exomphalos, lateralised overgrowth, organomegaly, hyperinsulinism, and an increased risk of embryonic tumor during early life. In about 80% of BWS cases, molecular defects are identified at the imprinted 11p15.5 region which contains the *IGF2* and the *CDKN1C* genes (most patients show methylation defects at either imprinting control region IC1 or IC2, or paternal uniparental isodisomy). Previously, many clinical scoring systems have been proposed to delineate BWS with variable sensitivity or specificity. Regarding clinical management, especially regarding tumor screening, no consensual approaches have hitherto been determined.

Aim: to establish recommendations regarding clinical and molecular diagnosis of BWS, and clinical management of patients with BWS.

Method: based on a PubMed search, a comprehensive literature review was performed by a group of international experts to establish a draft consensus statement. A 3-day face-to-face meeting involving 35 participants took place in March 2017 to discuss, formulate and vote on 72 consensus recommendations.

Results: a new scoring system based on clinical symptoms (including cardinal and suggestive features) has been established to 1) indicate molecular testing and 2) define patients with a clinical diagnosis of BWS. The experts introduced the notion of "Beckwith Wiedemann spectrum" (BWSp) which includes patients with a molecular defect at 11p15.5 (irrespective of the clinical presentation) and those with a clinical diagnosis of BWS (irrespective of the results of the molecular investigations). Consensus recommendations are applicable to all BWSp patients. A diagnostic tree has been established to guide molecular testing in case of suspicion of BWSp, with first-line diagnosis based on methylation studies of the 11p15.5 imprinted region. Regarding clinical management, recommendations include those for growth, lateralised overgrowth, macroglossia, exomphalos, hypoglycaemia and hyperinsulinism, cardiac, renal and neurological complications. Regarding tumor screening, the experts agreed about a surveillance program stratified by the molecular subtype, with no tumor screening recommended for patients with BWSp due to an IC2 hypomethylation because of their lower tumor risk, and an abdominal ultrasound scan every 3 months until the age of 7 years for all other BWSp patients, including patients with a clinical diagnosis of BWS and no molecular defect.

P1-P180

Silver Russell and Beckwith-Wiedemann Syndromes: Mosaic Distribution of Epigenetic Anomalies

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Background: Genomic imprinting is an epigenetic mechanism referring to the monoallelic silencing of genes according to their parental origin. Human chromosome 11p15.5 encompasses two imprinted domains (ICR1 and ICR2) playing an important role in controlling fetal and postnatal growth. Genetic (uniparental disomy or gain/loss of function mutations) or epigenetic alterations at the 11p15.5 imprinted region (loss or gain of DNA methylation) are associated with two clinical disorders with opposite phenotypes: Silver-Russell syndrome (SRS, growth restriction, pubertal and metabolic disturbances) and Beckwith-Wiedemann syndrome (BWS, overgrowth with enhanced tumor risk during childhood). These epigenetic anomalies are thought to occur in a mosaic manner, postzygotically. Therefore, recent consensus about SRS and BWS highlighted the usefulness of testing alternative tissues in case of a normal molecular test in leucocytes. However, only few data have hitherto been reported in Human.

Methods: Allele-Specific Methylated Multiplex Real-Time Quantitative PCR was performed in fibroblasts for patients with a clinical diagnosis of SRS or a meeting the clinical criteria for BW spectrum (because of the presence of lateralized overgrowth) in which 11p15.5 molecular testing was normal in blood samples.

Results: Ten patients (three SRS and seven BWS) have been detected with normal methylation in leucocytes and abnormal methylation in fibroblasts. Three SRS patients met the clinical criteria for diagnosis of SRS with a score ≥ 4/6 in Netchine-Harbison clinical scoring system. All seven BWS patients had lateralized overgrowth (LO). Two patients presented with isolated LO. Embryonic tumours occured in two BWS patients (one bilateral Wilms tumor and one hepatoplastoma). One patient had macroglossia, another an ombilical hernia and one a nephromegaly. 11p15 loss of methylation has been detected in skin fibroblasts in three SRS patients, ICR1 11p15 gain of methylation in five BWS patients and ICR2 11p15 loss of methylation in two BWS patients. By contrast, DNA methylation analysis in leucocytes was normal in all patients.

Conclusion: 11p15 Methylation patterns may vary between different tissues. This can explain some cases of a negative molecular diagnosis when tested in blood samples for SRS and BWS. This is indeed in favor of a tissue mosaic distribution of these epigenetic anomalies and their postzygotic onset, and reinforces the usefulness of testing alternative tissues in case of clinical suspicion of BWS/SRS.

P1-P181

Long Term Effects of Childhood Growth Hormone Treatment on Height and Body Mass Index in Adolescents and Adults with Silver-Russell Syndrome

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Growth hormone (GH) is commonly used during childhood to treat short stature in Silver-Russell syndrome (SRS), but final height and long-term body mass index (BMI) data are limited.

Objective: to evaluate height and BMI in older individuals with molecularly confirmed SRS and compare those previously treated with GH to those untreated.

Methods: growth data on individuals aged ≥13 years with SRS were evaluated from UK, French and German cohorts. Height and BMI values were converted to age- and sex-specific standard deviation scores (SDS) using country-specific reference data. Participants were stratified into two groups according to prior GH exposure and compared using the Mann-Whitney U test.

Results: 71 individuals (40 females, 31 males) aged 13.2-69.7 years (median 22.0) were studied. Molecular diagnoses included loss of methylation at H19/IGF2 in 80.3%, maternal uniparental disomy for chromosome 7 in 16.9% and IGF2 mutation in 2.8%. 77.5% received GH with a median treatment duration of 7.10 years (IQR 3.96 to 11.00). The median time since GH discontinuation was 9.97 years (IQR 2.68 to 15.94).

Median early height SDS in the GH-untreated and GH-treated groups were -2.91 (IQR -3.62 to -2.40) and -3.46 (IQR -5.15 to -2.76) respectively (p=0.055). Median height gain from early height SDS to final height SDS was 0.53 (IQR -0.13 to 1.37) in the GH-untreated group and 1.53 (IQR 0.80 to 2.52) in the GH-treated group (p=0.006). The median final height SDS of GH-untreated and GH-treated individuals were -2.74 (IQR -3.36 to -1.13) and -2.22 (IQR -3.66 to -1.16) respectively (p=0.720).

The median change in BMI from early BMI SDS to final BMI SDS was 3.58 (IQR 1.85 to 5.18) in the GH-untreated group and 1.95 (IQR 0.76 to 2.69) in the GH-treated group (p=0.005). The median BMI SDS of GH-untreated and GH-treated individuals were 1.66 (IQR -0.73 to 2.03) and -1.10 (IQR -1.80 to 0.00) respectively (p=0.002). In the GH-untreated group there was a positive correlation between duration of time since GH treatment and BMI SDS (Spearman's rank correlation coefficient 0.341, p=0.027).

Conclusions: although final height was comparable in GH-treated versus GH-untreated individuals, height gain was significantly greater in GH-treated individuals who were shorter in childhood. We speculate that strategies to prevent rapid bone-age maturation during puberty may further optimize the benefit of GH treatment until final height. Following GH discontinuation, treatment was associated with lower BMI and lower gain in BMI, suggesting a long-term effect.

P1-P182

Year-one Effectiveness and Overall Safety of NutropinAq® for Growth Hormone Deficiency (GHD) and Other Paediatric Growth Disorders: Completion of the International Cooperative Growth Study (iNCGS) European Registry

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Background: The iNCGS Registry monitored long-term safety and effectiveness of NutropinAq® (Somatropin injection) for paediatric growth disorders.

Objective: To report year-1 effectiveness and safety data from the iNCGS registry (NCT00455728).

Methods: Open-label, non-interventional, post-marketing surveillance study, in seven European countries from October 2005–December 2016. Measurements included height Standard Deviation Score (SDS) and height velocity. Investigators reported non-serious related treatment-emergent adverse events (TEAEs) and serious AEs, regardless of relationship to study treatment.

Results: Of 3657 screened patients, 2792 were enrolled. Mean (SD) age was 7.7 (4.1) years at diagnosis and 9.5 (3.6) years at first NutropinAq® treatment. 85.3% patients were treatment-naïve, 67.9% naïve pre-pubertal [NPP], 14.6% non-naïve (status missing, n=4). GHD was present in 2082 patients (74.6%) and idiopathic in 1825. Non-GHD diagnoses included: Turner Syndrome (n=199); idiopathic short stature (n=90); small for gestational age (n=254). The starting dose of NutropinAq® varied by indication and followed the label recommendations. Median duration of exposure was 38.2 months. At baseline, the Registry population (n=2714) had mean (SD) height SDS of -2.4 (1.0) and height velocity of 5.2 (2.4) cm/year. After 1 year of treatment, mean [95% CI] change from baseline in height SDS was: overall, 0.60 [0.58;0.62] (n=2125); treatment-naïve, 0.64 [0.61;0.66] (n=1839); NPP, 0.68 [0.65;0.70] (n=1465); NPP with organic GHD, 0.78 [0.67;0.88] (n=113). Height velocity after 1 year was: overall, 8.5 cm/year [8.4;8.6] (n=2131); treatment-naïve, 8.8 cm/year [8.7;8.9] (n=1843); NPP, 8.8 cm/year [8.7;8.9] (n=1467); NPP with organic GHD, 9.4 [8.9;10.0] (n=114). Improvements in effectiveness parameters occurred in all subgroups by disease aetiology, and were greatest in organic GHD. In the Safety Population (n=3493), 610 patients (17.5%) had ≥1 non-serious related TEAE, most frequently abnormal investigations (304 [8.7%]), including increased insulin-like growth factor (256 [7.3%]). 206 patients (5.9%) experienced ≥1 serious TEAE, considered related to NutropinAq® in 27 (0.8%). 20 patients (0.6%) experienced a neoplasm considered as a serious event (4 [0.1%] considered treatment-related) but 14 had a prior history of neoplasm. Seven deaths occurred, all considered not related to NutropinAq®.

Conclusions: After 1 year of treatment with NutropinAq®, there was an improvement in mean height SDS and height velocity in all subgroups by prior treatment status and aetiologies, despite a >1-year delay between diagnosis and start of treatment. These data confirm that the benefit-risk profile for NutropinAq® remains favourable, with no new safety concerns in children with growth failure treated within the recommended indication.

P1-P183

Carriers of IGF1-Receptor Mutations as a Subgroup of SGA Patients: a Comprehensive Retrospective Comparison of Response to rhGH Treatment and Health Profile

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Objective: IGF-1 receptor mutations (IGF1RM) are a rare abnormality; however, affected patients exhibit severe postnatal growth retardations without catch-up growth. Although several cases of IGF1RM have been described, a comprehensive retrospective analysis of the potential benefit of rhGH treatment is still missing. The aim of this study was therefore to investigate baseline auxology, response to rhGH therapy and potential metabolic effects in patients with IGF1RM in comparison to a cohort of children born small for gestational age (SGA).

Methods: Over the past 15 years we identified 23 patients with 17 different mutations within the IGF-1 receptor, with 17 being treated with rhGH. We compared these patients to 34 rhGH treated SGA children retrospectively. We analyzed birth parameters, growth before and under rhGH therapy, near final height, glucose homeostasis and insulin sensitivity. Additionally, health profiles of adult IGF1RM carriers were compared to those of former SGA patients.

Results: IGF1RM patients showed significantly decreased body growth both before and during rhGH treatment. In particular first-year response was diminished in IGF1RM patients (Δ height SDS of 0.29 vs. 0.65 for SGA), with many having very poor response (defined as growth < 0.3 SDS; 53 % of IGF1RM carriers vs. 17 % in SGA patients). However, when first-year response was good, some patients showed catch-up to the level seen in SGA children when treated for a longer period (≥ 3 years).

An association between IGF1R mutation and a disturbed glucose homeostasis has been suggested by some investigators. However, we observed no significant differences in glucose homeostasis before treatment (measured as fasting glucose, HbA1c and

HOMA-IR) in IGF1RM carriers compared to SGA controls. In contrast - during rhGH treatment - there was a stronger decrease in insulin sensitivity (HOMA-IR of 2.1 for IGF1RM vs. 1.15 for SGA). No differences in health profile could be seen in adult IGF1RM carriers compared to SGA controls.

Conclusion: The presence of IGF1R mutations in SGA children correlates with a more severe growth phenotype and poor response to rhGH therapy. However, individual variability is high, with some patients being good responders. But causes for these differences remain unclear. Therefore, we conclude that IGF1RM carriers should not be excluded from treatment with rhGH, but a critical reevaluation of success should be performed after 2-3 years of treatment. In addition, we observed no significant influence of IGF1RM on glucose metabolism and health profile later in life. However, close monitoring during rhGH therapy is recommended.

P1-P184

Characteristics, Effectiveness and Safety Data for Patients with Growth Failure Treated with Recombinant IGF-I (rhIGF-I) and Achieving Adult or Near-adult Height (AH): Results from The European Increlex® Growth Forum Database (EU-IGFD) Registry

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Background: The EU-IGFD registry comprises data for children with severe primary IGF-I deficiency (SPIGFD) receiving rhIGF-I (mecasermin [rDNA origin] injection; Increlex®) for growth failure.

Objective: To report patient characteristics, effectiveness and safety data for children receiving rhIGF-I for SPIGFD and achieving AH.

Methods: Patients from this ongoing observational study (NCT00903110) were included in analyses if reaching AH (last height velocity [HV] <1cm/year) by 10-Oct-2017. Population comprised patients discontinuing therapy at AH and those discontinuing for other reasons followed until AH.

Results: Characteristics: Of 247 patients enrolled, 67 achieved AH (43 [64%] male; 27 treatment naïve and prepubertal [NPP]; 40 non-treatment naïve or pubertal [including one undetermined] [NNP]). At baseline, median (Q1–Q3) highest stimulated GH levels were 21.35 (13.60–40.00) ng/mL. Most patients were pubertal stage 1 (42/64) and had SPIGFD (57/67) including 12 with Laron syndrome. At first rhIGF-I intake in this study, mean (SD) age was 12.9 (2.6) years (NPP, 11.9 [2.1]; NNP, 13.5 [2.8]) and mean (SD) height SDS was –3.73 (1.34) (n=60) (NPP, –3.46 [1.06]; NNP, –3.92 [1.50]). Additionally, HV was 4.47 (1.30) cm/year (n=36), predicted adult height SDS –2.5 (2.2) (n=35) (calculated using: Bayley-Pinneau [19/42], Tanner-Whitehouse [16/42], other [6/42], Roche-Wainer-Thissen [1/42]), weight SDS –2.84 (1.22) (n=60). AH reached was the main reason for treatment discontinuation (39/66: NPP, 15/26; NNP, 24/40), followed by lack of efficacy (9/66). Treatment: Median (Q1–Q3): duration was 44.3 (27.9–54.6) months and dose during last year of treatment was 102.3 (85.8–120.0) µg/kg twice daily. Effectiveness: HV improved at year 1 (mean [SD], 6.38 [2.53] cm/year; NPP, 7.11 [2.35]; NNP, 5.91 [2.57]) and remained above baseline level for 2–3 further years. Final adult height SDS: mean (SD), –3.08 (1.79) (NPP: –2.30 [1.35]; NNP: –3.62 [1.88]). Difference between final and baseline height SDS: mean (SD), 0.7 (1.0) (NPP: 1.1 [0.7]; NNP: 0.4 [1.0]). For NPP, lower baseline age predicted greater changes from baseline in final adult height SDS (multivariate analysis [estimate (95% CI) by 1-unit increment: 0.25 (0.13–0.36); $p<0.001$]). Safety: 32/67 patients reported targeted adverse events (most frequent: hypoglycaemia [13/67]).

Conclusions: Patients achieving AH were 12.9 years old at rhIGF-I treatment initiation. Nevertheless, rhIGF-I improved adult height in SPIGFD, with greater improvements for NPP than NNP patients. Age was a predictor for change from baseline in final adult height SDS. Safety is consistent with the known profile of mecasermin.

P1-P185

Growth Outcome in Girls with Idiopathic Central Precocious Puberty Treated with Gonadotropin-releasing Hormone Agonist

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Objective: Gonadotropin-releasing hormone agonists (GnRHa) are the treatment of choice for central precocious puberty (CPP) and have been widely used for decades. We determined the effect of GnRHa treatment on auxological outcomes of girls with idiopathic CPP.

Methods: This study included 84 girls treated monthly with depot leuprolide acetate who had reached adult height. We compared their final adult height (FAH) with their initial predicted adult height (PAH). We performed a multivariate analysis of the factors associated with FAH in all girls diagnosed with CPP.

Results: We performed the final evaluations at a mean age of 14.1 ± 0.8 years after a mean treatment duration of 2.98 ± 0.73 years (ranging from 1.5 - 4.8 years). Menarche had occurred at 12.6 ± 0.6 years of age, which was 16.5 ± 6.1 months after discontinuation of GnRHa therapy. Mean FAH was 160.1 ± 5.0 cm, which was significantly higher than that of initial PAH (156.1 ± 5.7 cm; $P < 0.001$). To investigate whether growth outcomes were influenced by the age at initial treatment, we divided all patients into two groups: those treated between 6 and 8 years (n = 23) and those treated after 8 years (n = 61); there were no significant differences in FAH between the two groups. FAH was significantly and positively correlated with height standard deviation score (SDS) at the end of treatment and with target height, whereas the difference between bone age and chronological age at the start and end of treatment was negatively correlated with FAH.

Conclusion: FAH was significantly higher than initial PAH in girls with CPP who were treated with GnRHa. Also, GnRHa treatment was still effective even after 8 years of age in girls with CPP.

P1-P186

Maternal Uniparental Disomy for Chromosome 20: Physical and Endocrinological Characteristics of Six Patients

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Context: Maternal uniparental disomy for chromosome 20 (UPD(20)mat) resulting in aberrant expression of imprinted transcripts at the GNAS locus is a poorly characterized condition. Only 10 non-mosaic cases have been studied clinically. These patients presented with pre- and post-natal growth failure and feeding difficulties. The phenotype of these cases overlapped with that of Silver-Russell syndrome (SRS) and small for gestational age-short stature (SGA-SS); however, the etiological relationship between UPD(20)mat and SRS/SGA-SS remains unclear. Moreover, no report has described endocrinological assessment of UPD(20)mat patients, although paternal UPD(20), the mirror image entity of UPD(20)mat, is known to cause multiple hormone resistance reflecting reduced Gsα expression.

Methods: We screened for DNA methylation abnormalities at the GNAS locus in 59 individuals who satisfied the diagnostic criteria for SRS using the Netchine-Harbison clinical scoring system and 98 patients clinically diagnosed with SGA-SS. Patients with abnormal methylation levels at the GNAS locus were subjected to microsatellite analysis for chromosome 20 using DNA samples obtained from these patients and their parents. In addition, we performed Comparative genomic hybridization (CGH) + single nucleotide polymorphism (SNP) array analysis for UPD(20)mat patients to detect the region of isodisomy or cryptic heterodisomy.

Case description: Six patients showed non-mosaic hetero- and/or iso-disomy for the entire chromosome 20. Four patients were identified through UPD(20)mat screening for 59 patients with etiology-unknown SRS and one patient was identified for 98 patients with SGA-SS, respectively. One patient was identified through molecular analysis for patients with developmental defects. They manifested postnatal growth failure and feeding problems with or without developmental delay and other clinical features. Five of four patients were born SGA. Two patients exhibited hypercalcemia and low or low-normal PTH levels. One patient showed constantly decreased TSH levels after 12 years of age, although she had a normal TSH level at 5.2 years of age.

Conclusion: The results suggest that UPD(20)mat underlies growth failure and feeding problems with additional features, and could account for more than 6% of etiology-unknown SRS and 1% of SGA-SS. One patient indicate that UPD(20)mat can also underlie SS without SGA. Most importantly, this study provides the first indication that UPD(20)mat can be associated with hypersensitivity of hormone receptors, which may gradually develop with age.

P1-P187

A Novel Deadly Variant in The TP53 Gene Causing Li-Fraumeni Syndrome. The Importance of Clinical Awareness and the Contribution of Molecular Diagnosis in Active Prevention Within Families with Multiple Tumor Incidents at a Young Age

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Background: Li-Fraumeni Syndrome (LFS) is an autosomal dominant hereditary cancer syndrome associated with germline pathogenic variants in in the TP53 gene and high risk of a broad range of early-onset malignancies. The 70-77% of LFS associated tumors are: breast cancer, soft-tissue sarcoma, brain tumor, osteosarcoma and adrenocortical carcinoma. However, ovarian, pancreatic and gastrointestinal track tumors are also LFS-related. The patients with LFS are at risk for a second and third primary tumor.

Patients and Methods: A 15-month old girl (generation V) was referred to our center because of clitoromegaly 1.5 cm and pubic hair. An adrenal ultrasound detected a large adrenal tumor at the lest side. No other tumors were detected. Left total adrenalectomy was performed confirming adrenocortical carcinoma. Considering the family history, with a maternal cousin operated of adrenocortical tumor at the age of 5 months and the maternal grandmother with a diagnosis of bilateral breast cancer at the age of 35 yrs, we performed genetic testing to all the available family members (mother, father, brother, maternal grandmother, maternal aunt, maternal cousin - not the one with adrenocortical tumor

in the past), as a genetic dominant trait seemed most probable. Our hypothesis was supported also by the fact that other family members of the maternal family tree experienced tumors like osteosarcoma (generation III), tumors of the cervical spine (generation I, II and III) and pancreas (generation III) and died before the age of 30 yrs. Whole genome sequencing was performed. Even before we had the results, we examined clinically the mother aged 24 and prescribed an extensive laboratory workup which revealed bilateral breast cancer for which she was operated immediately with bilateral total mastectomy and subsequent appropriate chemotherapy.

Results: The referred child, the mother and the maternal grandmother were positive for a novel variant (c. 892delGinsTTT, p. Glu298PhefsX48, NM_0005464) in the TP53 gene. This variant is predicted to cause loss of normal protein function either through protein truncation or non-sense mediated mRNA decay. Considering the current data, this variant is most probably a pathologic variant.

Conclusion: Clinical awareness and the detailed family history resulted in a timely diagnosis of adrenocortical tumor in the child and in early detection of a bilateral breast cancer in a very young mother. Simultaneously, affirming the molecular diagnosis allows for appropriate genetic counselling and planning an intensive follow-up of the affected members, considering the high probability of a second and a third primary tumor.

P1-P188

Mutations in *SHOX*, *GHR* and *IGFALS* Genes Among Indian Children with 'Idiopathic Short Stature'

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Background: Linear growth is a multifactorial trait.Short children in whom no definite etiology is found after thorough evaluation are considered to have idiopathic short stature (ISS). A proportion of these children have a monogenic basis of short stature.

Aim: To study the prevalence of mutations or pathogenic variants in *SHOX*, *GHR* and *IGFALS* genes among Indian children with ISS.

Methods: Children aged 4-16 years, with height below -2 standard deviation score (SDS), who were born appropriate for gestational age (AGA) and in whom step-wise investigative work-up (including stimulated Growth Hormone test) was normal, were recruited (n=61). Multiplex ligation-dependent probe amplification (MLPA), and direct sequencing were undertaken for identification of deletion/duplication and point mutations in *SHOX* gene. Bidirectional sequencing was performed for identification of mutations or likely pathogenic variants in *GHR* and *IGFALS* genes. *IGFALS* gene was sequenced only in children with fasting serum IGF-1 below -1SDS.

Results: Four children (6.5%) had mutations in SHOX gene. One had duplication of exon 5, the second had heterozygous splice site point mutation c.278-1G>C at acceptor site of exon 3, and one child each had partial and complete heterozygous deletion of *SHOX* gene. Height was worst affected in the children with the splice site point mutation c.278-1G>C, and complete delection (height SDS of -3.9 and -3.8, respectively), while it was much less affected in the children with duplication of exon 5 and partial deletion (height SDS of -2.4 and -2.1, respectively). None of the patients had mutation in *GHR* gene, although 7 non-pathogenic polymorphisms were observed. Out of 39 patients in whom *IGFALS* gene was sequenced, heterozygous frameshift or missense variants were found in 3 (7.8%) patients. One patient (height SDS -3.8) had a novel heterozygous frameshift variant (c.764_765insT, p.A265Gfs*114), which was predicted as disease causing variant by MutationTaster software. One patient (height -3.1 SDS) had heterozygous missense variant c.1756C>T, R586W in exon 2, which is a reported pathogenic variant. The third patient (height SDS -3.3) had heterozygous missense variant c.1793G>A, p.R598H in exon 2 which was predicted by Polyphen and MutationTaster softwares as possibly damaging and disease causing, respectively. The variants c.764_765insT, p.A265Gfs*114 and c.1756C>T, R586W were not found in a large normative data repository of Indian patients (MedGeneome Labs Pvt Ltd. Bangalore, India).

Conclusion: Mutations/ pathogenic variants in SHOX and IGFALS genes account for about 15% of ISS in Indian children.

Growth & Syndromes P2

P2-P239

Heart and Aorta Anomalies in Turner Syndrome and Relation with Karyotype

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Introduction: Turner Syndrome(TS) is known to be associated with a high risk of cardiac anomalies and cardiovascular diseases. Detailed cardiac evaluation at diagnosis and serial evaluation for dissection is warranted.

Aim: This study aimed to evaluate TS patients for cardiac pathology using magnetic resonance imaging(MRI).

Methods: Clinical findings, karyotypes, echocardiogram results, cardiac MRI findings of 33 patients with TS were evaluated. Measurements of the aortic diameter at various points were recorded and Z scores and Aortic size index(ASI) were calculated.

Results: All patients had presented with short stature at the age of 9.0±3.0 years. Karyotype analysis revealed 45,X in 15 patients(46%). 14 patients(42%) had mosaicism and 4(12%) had 46, XX;X chromosomal anomaly. MRI's were taken at a mean age of 13.7±3.4 years. Mean BMI SDS at the time of MRI was 0.75±1.4.On echocardiogram five patients had bicuspid aortic valve, two patient had coarctation of the aorta. Four patients had hypertension. No patient had aortic dissection. MRI revealed cardiac pathology in 10 patients(30%). Namely, coarctation of the aorta(n=4), aberrant right subclavian artery(SCA)(n=3), tortuosity of the descending aorta(n=1) and fusiform dilatation of the left SCA (n=1) was revealed. Two of the four coarctation patients detected on MRI

were detected also on echocardiogram. One patient had a post-ductal coarctation that was located too distally to be seen on echocardiogram, whereas the other patient had a very mild coarctation that was undetectable on echocardiogram due to lack of a gradient on Doppler imaging.

Diameter of the sinotubular junction was found to be higher than 2SD's above mean [2,4±1,5; min-max:0,35 and 5,7]. The median Z score for the diameter of the isthmus was 0.9 (-2.0to-4.0). The median Z score for the diameter of the ascending aorta was 0.4 (-1.7to2.8). The median Z score for the diameter of the descending aorta was - 0.4 (-1.9to-2.6). Aortic diameters and aortic size index values of the 45,X and non-45,X patients were compared and the 45,X group was found to have a significantly higher mean ASI value (1.7±0.3 and 1.5±0.3; p=0.036).

Conclusion: We conclude that MRI of the heart and the great vessels is warranted in patients with TS to detect all possible anomalies. 45,X patients with increased ASI may have increased risk of aortic dissection and these patients need closer follow-up.

P2-P240

The Validation of an Automated Bone Age Assessment in Girls with Turner Syndrome – A Pilot Study

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Background: Bone age evaluation is a basic tool to manage the treatment of girls with Turner syndrome (TS). The current standard of care is to involve an experienced medical staff to use the Tanner Whitehouse 3 (TW3) or Greulich-Pyle (GP) method for manual evaluation of the bone age. As this is time consuming and may be partially influenced by the evaluator's skills, automated systems may prove more efficient.

Objective and hypothesis: The aim of this study was to compare the manual and automated bone age analysis in a pilot group of girls with Turner syndrome of different age. We expected good concordance between the two methods.

Methods: The manual bone age evaluation was performed by an experienced anthropologist while using the TW3 method. The BoneXpert software (Visiana, Denmark) was used for the automated analyses. The difference in the RUS parameter between the two methods was calculated (t-test) and the influence of age and pubertal status was tested (multiple linear regression).

Results: There were 41 girls with TS participating in this study and their mean age was 10.7±3.3 year. The breast stage development according to Tanner's pubertal scale was 1, 2+3 and 4+5 in 19, 12 and 10 girls, respectively. The mean RUS parameter difference (manual – automated) was +0.6±0.7 year (min. -0.7, max. +2.4) and there was no statistically significant difference between the two methods (p=0.37). In four girls (10%), the automated system computed bone age more than 1.5 years lower than were the manually assessed bone age values. Neither the age nor the pubertal status influenced the difference between the manual and automated bone age measurement.

Conclusions: The automated bone age analysis software produces similar values compared to the manual assessment. Therefore, it keeps promise for more efficiency in daily clinical routine. However, in some girls with TS the extent of underestimation may be of clinical concern. Therefore, validation on larger populations of different diseases is needed to draw the final conclusions and identify the potential pitfalls of the otherwise very convenient endocrinology tool.

P2-P241

Turner Syndrome and Autoimmune Thyroid Disease: Pecularities of Evolution in 93 Turner Syndrome Patients

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Turner Syndrome (TS) is a relatively common chromosomopathy and according to epidemiological studies the prevalence of Autoimmune thyroiditis (AIT) in TS fluctuates from 10% to 21% versus 1.3% in the general population.

Objective: - to retrospectively evaluate thyroid autoimmune disorders and thyroid function in a group of 93 TS patients

- to compare the prevalence of AIT and thyroid dysfunction in subgroups of TS according to karyothype

Patients and method: 93 girls diagnosed with TS in the Pediatric Endocrinology Department of the C. I. Parhon National Institute of Endocrinology were evaluated every 6 months: TSH, FT4 and ATPO, ATGL where measured. The follow-up period: 6 months - 6 years

Patterns of thyroid function where classified according to TSH and FT4 values into:

1. euthyroidism: TSH, FT4 into the normal limits
2. subclinical hypothyroidism (SH): normal FT4 and high TSH
3. frank hypothyroidism: high TSH together with low FT4

TS patients were divided in 3 groups according to karyothype

karyothype 1: 45X

karyothype 2: X abnormalities

karyothype 3: mosaicisms

Results: AIT have been documented in 28,7 % of TS patients group

According to karyothype AIT was more frequent in X abnormalities compared with 45X and mosaicisms: 35,7% vs. 25,8% and 31,8 % respectively. The difference was not statistically significant

Age for AIT diagnosis was > 10 years in at least 80% of patients in all the groups, and median age was smaller in karyothype 2-11,53 vs. 14,36 in karyothype 1 (p=0.09)

Hypothyroidism was present in 67% of TS with AIT : SH in 18,2 % and frank hypothyroidism in 48,2%

According to karyothype, hypothyroidism was more frequent in karyothype 2 and 3 - 83% compared with type 1 karyothype -53,3%

Median age at diagnosis of hypothyroidism in AIT TS subgroups was significantly different: 8,26 Y in karyothype 2 vs 12,51 and 12,9 in karyothype 1 and 3 (p=0.01)

Associated autoimmune disorder was celiac disease found in 3 TS patients (3,2%), one in each karyothype subgroup.

Conclusions: We confirm the increased prevalence of AIT (28,7%) and hypothyroidism (67%) in our 93 patients with TS

In our TS group the prevalence on AIT was higher in X abnormalities karyothype and median age at hypothyroidism diagnosis was significantly lower (p=0,01) in this karyothype. Our results support the importance of close monitoring of TS patients for autoimmune thyroid diseases and thyroid function.

P2-P242

Unusual Clinical Manifestations in Turner Syndrome

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Turner syndrome (TS) is characterized by partly or completely missing of an X chromosome and variability of clinical signs.

We present tree Caucasian mosaic TS girls with unusual clinical course and discuss some literature.

Case 1. A girl referred first to paediatric endocrinologist at the age of 8,5y. for metabolic problems (an excessive weight gain, acanthosis nigricans, impaired glucose tolerance, hyperinsulinemia). The height was not a concern (Median for age). Further examination detected several stigmas and 45,XO/46XX mosaic karyotype. The patient received life style intervention and metformin treatment. She had an advanced bone age, spontaneous puberty and early menarche at the age of 9y.9mo. with regular periods. Her final height is 142,5 cm, she has stopped growing when she was 11 y.o., never treated with GH, thyroid or sex hormones.

Case 2. The patient first come to our center at the age of 8,5 years for the short stature. The investigation revealed several stigmas, primary hypothyroidism, bicuspid aortic valve, kidney abnormality and 45,XO/46XX karyotype. She received GH and L-T4 therapy with final height 152cm by the age of 15y. Under such treatment, nodular thyroid lesions were observed with benign thyroid cytology at FNAB. The patient had never sex hormone replacement, her menarche was spontaneous at 13y.8.mo., the cycle was regular for 3 years. One year after GH withdrawn, a tumor 16*10*13 cm in size was found at pelvic US and CT and surgically removed. Cytology described the serous papillary cystic adenoma of the left ovary. She is currently under follow-up by endocrinologist, gynecologist and oncologist.

Case 3. The girl was examined for poor growth at the age 5y.9mo. with the karyotype 46,Xdel(x)(p21). The girl's mother (146 cm), maternal grand-mother (144 cm) and her sister have similar karyotype with preserved fertility and had never received any hormonal replacement.During the insulin GH stimulation test performance the girl demonstrated poor response and hypoglycemia, pituitary MRI was normal. She has no thyroid, cardiac and kidney abnormalities. The parents agreed with GH treatment when the patient was 9 y.o. In two years she gained 17 cm and entered puberty spontaneously at 9,5 years.Her metabolic paremeters are within normal range.

Our observations demonstrate a differences in mosaic TS clinical presentation and stress the need of a careful multi-disciplinary follow-up for such girls with a concern for their future.

P2-P243

Effect of Combined Growth Hormone and Estrogen Treatment on the Lipid Profile and Systolic Function of the Left Ventricle in Girls with Turner Syndrome (TS)

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Background: The risk of cardiovascular diseases is increased in girls with TS. The influence by combined growth hormone and estrogen treatment on a condition of cardiovascular system is actively discussed.

Objective and hypotheses: We performed this study to assess the effects of combined growth hormone (GH) and estrogen treatment on lipid metabolism and systolic function of the left ventricle (LV) in girls with Turner syndrome without clinically relevant cardiac abnormalities.

Method: 16 girls with TS 12,2±0,9 years old, not treated before, were recruited in the study and treated with GH (0,05 mg/kg/daily) and estrogens (17β-estradiol, applicated 0.25-0.5-1 mg/daily with a dose increase every 6 months) during 2 years. Anthropometry and systemic blood pressure (BP) were assessed every 3 months. Total cholesterol (TH), low density lipoproteins (LDL), high density lipoproteins (HDL), triglycerides (TG) levels were measured every 6 months, LV systolic function (LVSF) was estimated by echocardiography every 12 months. The measurement parameters were: LV end diastolic (LVED), LV end systolic (LVES), LV ejection fraction (LVEF).

Results: The height gain was 14.9±2.6 cm over a period of treatment. Mean BP was within the age-related normal range and without statistically significant changes before and during 2 years of treatment.

During 2 years of GH-therapy TH was significally decreased from 5.1±1.1 to 4.6±0.7 mmol/l (p= 0,023) and LDL was significally decreased from 3.3± 0.9 to 2.7±0.7 mmol/l (p=0,0003). TG and HDL levels were not changed related to baseline.

At baseline the LV dimensions of all the girls were within normal range. LVED was significally increased from 45,2±10.1 to 57.1±10.7 (p= 0,0002), LVES was significally increased from 17.4± 4.9 to 21.6±5.3 (p=0,00012) during 2 years of therapy. There were not significant changes in LVEF between baseline and 2-years timepoint. These data give evidence that systolic function of the left ventricle did not become lower.

Conclusion: combined GH and estrogen treatment in girls with TS improved the lipid profile and did not impair the systolic function of the left ventricle.

P2-P244

Familial Turner Syndrome: Case Report

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Introduction: Turner syndrome (TS) is one of the most common chromosomic disorders characterized by partial or complete lack of one of X chromosomes. It presents variable phenotypic spectrum. Isochromosome of long arm (iXq10) is the third most frequent karyotype and could be in mosaicism in 10-15% of TS. The phenotypic manifestation are similar than girls 45X. It is described a higher incidence of thyroid autoimmunity (even though is currently under discussion) and of diabetes mellitus. Congenital heart malformations and premature ovarian failure are less frequent.

One third of the girls with TS have spontaneous puberal development, more often in those with mosaicism and some structural anomalies. Spontaneous pregnancies are rare (3-5%).

Case Report: We describe a family with vertical transmission of TS carrying non-mosaic isochromosome X (karyotype 46Xi[Xq]), which involves 4 women of two generations.

The index case is a girl of 8.7 years old who was referred at 2.9 years old because of horseshoe kidney and phenotypic features compatible with TS. She was 92,8 cm tall (-1,23 SDS) and has high-arched palate, lower implanted ears, cubitus valgus and broad chest. She has been on growth hormone treatment since she was 4.3 years old. Additionally, she has mild intellectual disability (IQ 76). Her mother has short stature, with a height of 135 cm (- 4.6 SDS). She had three full-term pregnancies and two spontaneous abortions. Because of her short stature a karyotype was performed, with the same results as her daughter. She has cubitus valgus, Madelung deformity and altered sitting height. The two sisters had same karyotype, the older one with spontaneous puberty, cubitus valgus, Madelung deformity, altered sitting height, and mild intellectual disability (IQ 78), with thyroid autoimmunity; and the younger one with cubitus valgus, broad chest and more severe intellectual disability.

Conclusion: Despite the low frequency of spontaneous pregnancies in patients with TS and even more infrequent TS transmission, when ovarian function is preserved, it is possible to transmit TS to next generations. Two of the 4 exposed cases developed spontaneous puberty, and the mother had 5 pregnancies, 2 full term. The phenotypic expression was variable despite having the same karyotype. The index case is the only that does not have marked corporal disproportion and we think this could be related with growth hormone treatment. In this family, we think that it is important to have genetic counseling, as it is possible to continue with TS transmission.

P2-P245

Clinical Review of 7 Patients Affected with 49,XXXXY Syndrome

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Introduction: 49,XXXXY polysomy incidence is about 1 per 85000 to 100000 male births. As a rare condition with medical problems affecting different systems it should be evaluated under a multidisciplinary approach.

We have reviewed the clinical characteristics of patients with this anomaly from all the country who contacted the program for evaluation.

Methods: In 2016 we started a multidisciplinary program for the care of patients with sex chromosomal aneuploidies. Patients contacted trough family organizations or social networks. All patients were evaluated by an endocrinologist, psychiatrist, neuropsychologist, neurologist and clinical geneticist.

Results: Seven patients were evaluated with 49, XXXXY aneuploidy, one of them had a mosaic with 3 cellular types (47,XXY, 48,XXXY and 49,XXXXY), aged 3 to 16 years old.

All had a variable degree of facial dysmorphism, the most frequent were hypertelorism and epicanthal folds, along with radioulnar synostosis and elbow dislocation.

The endocrinology evaluation showed testicular size below normal range even in prepubertal boys with decreased phallus length in 4/7. Cryptorchidism was present in 4/7. All but one were small for gestational age. Height in normal range (-2,15 to +0,7 SD) but below midparental height (-1,1 to +1.3 SD). Four patients were treated with prepubertal testosterone for micropenis and two of them are in puberty under testosterone replacement treatment.

Motor delay and neonatal hypotonia were found in all patients, three of them with failure to thrive. Cognitive development was affected in some degree in all the patients, specially in language and verbal skills. We found attention deficit hyperactivity disorder in 5/7 patients and anxiety behaviors in 5 of the seven boys.

Comments: The clinical and developmental features found in these patients were similar to those previously reported, with the exception of intrauterine growth retardation.

The diversity of clinical and developmental symptoms of this disorder make necessary a multidisciplinary approach to detect and treat early medical problems.

P2-P246

Poor Weight Gain in Prader-Willi Syndrome – Not Always Over-Restriction Consider Coeliac Disease

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Introduction: Prader-Willi Syndrome (PWS) is a complex genetic condition associated with feeding difficulties, hypotonia, developmental delay in infancy; hyperphagia leading to extreme obesity, growth failure and behavioral problems in childhood. Coeliac disease (CD), is an autoimmune disease characterized by gluten intolerance and a variety of symptoms most commonly diarrhea or constipation and failure to thrive. In PWS the challenge is to optimize growth while avoiding obesity. Dietary over-restriction can result from the careful regulation of food intake by families. We present two children with an alternative cause of poor growth, to our knowledge not previously reported.

Case presentation: *Case 1:* a girl (3y 8m) born 2 kg, with poor feeding, diagnosed with genetically confirmed PWS in neonatal period. She demonstrated poor weight gain but no GI symptoms. Serum tTG was positive at 41 U/ml (0-6.99) with positive endomysial antibodies, the diagnosis of CD was histologically confirmed following intestinal biopsy. Commencement of a Gluten Free Diet (GFD) was associated with a marked improvement in mood and general wellbeing.

Case 2: a girl (7y) with poor weight gain, who required NG tube feeding (until 7m old), diagnosed with genetically confirmed PWS. GH commenced at 5 years. On recent review despite a good appetite, weight gain was poor and abdominal swelling noted. There were no other GI symptoms and no family history of CD. Further investigation revealed an elevated tTG 124 U/ml (0.6-6.99) and positive endomysial antibodies, the diagnosis of CD was confirmed histologically. Following commencement of GFD, the abdominal swelling resolved.

Conclusion: Other than poor weight gain these patients were relatively asymptomatic and did not display the classic GI symptoms of CD. We believe this diagnosis should be considered in those patients with PWS with poor weight gain. We are currently monitoring for CD in our PWS patients.

P2-P247

Growth Hormone Unmasked Laryngomalacia and worsened Obstructive Sleep Apnea in Infants with Prader-Willi Syndrome

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Background: Prader-Willi Syndrome (PWS), due to loss of paternal gene expression on chromosome 15q11.2-13, is characterized by hypotonia, hypothalamic-pituitary dysregulation, abnormal respiratory drive, and hyperphagia. Growth hormone (GH), often started in infancy, improves tone, body composition, and height. Concerns about sudden death in children with PWS started on growth hormone, hypothesized secondary to worsening obstructive sleep apnea (OSA) from adenotonsillar hypertrophy, resulted in guidelines for polysomnography (PSG) evaluation before and after starting GH.

Method: We report two cases of worsened OSA in infants with PWS after GH due to unmasked laryngomalacia.

Results: Case 1 - Female with PWS due to imprinting center epimutation. Initial PSG at 2 months old (mo) showed apnea hypopnea index (AHI) 15, obstructive AHI (oAHI) 12, nadir oxygen saturation (nO2) 94%. GH was started soon after (0.5 mg/m2/d). PSG at 4 mo was significantly worse (AHI 31, oAHI 29, nO2 81%). GH was held and a flexible fiberoptic laryngoscopy (FFL) showed laryngomalacia. Supraglottoplasty was done at 5 mo. PSG at 6 mo showed improvement (AHI 6, oAHI 1.8, nO2 90%) so GH was restarted at 7 mo. Repeat PSG at 8 mo was stable (AHI 6, oAHI 4, nO2 88%).

Case 2 - Female with PWS due to deletion. Initial PSG at 5 mo (AHI 15, oAHI 9, nO2 75%). GH was started at 7 mo (0.5 mg/m2/d). PSG at 8 mo was significantly worse (AHI 33, oAHI 28, nO2 57%). GH was held and she had a adenotonsillectomy at 11 mo. Soon after, FFL showed laryngomalacia which was monitored and repeat PSG at 12 mo showed improvement (AHI 12, oAHI 8, nO2 71%). GH was resumed at 13 mo but repeat PSG at 16 mo was significantly worse (AHI 44, oAHI 30, nO2 61%) so GH was held again. PSG off GH at 22 mo was improved (AHI 13, oAHI 9, nO2 64%). Supraglottoplasty was done at 22 mo and PSG at 24 mo showed further improvement (AHI 8, oAHI 6, nO2 72%).

Conclusion: Respiratory difficulties can lead to significant morbidity in PWS. Laryngomalacia is not well described in this population but can exacerbate OSA. GH has significant benefit for infants with PWS but is monitored carefully due to concerns about aggravating OSA secondary to adenotonsillar hypertrophy. However, our cases demonstrate that growth hormone may also unmask underlying laryngomalacia, possibly due to improved inspiratory force, which requires separate evaluation and treatment.

P2-P248

How Frequent Are Growth Charts Used in Paediatric Clinics? An Audit of Growth Chart Use in a District General Hospital in Scotland

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Introduction: The Royal College of Paediatrics and Child Health[1] highlights the importance of growth as a measurement of health and wellbeing in children. Growth measurements in children can only be evaluated if plotted on a growth chart.

The use of growth charts was reviewed in Forth Valley Royal Hospital Paediatric department over 10 days in all clinics held in the paediatric outpatient department.

Method: Case notes of all children attending paediatric clinics over 10 days were reviewed.

Information recorded was: type of clinic; consultant; age and gender of patient; height and weight in notes; growth chart completion.

Results: 25 outpatient clinics were reviewed, with a total of 164 patients. 57.3% were male. Patients' age range was 17 days to 17.1 years.

78.6% of children had height and weight recorded.

51.8% of children had growth data plotted on the growth chart.

If surgical clinics were excluded from the data, 98.6% of children had height and weight recorded in case notes at clinic visit.

62% of these children had a growth chart completed in clinic.

Discussion: Despite the height and weight being clearly documented in case notes of children attending clinics, less than two thirds of case notes had completed growth charts.

Surgical clinics tended not to measure children.

Other clinics where children were not measured were neurodisability clinics, where measurement of children is challenging.

Growth chart use is part of general assessment of a child's health and well being. However, this audit demonstrated that in spite of this, growth chart use is significantly lower than was expected.

Growth chart use can be improved by ongoing education of all clinicians, highlighting growth as an important aspect of a child's health assessment. Growth chart use may be improved by the introduction of electronic growth charts. However, having electronic growth charts in place does not necessarily imply that clinicians will look at the charts when assessing children. Ensuring ongoing education remains important.

References

1 Royal College of Paediatrics and Child Health. *What are growth charts and why do we need them?* Available from: http://www.rcpch.ac.uk/child-health/research-projects/uk-who-growth-charts/uk-who-growth-chart-faqs/uk-who-growth-chart-faq#whenaretheyused [accessed March 2017]

2 Garza C, de Onis M, for the WHO Multicentre Growth reference Study Group (2004). Rationale for developing a new international growth reference. *Food and Nutrition Bulletin,* 25(Suppl 1): S5-S14.

P2-P249

Growinform – A Campaign for Early Diagnosis and Treatment of Growth Disorders

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In 2014 Varna Pediatric Endocrine Society started a program for timely diagnosis and treatment of stature deviations. GPs with 23 058 children under their care were trained and provided with a specialized auxological software to warn them for every stature deviation. From the expected 692 children with short stature (3% of the total), only 33 (0.14%) were sent for further evaluation. Due to the unsatisfactory results we decided to organise a new campaign with the help of media - "GrowInform", with the main purpose to raise awareness of growth disorders and underline the importance of regular anthropometric measurements and assessment. Our secondary goal was to identify and if necessary, refer for further evaluation children with growth deviations in areas with no easy access to paediatric endocrinologists.

We targeted 10 regional towns in the broad geographical region of our clinic, planning to make an on-place visit twice. In each region local media, social media and leaflets were used to raise awareness of growth deviations, and to advertise upcoming lectures and screening examinations, organised by an outreach team, consisting of 2 paediatric endocrinologists, a trainee and a PR specialist. Online consultations were freely available at our Facebook page and Internet site. A short informational movie was created specifically for the campaign. A process of referral for further evaluation when needed was established.

We started the first part of the campaign in March, 2017, by visiting 6 towns with population of 117 706 children (2-18 years of age). For 1 year, a total of 146 children were evaluated (107 on place and 39 through the electronic means of communication). Out of the children found to have short stature (52 children, 35.6% of all), 44(30.0%) needed further evaluation at tertiary clinic. Until this moment, 12 (23.1%) children at a mean age of 8.7±3.5 years have been assessed at clinic and received definitive diagnosis: combined or isolated GH deficiency (25.0%), celiac disease (25.0%), Noonan syndrome (16.7%), familial and syndromic short stature (25%), Turner syndrome (8.3%). Treatment was started accordingly. Further 22(42.3%) children presented auxology consistent with constitutional delay in growth and remained under subsequent follow-up.

The informational approach proved to be more successful for the year of operation of the GrowInform campaign than all previously taken approaches. During the second year, the project will go nationally with the help of all tertiary paediatric endocrinology clinics in the country.

P2-P250

Growth and Body Composition of Term Healthy Indian Infants from Birth to 2 Years of Age

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Objective: To do longitudinal assessment of fat mass (FM)% of term, healthy Indian infants by stable isotope dilution method and skinfold thicknesses.

Methods: Term healthy singleton newborns, with birth weight between 1.8 to 4.0 Kg, were followed from birth to 2 years. Anthropometry and skinfold thickness measurement at biceps, triceps, subscapular and supra-iliac sites was done serially at 10 days, 3 months, 1 and 2 years. Anthropometric data was converted to z-scores using WHO Anthro software. Body composition was assessed by deuterium dilution method in a subset of infants at all these time points. FM% was also calculated from the sum of skinfolds using Weststrate and Deurenberg's equations.

Results: 147 boys and 103 girls were enrolled. Anthropometry and FM% is summarized in **Table**. The median z-scores of weight, length as well as BMI were negative at all points, but showed gradual improvement. FM% measured by skinfold thickness and deuterium were significantly different from each other, and did not show any correlation. The difference was the greatest at 10 days and minimum at 3 months.

Conclusion: FM% of term Indian infants by deuterium dilution technique is 11.5 ± 7.2% at birth, nearly doubles by 3 months, and then remains relatively stable till 2 years. It is not correlated with skinfold thickness derived FM%.

P2-P251

Growth, Body Composition and Metabolic Parameters During Childhood in a Cohort of Children Born with a Small for Gestational Age

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Aims: To examine growth, body composition and glucose metabolism during childhood in children born small for gestational age (SGA).

Methods: Single centre cohort study of 150 children (63 boys), identified from newborn records as being born SGA (birth weight SDS <-1.5) and assessed between the age of 4 and 7 years. Data collected included: anthropometric parameters (height, weight, BMI: transformed into age- and sex-adjusted SDS), lean and fat mass assessed by DEXA scans, blood pressure, fasting glucose and C-peptide. Children were compared based on the presence or absence of catch-up growth in weight, defined as a difference in weight SDS between birth and study visit >0.67 SD; or in height, defined as the difference between the child's height SDS and mid-parental height SDS (> or <1 SD).

Results: 150 children with a birth weight of 2485±377gr (SDS: -2.0±0.5) were assessed at a mean age of 6.1±0.8 years. At study visits, height SDS was -0.5±0.9, weight SDS: -0.6±1.0, BMI SDS: -0.5±1.0.

Eleven children (7.3%) had a height <-2 SD. 122 (81.3%) children showed catch-up growth in weight; they were taller (height SDS: -0.24±0.76 vs -1.45±0.93, p<0.001), heavier (BMI SDS: -0.31±0.98

Table 1. Serial anthropometry and fat mass percentage P2-P250

Parameters	10 days	3 months	1 year	2 years
N	250	217	223	186
Age (Days)	13 ± 3	102 ± 14	400 ± 25	743 ± 32
Weight (Kg)	3.0 ± 0.5	5.6 ± 0.8	9.0 ± 1.3	11.0 ± 1.4
Weight Z-score#	–1.3 (-5.0 - 1.1)	–1.2 (-4.7 - 1.8)	–0.7 (-9.8 - 2.9)	–0.9 (-3.2 - 2.5)
<-2*	60 (24.0)	38 (17.5)	24 (10.8)	22 (11.8)
Length (cm)	50.5 ± 2.3	61.0 ± 3.1	75.2 ± 3.1	84.6 ± 3.2
Length Z-score#	–0.6 (-4.6 - 3.2)	–0.2 (-3.9 - 3.3)	–0.5 (-4.1 - 3.0)	–0.9 (-3.8 - 1.6)
<-2*	35 (14.0)	23 (10.6)	19 (8.5)	18 (9.6)
BMI	11.9 ± 1.5	15.0 ± 1.8	15.9 ± 1.8	15.3 ± 1.6
BMI Z-score#	–1.5 (-5.6 - 3.2)	–1.3 (-5.6 - 2.2)	–0.7 (-12.9 - 2.9)	–0.5 (-3.6 - 3.9)
<-2*	69 (27.6)	62 (28.6)	20 (9.0)	16 (8.6)
FM% from skinfold thicknesses	16.9 ± 3.6	24.0 ± 3.1	21.7 ± 3.2	20.1 ± 2.9
FM% by deuterium dilution	11.5 ± 7.2	21.2 ± 7.6	17.7 ± 8.3	25.7 ± 10.1
(N)	(129)	(163)	(70)	(82)

*N (%),# Median (range).

vs-1.20±0.63, p<0.001), and showed higher systolic blood pressure SDS (0.08±0.71 vs -0.32±0.63, p=0.009), fasting glucose (4.5±0.5 vs 4.3±0.5 mmol/l, p=0.03) and a trend towards higher C-peptide levels (305.6±116.4 vs 258.5±112.0 pmol/l, p=0.08) compared with those without weight-catch up. They also showed increased total fat mass (adjusted for height) (36.5±16.2 vs 28.3±9.4 g/cm, p=0.01) and lean mass (129.0±14.0 vs 117.2±12.9 g/cm, p<0.001).

Classifying children based on catch-up in height, those who did not show any catch-up growth had lower lean mass (adjusted for height): 119±13.3 vs 131±12.8 g/cm, p<0.001, but there were no differences in BMI, fat mass, glucose, C-peptide or blood pressure compared with those with height-catch-up.

Conclusion: Within this cohort of children born SGA and assessed during childhood, those who showed catch-up growth in weight were relatively taller, had higher fat and lean mass, higher blood pressure and fasting glucose, whereas those children who did not show any catch-up growth in height showed mainly reduced lean mass.

P2-P252

Final Results of Nordinet® International Outcome Study: Key Outcomes in Paediatric Patients

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Background: NordiNet® International Outcome Study ([IOS]; NCT00960128), a non-interventional study (2006–2016), assessed the effectiveness and safety of real-world treatment with Norditropin®. Outcomes were assessed in children with growth hormone deficiency (GHD), born small for gestational age (SGA), Turner syndrome (TS), chronic renal disease (CRD), idiopathic short stature (ISS), Noonan syndrome (NS) and Prader-Willi syndrome (PWS).

Methods: Patient information was entered using a web-based system. 17,995 paediatric patients enrolled: 17,711 included in the full analysis set (FAS) (safety evaluation); 11,967 in the effectiveness analysis set (EAS). Endpoints included change from baseline in height standard deviation scores (ΔHSDS) and near-adult height (NAH) SDS (height at age >16 [boys]/>15 [girls] and height velocity <2 cm/year, or height at >18 years). Non-serious adverse reactions (NSARs), SARs and serious adverse events (SAEs) were recorded. Data are mean (standard deviation).

Results: Patient numbers by indication were FAS/EAS: GHD, 9967/7141; SGA, 4274/3200; TS, 1374/936; CRD, 290/200; ISS, 485/317; NS, 154/106; PWS, 132/67. At treatment start, patients with PWS (4.7 [5.00] years) were the youngest: GHD, 9.1 (4.1); SGA, 7.9 (3.4); TS, 8.7 (3.8); CRD, 8.3 (4.4); ISS, 10.1 (3.5); NS, 8.9 (3.8). Patients born SGA were shortest (HSDS) at baseline (−2.97 [0.91]): GHD, −2.55 (1.10); TS, −2.66 (0.93); CRD, −2.74 (1.17); ISS, −2.82 (0.99); NS, −2.83 (1.13); PWS, −1.94 (1.48). Average GH dose (mg/kg/day) was lower for PWS (0.026 [0.008]) versus GHD (0.032 [0.008]); SGA, 0.038 (0.009); TS, 0.044 (0.009); CRD, 0.041 (0.011); ISS, 0.038 (0.014); NS, 0.040 (0.009). Treatment follow-up (years) was longest for patients with TS (4.3 [2.8]): GHD, 3.8 (2.9); SGA, 3.6 (2.8); CRD, 2.8 (2.6); ISS, 3.3 (2.4); NS, 3.4 (2.9); PWS, 4.0 (3.5). ΔHSDS was greatest in year 1: GHD, 0.69 (0.56); SGA, 0.65 (0.44); TS, 0.54 (0.36); CRD, 0.61 (1.19); ISS, 0.52 (0.38); NS, 0.51 (0.38); PWS, 0.85 (0.90). Proportion (%) of patients with HSDS >−2 was (baseline/year 3): GHD, 26.2/79.3; SGA, 9.3/64.4; TS, 22.1/63.5; CRD, 23.5/59.4; ISS, 18.3/56.8; NS, 17.9/67.5; PWS, 59.7/89.3. NAH SDS was: GHD, −1.16 (1.22) (n=943); SGA, −1.97 (0.95) (n=190); TS, −2.08 (0.84) (n=189); small numbers of patients achieved NAH during the observation period in other indications. Safety: no new signals were observed. Number of events/number of patients were: NSARs, 288/249; SARs, 133/90; SAEs, 352/224.

Conclusions: In paediatric patients, growth hormone was associated with increased HSDS and increased proportion with HSDS >−2. No new safety signals were revealed.

P2-P253

Influence of Puberty on Adult Height of SGA Children Treated with GH

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Introduction: Published studies on pubertal growth of SGA patients on GH therapy are scarce. An earlier and shorter duration of puberty has been described. Treatment optimization may be necessary and also know their influence on adult height.

Objetives: Analyse the evolution of height durig puberty in SGA patients treated with GH. Asses the age of onset of puberty and its relationship to adult and target height.

Methods: Retrospective analytical study. We analysed 101 SGA patients that have received GH treatment since 2005. Main variable analysed was adult height. Uncensored data was collected and analysed.

Results: Since 2005, 101 SGA patients started treatment (57 male), with a median age of 6,6 years (IQR 4,3), and initial height of -2,87 sds (IQR 0,67). 89 Patients have reached puberty with a mean age of onset in males of 11,8 years (1 sd) and 10,4 (1,4 sd) in women. In men, the age of onset was 0,5 years less the reference spanish population (p<0,05), and 0,3 years in women (NS).

In 12 patients the treatment was suspended due to poor efectiveness, adherence or adverse effects. In 4 patients we used GNRH-a due an early puberty.

Currently 44 patients have reached adult height (28 women):

Adult height (sds): -2,15 (1,2) (18 men); -1,8 (1,9) (26 women).

Target height (sds): -1,23 (0,8) (men); -1,05 (0,9) (women).

Height increased: 0,85 (1,1) sds (men); 1,35 (1) sds (women).

Gain height in puberty (cms): 21,7 (6) (men); 19,7 (5) (women).

Height decreased during puberty (sds): -0,95 (1,2) (men); -0,11 (0,9) (women).

Adult-Target height (sds): -0,9 (0,8) (men); -0,74 (1,1) (women).

Height decresed during puberty was significant in men ($p<0,009$), but this did not occur in women.

The difference between target and adult height was significant in both sexes ($p<0,001$).

Conclusions: Males SGA patients treated with GH, show a decreased height during puberty, as well as an earlier pubertal onset, compared with reference population.

Adult height in this patients do not achived the target height.

P2-P254

Burden and Impacts of Daily Recombinant Human Growth Hormone (r-hGH) Injections in Growth Hormone Deficient (GHD) Paediatric Patients

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Background: Daily r-hGH injection has been safely and effectively used in paediatric patients with GHD for more than 30 years. However, little information is available describing the burden and life impacts experienced by paediatric patients related to daily r-hGH injections.

Objective: To identify the burden and impacts of a daily r-hGH injection regimen on the lives of paediatric GHD patients.

Methods: A retrospective meta-analysis was conducted of data drawn from four sources: qualitative interviews with 15 paediatric patients in the United States (US) conducted from September to December 2016; qualitative market research interviews conducted in early 2017 with 16 paediatric patients in the Czech Republic, Spain, Turkey, and the United Kingdom; responses to an online questionnaire completed by 149 paediatric patients in the US from January to May 2017; and an advisory panel discussion with three paediatric patients in the US conducted on September 8, 2017. Patient-reported burdens and impacts identified in each data source were tabulated and compared.

Results: In total, data across all four sources represent a total of N=184 paediatric patients (n=94 adolescents aged 12 to 17 years; n=90 children aged 3 to 11 years). In qualitative interviews, patients indicated that they had become largely acclimated to daily r-hGH injections. However, emotional impacts, activity limitations, social impacts, and impacts on family life due to daily injections were reported across all four sources. Limitations to participate in overnight activities (50% of adolescents and 64% of children) such as summer camp, and increased travel burden (75% of adolescents and 45% of children) were most frequently reported across sources. Patients also reported impacts on relationships with friends; limitations in social activities; and the burden of preserving secrecy about one's condition and the use of injections. Across all sources (and particularly highlighted in the online questionnaire), participants stated a clear preference for a less-frequent r-hGH injection regimen (84% of adolescents and 79% of children).

Conclusions: Although paediatric patients may become acclimated to daily r-hGH injections, qualitative data from such patients provide growing evidence that they experience some burden due to the daily injection regimen, and would prefer a less frequent regimen.

P2-P255

Clinical and Cost-Effectiveness of GH Treatment for Children in Wales

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Background: GH treatment has been used for the last 30 years for children with short stature with varying individual responses.

Objective: Analysis of final height SDS (standard deviation score) and the factors influencing it in children treated with growth hormone.

Material and methods: Subjects across Wales who received GH treatment, part supervised by tertiary center staff and reached final height while on treatment, were identified by database searching. Final height was defined when the switch to adult dosing occurred or a height velocity (HV) <1cm/year. Exclusion criteria included subjects on GH treatment for less than a year, a HV <1cm/year on GH or GH started after growth completion. Variables analyzed included age, sex, diagnosis, presence of concomitant hypothyroidism, adrenal failure, age at GH initiation, height SDS at diagnosis, number of years on treatment, puberty induction, mid-parental height SDS, age at GH cessation, mean GH dose throughout treatment, height gain at 1 year, total height gain, cost of treatment (£/cm gained). SPSS v. 17.0 was used for statistical analysis, with a level of significance of $\alpha=0.05$.

Results: 141 subjects were identified with a sex ratio of F:M of 1.2:1. 101 (71.6%) had GH deficiency (GHD) from various causes, 26 (18.4%) had Turner syndrome (TS) and 14 (9.9%) had other diagnoses (Prader-Willi Syndrome, constitutional delay in growth and puberty, small for gestational age, renal disorders, idiopathic short stature). Mean age at treatment initiation was 10.4±3.3 years for the whole sample. The median period on GH treatment was 5.1years. 71 (50.3%) subjects required puberty induction. Total height gain was 0.87SD for GHD, 0.09SD for TS and 0.74SD for the other diagnoses ($p=0.043$) with a cost of £6323.8/cm for GHD, £8465.9/cm for TS and £4272.6/cm for other diagnoses ($p=0.045$). 56 (53.3%) children reached a final height within mid-parental

height range. Best predictors for response to treatment were height SD at diagnosis, HV in the first year, years on treatment, and age at treatment start. The mean final height for the group with Turner syndrome was 148.7±6.1cm.

Conclusions: GH treatment recommendation in Wales follows current guidelines. The response to treatment is variable, with a significant proportion of subjects not reaching the predicted final height. Turner syndrome benefits the least from GH therapy.

Keywords: final height, GH treatment, audit

P2-P256

Bone Mineral Density and Body Composition of Young Adults Who Were Born Small for Gestational Age and Treated with Growth Hormone, after Treatment Completion

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Background: Small for gestational age (SGA) children are at increased risk of metabolic syndrome in adulthood and have below-average bone mineral density (BMD). Growth hormone treatment reduces fat mass and insulin sensitivity, increases lean body mass and improves height and BMD in short SGA children. We aimed to evaluate changes in body composition in SGA patients treated with growth hormone (GH), after its cessation, compared with young adults born appropriate for gestational age (AGA).

Methods: We performed a longitudinal study of twenty-one SGA patients without catch-up growth and previously treated with growth hormone. Individuals were followed up from the start for when growth hormone treatment was discontinued. Children's body composition variables (BMD in femoral neck, in lumbar vertebrae, fat and lean body mass proportion) were evaluated annually with dual-energy X-ray absorptiometry and after treatment completion and was compared with data from untreated age and sex matched controls.

Findings: Twenty-one SGA and matched controls were included in the analysis. 70 percent of the patients SGA are females. At GH-stop, mean age 16.4 years and the mean final height of the group SGA was -1,57 SD. Fat mass and lean mass were similar for SGA patients and for controls [21,85% (8,75) and 77,95% (8,88) vs 23,22% (6,30) and 76,77% (6,30)] (p=0.155 and p=0.128, respectively). On the contrary, BMD in lumbar vertebrae was higher in SGA patients than in controls [-0,6 (0,85) vs. -0,83 (1,63)] (p= 0.020). However, BMD in femoral neck did not differ between these two groups [-1,13 (0,97) SGA vs -0,47 (1,44) AGA], (p=0.731).

Interpretation: Significant changes in body composition are observed in SGA patients after completion of GH treatment, reflecting a loss of pharmacological effects of growth hormone. Once treatment is discontinued, fat mass, lean mass and bone mineral density in femoral neck show no significant differences compared to those of matched controls. BMD in lumbar vertebrae was higher in SGA patients compare to controls, indicating that long- term growth hormone treatment in SGA children has no unfavourable effects on metabolic health after cessation treatment.

P2-P257

Clinical Effectiveness and Cost-Effectiveness of Somatropin Treatment for Short Children in Egypt: Analysis of 1-Year Data

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Recombinant human growth hormone (rhGH) is approved for short stature associated with growth hormone deficiency (GHD), idiopathic short stature (ISS), Turner syndrome (TS), multiple pituitary hormone deficiencies (MPHD), Silver Russell syndrome (SRS) and being born small for gestational age non syndromic (SGA).

Objectives: To assess the clinical effectiveness and cost-effectiveness of rhGH in children with GHD, TS and those born SGA.

Methods: Five hundred children 331(66.2%) females & 169 (33.8%) males; 98 with GHD, 149 with ISS, 190 with TS, 18 with MPHD, 33 with SRS and 12 with SGA were referred from different schools all over Egypt to the GH National Committee of the school health insurance, where they were diagnosed, provided by growth hormone therapy in the period from (March 2015 to March 2016). Demographic, auxiological and laboratory variables were tested as being predictors for height gain (cm/year) using multiple regression analysis. Markov cost-effectiveness simulation model was used for estimation of the cost-effectiveness of growth hormone therapy for each diagnosis.

Results: The cost in GHD, ISS, TS, MPHD, SRS and SGA groups were 168.88±131.57 dollars per 5.66±1.52cm, 182.83±78.31 dollars per 6.19±1.46 cm, 339.93±202.61 dollars per 5.04±1.62cm, 383.15±183.42 dollars per 3.5±0.47 cm, 71±13.98 dollars per 5.49±0.93cm and 139.43±62.11 dollars per 5.13±0.21 cm height gain/year respectively. There was a significant correlation between cost & height gain (P-value = 0.0001, 0.001 & 0.01) in ISS, GHD and SGA respectively.

Conclusion: The study identified the predictor variables for height gain/year for the different diagnoses receiving GH therapy. Given that the rising cost of prescription drug therapies is a prominent issue for our health care system, rhGH is a cost-effective treatment strategy in Egypt for children with GHD, ISS, TS and SGA patients.

P2-P258

Clinical and Molecular Analyses of 24 Patients with Beckwith-Wiedemann Syndrome

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Objective: Beckwith-Wiedemann syndrome (BWS) is a genetic disorder that results from abnormal expression of function of imprinting genes. Clinical manifestations vary greatly. To study the molecular genetic mechanism of BWS by Methylation Specific Multiplex Ligation-dependent Probe Amplification (MS-MPLA) and to analyze the relationship between genotype and phenotype, that will be helpful to improve the understanding of this disease.

Methods: The copy number and methylation status of imprinted gene in chromosome 11p15.5 BWS region of peripheral blood were detected by MS-MLPA. The birth history, clinical phenotype and laboratory test results of the diagnosed patients were recorded and analyzed, and the relationship between different molecular genetic mechanisms and clinical phenotypes was analyzed.

Results: 24 patients were confirmed with BWS by MS-MLPA (10 males and 14 females; age range, 1 day to 4 years). Among these 24 patients, 16 were identified with IC2 hypomethylation (67%), 2 with IC 1 hypermethylation (8%), 5 with pUPD (21 %), 1 with microdeletion in the region of chromosome 11p15.5 (4%). This diagnostic technique could not detect the inversion, translocation and mutation of gene *CDKN1C* in 11p15.5 region. Among these patients, abdominal wall defect were present in 13 patients, pre- or postnatal overgrowth in 9 patients, 6 patients with hypoglycemia, 15 with macroglossia, 5 showed ear creases, 7 showed facial nevus flammeus and hemihyperplasia was found in 8 patients. 5 cases were complicated with cardiovascular malformation (atrial septal defect), 6 cases with abdominal visceral organomegaly, 1 cases with severe abdominal rhabdomyosarcoma. Among them, patients with IC2 hypomethylation had higher incidence of macroglossia, abdominal wall defect and overgrowth, while patients with IC1 hypermethylation had higher incidence of facial nevus flammeus, ear crease and hemihyperplasia.

Conclusions: Macroglossia, umbilical hernia, excessive growth are the three main features of BWS, about 2/3 of the patients may show excessive growth, macroglossia, abdominal wall defecs. Facial nevus nevi, ear creases, hypoglycemia and abdominal visceral organomegaly are common clinical manifestations. This syndrome is associated with expression defect of imprinted genes in chromosome 11p15.5 BWS region, in which more than half of the patients are due to hypomethylation of IC2. When encountered great children with clinical giant tongue, umbilical herniation, excessive growth of limb asymmetry, consideration should be given to this disease. For children with high clinical suspicion but negative MS-MLPA result, mutation of gene *CDKN1C* or chromosome inversion and displacement in 11p15.5 region should be considered, and the related genetic tests should be further performed.

P2-P259

Unusual Case of Combination of Beckwith-Wiedemann Syndrome and Shox Gene Deficiency

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Background: Beckwith-Wiedemann Syndrome (BWS) is an overgrowth disorder involving a predisposition to tumor development, etiologically connected with genetic/epigenetic dysregulation. The main features of BWS include omphalocele, macroglossia and macrosomia; however there is significant clinical heterogeneity. SHOX mutation is a frequent cause of short stature with high penetrance, but extremely variable clinical expression. The mean adult height is -2.2 SDS. The presence of mesomelia, minor auxological abnormalities and radiographic sign are important keys to the diagnosis which has to be confirmed by genetic analysis. GH therapy was approved for individuals with SHOX mutation with benefit on the final stature.

Clinical case: Male patient, 4 years old, with history of neonatal macrosomia and hypoglycemia. Clinical examination revealed macroglossia and ear pits, in the absence of hemipertrophy. Genetic diagnosis of BWS was performed using MLPA followed by molecular genetic tests. They showed a gain of methylation in IC1 region caused by paternal uniparental disomy of a chromosomal segment including the 11p15.5 region. The double paternal content is due to de novo unbalanced traslocation t(Y, 11); so there is a supernumerary 11p15.5 region located on the short arm of the Y instead of the subtelomeric region which is lost. Analysis of Yp deletion has allowed to identify the lack of the whole SHOX gene and the area upstream SHOX. Deletion in this area can be associated to short stature and Leri-Weill Syndrome. Currently the stature is adequate (50°ple) and in line with the target of the parents. A slight Madelung deformity was found at wirst X-Ray.

Conclusion: The article describes an unusual clinical case: combination of BWS, an overgrowth syndrome, with SHOX deletion, a condition associated to growth failure. At present time the growth is adequate; so, taking into account the high tumor risk related to BWS, there is not indication to GH therapy. It is important to keep in mind that the SHOX deficiency becomes more pronounced with age while the cancer risk related to BWS decreases with the age. So a careful long-time auxological follow up is necessary and the balance of the risks and benefits associated with GH therapy should be evaluated step by step.

P2-P260

An Irish Regional Study of Paediatric Growth Hormone Deficiency (CO-GHD): Classification of Causes and Factors Associated with Persistent GHD at Transition

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Childhood-onset growth hormone deficiency (CO-GHD) is topical at present due to the increasing understanding of underlying genetic aetiologies, influence on childhood growth, and future effects on adolescence and adult health. There is no previous Irish data of this group of children.

Methods: A retrospective cohort study over 2 years (2013-2015) including all children diagnosed with GHD who received recombinant growth hormone treatment (rGH). Predictors of persistent GHD at final height were examined.

Results: A total of 43 children fulfilled inclusion criteria of which congenital GHD was identified in 37. Of these46% had structural pituitary abnormalities (n=15)/ a novel genetic mutation of the POU1F1pituitary transcription factor (n=2), with a 2:1 male: female ratio. Idiopathic GHD was identified in 54% of children (n=20) which had a 9:1 male to female ratio. Acquired GHD due pituitary tumours were identified in 6 children with a 5:1 male to female ratio, and clinically presented with stunted growth, increased BMI and other pituitary hormone deficits. Median age at presentation in children with pituitary tumours was advanced (12.2 years - interquartile range 4.3) compared to children with congenital idiopathic GHD and GHD due to structural pituitary abnormalities; 7.6 and 3.7 years respectively.

The assessment of children >14 years of age following rGH treatment revealed a mean gain in height SDS (Ht gain SDS) of 1.2 ± 0.76 SD in the idiopathic group and positively correlated to the period of rGH treatment (p=0.016), however, children with structural/ genetic pituitary abnormalities had mean Ht gain SDS of 2.3 ± 1.6 SD with a significant negative correlation to the Ht SDS at diagnosis (p<0.001).

At final height, 4 of 7 adolescents retested for GHD (57%) exhibited persistent GHD. IGF-1 SDS after interruption of treatment < -2 SD correlated with GH status at transition (p=0.04). The underlying aetiology was a factor in prediction of GH status at final height, with complex pituitary defects more likely to be associated with persistent GHD (p=0.02).

Conclusions: This Irish study revealed novel characteristics such as higher male predominance in congenital idiopathic and acquired GHD due to pituitary tumours. A higher percentage of pathological congenital GHD was noted in this cohort compared to the literature. New insights on pituitary genetic mutations have emerged during the study, with future implications on the management of GHD at childhood and at the transition to adult care in the affected patients.

P2-P261

Two Different Variants of Short Stature Homeobox-Containing Gene (SHOX) Mutation in the Same Family

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Objectives: Deficiency of the short stature homeobox-containing (SHOX) gene is a potential etiology of short stature in children. The phenotypic spectrum of SHOX deficiency disorders, caused by haploinsufficiency of the SHOX-gene and inherited in a pseudo-autosomal dominant manner, is highly variable, even within the same family, ranging from nonspecific short stature to Leri-Weill dyschondrosteosis (LWD). Short stature, mesomelia and Madelung deformity define the classic clinical triad in LWD. SHOX deficiency can be caused either by single nucleotide variants or deletions encompassing the SHOX coding region and/or the enhancer region regulating SHOX expression.

We describe two brothers (21-month and 4-year old) with short stature and disproportion. Both children had an unremarkable past medical history. Family history was notable for several individuals with short stature. The parents presented both with short stature, but the father was proportioned, while the mother showed stigmas indicating LWD. Physical exam revealed short stature with disproportion and height standard deviation score (SDS) of -3.4 SDS for the older- and -3.2 SDS for the younger child. In both children laboratory was noncontributory for common causes of short stature and growth hormone stimulation test showed normal response. Due to family history, we performed *SHOX* gene analysis with a surprising result.

Methods: Multiplex Ligation-dependent Probe Amplification (MLPA) of the PAR region on Xp22.32 and Yp11.32 containing the coding region and 5' and 3' flanking sequences of the SHOX gene was performed using the MRC-Holland kit P018-G1 according to the manufacturer's instructions.

Results: *SHOX* gene analysis revealed a known heterozygous ~47, 5 kb deletion in the 3'-flanking region (probes L25091-L24249) in the mother and the older child, whereas a novel duplication in the SHOX 5'-flanking sequence (probes L24430-L20651) was found in the father and the younger child. This duplication has not been described previously, but likely influences the regulation of SHOX protein expression.

Conclusions: Short stature can be caused by different SHOX gene mutations and there is no established correlation between the severity of phenotype and the underlying pathogenic variant. The penetrance of SHOX deficiency is high, and it's clinical expression highly variable, even in the same family. Phenotypic characteristics become more pronounced with age and are more severe in females. All the more it was a surprise to find two different *SHOX* gene variants in two short siblings.

P2-P262

Identification of a Novel Heterozygous ACAN Mutation in a Patient with Non-Syndromic Short Stature

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Aggrecan, encoded by ACAN, is a major proteoglycan component in the extracellular matrix of the growth plate. At least 25 pathological ACAN mutations have been identified in patients with highly variable phenotypes of syndromic or non-syndromic short stature.

A 6-year-old boy was referred to our Centre for short stature (height 103,60 cm, -3,14 SDS) in familial short stature. Mid-Parental target height was 161.15 cm (-2.38 SDS); His father (height 167.3 cm) is from Ecuador; his mother of Italian origin displays a lightly disproportionate short stature (height 143 cm). The boy was born at 41 weeks of gestation with a birth length of 49 cm (−1.17 SDS) and a birth weight of 2840 g (−1.73 SDS). He had normal psychomotor development. The physical examination did not show dysmorphic features. Bone age corresponded to the chronological age.

Growth hormone (GH) stimulation tests showed discordant results (GH peak of 20.9 ng/mL with dexamethasone, 5.6 ng/mL and 11.1 ng/ml with arginine). Other blood tests (liver and renal function, screening for coeliac disease, thyroid and adrenal function tests) resulted within limits. Brain MRI was normal.

At the age of 6 years 8 months he was started on rhGH therapy for a reduction on height velocity (-1.51 SDS) starting at a dosage of 0.03 mg/Kg/die (7 days a week); this treatment was gradually reduced in dosage and then definitively suspended 21 months later due to poor response (increase in height: +0.36 SDS) and high IGF1 levels.

Genetic screening for short stature with Next Generation Sequencing revealed a heterozygous variant of uncertain significance of the ACAN gene p.(Gly676Ser), never described previously.

Currently he is 12.5 years old, 134 cm tall (-2.64 SDS) with a height velocity of 7.8 cm/yr (+2.9 SDS). Arm span is greater than his height (140 cm). His Tanner stage is P3G3. Pubertal development started at the age of 11 years 7 months. Bone age is equal to his calendar age, but advanced compared to his height. He does not report any pain or dysfunction of joints. IGF1 is within limits (281 ng/mL-normal range 100-460).

This case report implies to consider ACAN mutations in the genetic evaluation of patients with idiopathic short stature, even in the absence of characteristic features of a skeletal dysplasia. GH treatment efficacy is still controversial.

P2-P263

Genetic Investigation of Short Stature: A Case Report of Complex Constitutive Rearrangement Involving Chromosome 15

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Introduction: Growth is a complex process influenced by several genetic factors both pre and postnatal, in which 80% of the height variation is explained by genetic factors. Nevertheless, the standard medical evaluation of short stature (SS) relies upon physical examination and laboratory parameters and identifies a pathological cause of SS in 1–40% of individuals.

Rearrangements affecting chromosome 15 are rare and affected patients show a variety of nonspecific features, including complex congenital malformations, growth deficiency, and developmental delay.

Case Report: LDG 1 year 11 months years old girl, first daughter of a non-consanguineous young couple presented to the Pediatric Endocrinology service with a short stature complaint. She was born AGA (2760g and 48cm) at 37 weeks of gestation.

Physical examination revealed brachydactyly, triangular face, and facial dysmorphisms with prominent forehead, hypertelorism, bulbous nasal tip, long philtrum, thin upper lip, and micrognathism. The height was 71 cm (-4,2 SD) weight 7000 g (-3,7 SD), cephalic perimeter 43,5cm (-1,39SD).

G-banding analysis was performed, followed by FISH using probes 15q11-13 (SNRPN) for Prader-Willi/Angelman and 15q26.3 for internal control.

The karyotype showed a constitutive chromosomal aberration, 46,XX,r(15)[64]/46,XX,r(15)dup(15)[16]/47,XX,+r(15)[5]. FISH analysis confirmed the karyotype results and showed two more different cell lines 46,XX[9]/45,XX,-15[6]. In r(15) was detected the absence of the 15q26.3 signal resulting in a genetic material loss, region that harbor *IGF1R* gene, wich is responsible for the biological activity of IGF1.

Conclusions: Ring chromosome results from breakage in both arms of a chromosome, with fusion of the points of fracture and loss of the distal fragments. In this context, a ring induces chromosomal instability, which in turn generates a diversity of cell lines harboring different chromosome configurations. In the case described here, we hypothesized that a 46,XX zygote acquired a r(15) leading to the instability subjacent to the other cell lines that had ring duplication, monosomy 15, trisomy 15, which included r(15), most likely due to different approaches to restore balanced genome in the cells, such as trisomy rescue and Uniparental Disomy.

Genetic diagnosis in cases of SS is important because it can end the diagnostic workup for the patient, it may alert the clinician to other medical comorbidities for which the patient is at risk, and it is extremely valuable for the genetic counselling

P2-P264

Targeted/Exome Sequencing Identified Mutations in 55 Chinese Children Diagnosed with Noonan Syndrome and a Autosomal Recessive Form Associated With *LZTR1* Variants

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Background: Noonan syndrome (NS) is generally considered an autosomal dominant, multisystemic disorder caused by dysregulation of the RAS/mitogen activated protein kinase (MAPK) pathway. The latest research confirmed the existence of a form of Noonan syndrome that is inherited in an autosomal recessive pattern and identify biallelic mutations in *LZTR1*. In this study, we diagnosed 55 Chinese NS Children via targeted sequencing or whole exome sequencing (TS/WES).

Methods: TS/WES was performed to identify mutations in 55 Chinese Children who exhibited the following manifestations: potential NS facial dysmorphisms, short stature, congenital heart defects, and developmental delay. Sanger sequencing was used to confirm the suspected pathological variants in the patients and their family members.

Results: TS/WES revealed 25 NS patients (45.5%) caused by mutation in *PTPN11* gene, 10 NS patients (18.2%) caused by mutation in *SOS1* gene, 6 NS patients (10.9%) caused by mutation in *SHOC2,* 6 NS patients (10.9%) caused by mutation in *KRAS* gene, 3 mutations in the *MAP2K1* gene, 2 mutations in *RAF1* gene and 2 mutations in RIT1 gene. Specially, we identified a NS patient with a novel compound heterozygous mutation in the LZTR1 gene and inherited in an autosomal recessive pattern.

Conclusions: TS/WES has emerged as a useful tool for definitive diagnosis and accurate genetic counseling of atypical cases. This is a large sample study using TS/WES to diagnose Chinese patients with Noonan syndrome, and helping to reveal gene spectrum of Chinese NS patients. Our study also identified an autosomal recessive pattern in NS Patients with novel mutations in *LZTR1*. And it is the first report about a Chineses NS Patient with mutations in *LZTR1* and Changed our traditional understanding about the inherited pattern of Noonan syndrome.

P2-P265

A Novel Heterozygous Missense Variant in the LZTR1 Gene as a cause of Noonan Syndrome

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Background: Noonan syndrome (NS) is an autosomal dominant disorder characterized by a short stature, congenital heart defects, and characteristic facial features. Gain-of-function mutations of multiple genes in the Ras/mitogen activated protein kinase pathway have been identified in 70%-80% of patients with NS. Recently, leucine-zipper-like transcription regulator 1 (*LZTR1*), which has not previously been associated with the pathway, was reported as a new causative gene for the NS phenotype.

Objective: To report the clinical and molecular findings in a Japanese boy with NS phenotype and a novel heterozygous missense variant in the *LZTR1* gene.

Patient: A Japanese male patient was born at 40 weeks of gestation after an uncomplicated pregnancy and delivery. At birth, his length was 49.0 cm (+0 standard deviations [SD]), weight 3.42 kg (+0.9 SD), and occipital frontal circumference (OFC) 34 cm (+2.2 SD). He had distinctive facial features consisting of right-sided ptosis, hypertelorism, downslanting palpebral fissures, low-set ears, a webbed neck, and motor developmental delay. At 5 years and 8 months of age, the patient was referred to us because of a short stature. His height was 99.8 cm (–2.5 SD), weight 15.6 kg (–1.3 SD), and OFC 51 cm (+1.8 SD). Endocrine studies indicated growth hormone (GH) deficiency (peak serum GH values: 3.42 ng/mL at insulin stimulation test, and 2.49 ng/mL at L-dopa stimulation test [cut off values: <6 ng/mL]), and his bone age was assessed as 3 years. The results of provocation tests for other anterior pituitary hormones were within normal ranges. Based on these results, recombinant human GH therapy (0.175 mg/kg/week) was started at 6 years of age, leading to acceleration of his height growth. Brain magnetic resonance imaging, echocardiography, and a skeletal survey revealed no abnormalities. He also had severe intellectual disability (IQ56) and autism spectrum disorder.

Genetic analyses: Trio-whole-exome sequencing identified a *de novo* heterozygous missense variant in *LZTR1* (c.1234C>T, p.Arg412Cys). No pathogenic variants in other genes associated with NS were identified in the patient.

Conclusions: The present report has provided further evidence that a heterozygous germ line missense mutation in *LZTR1* can cause the typical phenotype of NS. Further studies are needed to clarify the mechanism by which *LZTR1* mutations result in the phenotype of NS.

P2-P266

A Novel FGFR1 Mutation in Kallmann Syndrome with Growth Hormone Deficiency

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Background: Kallmann syndrome (KS) is a genetic disorder, mainly characterized by the association of anosmia (due to hypo/aplasia of the olfactory bulbs) and hypogonadotropic hypogonadism (due to GnRH deficiency). Both partial or complete forms are described. Other features (skeletal and renal malformations, deafness, bimanual synkinesis) can be variably associated. Behind this phenotypic heterogeneity, there is a considerable complexity of genetic mutations. *KAL1*, *FGFR1*, *PROKR2*, *PROK2*, *CHD7*, *FGF8* are the principal genes involved, accounting up to 35% of KS cases.

Case presentation: A 4-years old boy presented to our Pediatric Endocrinology Unit for deceleration in growth velocity in the previous two years (- 1.8 SD), with normal height (-0.1 SD, according to Italian curves), weight and body proportion. He was prepubertal, without micropenis and cryptorchidism. Past medical history was unremarkable, he was born at term from non-consanguineous parents. His father was affected by KS, clinically diagnosed at the age of 14 because of anosmia and pubertal delay. A diagnosis of GH deficiency was confirmed by two stimulation tests (peak 5.74 ng/ml and 7.61 ng/ml, respectively), associated to low level of IGF-1 (25.7 ng/ml, nv 50-286). Brain MRI showed no morphological alteration of pituitary gland but, unexpectedly, highlighted olfactory bulbs hypoplasia. Anosmia was further confirmed by the olfactory test. Alteration of kidneys, limbs movement and hearing were excluded.

Genetic investigation showed a heterozygous mutation in the *FGFR1* gene (c.976C→G), both in the proband and his father, but not in his grandparents. This mutation has neither been previously reported by literature, nor it is comprised by the Single Nucleotide Polymorphisms (SNPs) database. Therefore, it is a de novo mutation, who passed from the father to the child. The pathogenicity was evaluated with prediction software (positive predictive value 0.99 and 0.89 of Mutation Tester and PoliPhen2, respectively). GH replacement therapy was started, with a good clinical response. At 9 years of age, he is still prepuberal.

Conclusions: Despite phenotypic variability, KS has been rarely associated to GH deficiency and short stature. KS is usually suspected in the pubertal period as a result of primary or secondary signs of hypogonadism, and not as a result of poor height growth. FGFR1 gene has been independently associated both to KS and to pituitary dysfunction. This novel mutation of *FGFR1* might determine the concurrence of these both clinical situations.

P2-P267

Clinical and Molecular Characterization of Eight Chinese Children with Cornelia de Lange Syndrome Using Targeted Next Generation Sequencing

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Cornelia de Lange Syndrome (CdLS) is a very rare genetic disorder present from birth, but not always diagnosed at birth. It causes a range of physical, cognitive and medical challenges and affects both genders equally. The present study described eight unrelated Chinese children who present with delayed growth and small stature, developmental delay, unusual facial features, limb abnormalities and a wide range of health conditions. Targeted-next generation sequencing using the Agilent SureSelect XT Inherited Disease Panel was used to screen for causal variants in the genome, and the clinically-relevant variants were subsequently verified using Sanger sequencing.

In our study, DNA sequencing identified eight gene variations in these patients, of which, 6 was novel. In Patient 1(P1), we found a heterozygous mutation of c.6109-1G>A in *NIPBL* gene (novel). In P2, we found a heterozygous mutation of c.6854_6855delAG (p.Gln2285Argfs*3) in *NIPBL* gene (novel). In P3, we found a heterozygous mutation of c.2342G>A (p.Cys781Phe) in *SMC1A* gene (reported). In P4, a heterozygous mutation of c.5683A>G (p.Arg1895Gly) in *NIPBL* gene was confirmed (novel). P5 had a novel heterozygous mutation of c.3344G>A (p.Trp1115*) in *NIPBL* gene. P6, a heterozygous mutation of c.1553_1554delAG (p.Glu518Valfs*18) in RAD21 gene (reported) was found. P7 had a novel heterozygous mutation of c.5615T>A (p.Leu1872His) in *NIPBL* gene. P8, we found a heterozygous mutation of c.6763+5G>T in *NIPBL* gene. These findings not only expands upon the mutation spectrum of gene variations in CdLS, but also broaden our understanding of the clinical features of CdLS.

P2-P268

A New Mutation in IHH Gene Causing Severe Short Stature

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Introduction: Heterozygous mutations in IHH are known to cause Brachydactyly type A1 (BDA1), in which the typical clinical features are bilaterally shortening or absence of the middle phalanges of most digits of hands and feet, shortness of 1st proximal bone and short stature ; althougt short stature is considered part of

BDA1, in most reported cases is not always present or unrelevant compared to the stature of unaffected relatives.

Recently heterozygous mutations in IHH were found in children and adults with short stature without specific skeletal signs of BDA1, adding IHH defects among genetic causes of short stature. Our case is in line with this findings but with several phenotypic differences.

Case description: A girl of 11 years and 7 months was referred to our clinic for short stature.

She was born from unrelated parents at 40 weeks, birth parameters were weight 2.7 kg (-1.85DS), length 48 cm (-1.32DS), head circumference 35 cm (0.53DS).

The mother's height was 150.2 cm (-2.1 DS), the father's height was 166.1 cm (-1.6 DS) with target height 151.6 cm (-1.8 DS).

After one year of life she had poor growth, psycomothor development was normal, menarche occurred at 11 years.

At our visit she showed height 129.1 cm (-2.9 SDS), sitting height 65.6 cm, sitting height/height ratio 0.51 (-0.65 DS), armspan 127.5 cm, armspan/height ratio 0.98, head circumference 49 cm (-2.7 SDS), weight 30.8 kg (-1.64DS), BMI 18.5 (-0.34DS), pubertal stage PH4 B3, cubitus valgus and scoliosis.

The karyotype, thyroid function and IGF1 were normal, SHOX gene defects were excluded, hand radiograph showed adult bone age without classical features of BDA1, but with overtubulation of distal phalanges.

Considering the poor height prognosis given the very advanced bone age, we performed a next generation sequencing (NGS) analysis by a panel including 254 genes causing short stature.

The NGS analysis revealed a new mutation in IHH gene, exon3:c.G1045A:p.A349T, that was confirmed by Sanger sequencing and found also in the mother.

The prediction software SIFT, Polyphen and Mutation Tester confirmed the pathogenicity of the identified variant, located in the C-terminal domain of IHH protein.

Conclusions: Our case confirms the role of IHH gene in short stature and adds new phenotypic features: very severe short stature, SGA, very mild radiographic features and great phenotypic variability in the same family.

P2-P269

Case Report: Ellis Van Creveld Syndrome with a Novel Mutation

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Introduction: Ellis Van Creveld syndrome (EVC) is a rare condition which is characterized with disproportionate short stature, postaxial polydactyly, and dysplastic nails and teeth. It is a rare autosomal recessive disorder due to mutations of EVC 1 and 2 genes located on chromosome 4p16. EVC syndrome is a chondroectodermal dysplasia. Congenital heart defects; especially atrial septal defect and single atrium occurs in 60% of affected individuals. Here we report a 5 year-old female patient admitted to our clinic with short stature. A novel homozygous mutation of EVC2 gene is detected.

Case: A 5-year-old female patient admitted to pediatric endocrinology department with the complaint of short stature. She was born at term via cesarean section. Her parents were second-degree cousins and there was no similar cases in the family. Birth height was unknown but family described short stature was prominent at birth.. She had the history of natal mandibular anterior teeth, they exfoliated spontaneously within the first month of life and noneruption of anterior maxillary and mandibular teeth. She had typically dysplastic finger- and toenails, which never needed to be cut.

She was operated for postaxial polydactyly. In physical examination height 93.5 cm (- 4.57 SD), weight 16 kg (-1.72 SD), head circumference 52 cm (0.69 SD), arm length 17 cm, forearm 14 cm measured. Despite most of the affected individuals had congenital cardiac defects her echocardiography was normal. With these clinical features Ellis Van Creveld syndrome was suspected. The whole exome sequencing of EVC2 gene in this patient revealed homozygous p.Gln1074* (c.3220 C>T) mutation. This mutation has not been described in the human gene database previously but in silico studies show that this mutation is the possible cause of the disease.

Conclusion: The EVC syndrome (OMIM #225500) is a rare autosomal recessive disorder. Despite it is a rare disorder of chondroectodermal tissue,it is more common in communities where consanguineous marriages are frequent. The diagnosis of the EVC syndrome is based on the clinical and radiographic findings of skeleton. Disproportionate short stature, postaxial polydactyly, displastic nails and teeth, congenital heart defects are main features.. The direct sequencing of the EVC syndrome 1 and 2 genes may also be performed. We detected a novel homozygous mutation in EVC2 gene. EVC syndrome must be kept in mind in the patients who has ectodermal dysplasia associated to disproportionate short stature.

P2-P270

A Homozygous Pathogenic Variant in the *TRHR* Gene in a Boy Who Presented with Severe Familial Short Stature and Central Hypothyroidism

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Introduction: Congenital central hypothyroidism (CCH) is a rare disease with inappropriate thyroid hormone secretion due to impaired TSH stimulation. TSH levels are not elevated; the patients are not diagnosed in TSH-based newborn screening. Biallelic variants in *TRHR* gene (encoding TRH receptor) are one of four genetic defects known to cause isolated CCH (*THRH*, *THSB*, *IGSF1*, *TBL1X*). The phenotype is variable but generally mild (neonatal jaundice, short stature, delayed bone maturation); the mental development is not significantly impaired. Only four patients have been described so far, thus the information about the phenotype is limited.

Case presentation: A boy with familial short stature (father 160 cm [-2.89 SD], mother 156.6 cm [-1.7 SD]) was born to non-

consanguineous parents in the 40th week of gestation short for gestational age – birth height 2900 g (-1.64 SD), birth length 47 cm (-2.39 SD). He was endocrinologically examined in 9.6 years for severe short stature (114.3 cm, -4.27 SD) and significantly delayed bone age (6.2 years). His mental status was normal; he had no other signs of hypothyroidism. Tests showed central hypothyroidism (fT4 8.65 pmol/l, TSH 1.642 mIU/l), low IGF-1 level (-1.91 SD), maximum stimulated growth hormone level was 10 ug/l. TRH stimulated TSH concentration was lower-normal (10.9 mIU/l). L-thyroxin substitution and recombinant growth hormone treatment was initiated (due to SGA indication) with relatively mild effect to proband's height (14.3 years, 3 years after the treatment initiation: height 143.7 cm [-3.32 SD]).

Genetic examination: Whole exome sequencing was performed and a homozygous variant p.Ile131Thr in the *TRHR* gene discovered. The variant has already been described as pathogenic. The replacement adds a polar hydroxyl group to the highly conservated hydrophobic position. It reduces the receptor affinity for TRH and impairs signal transduction as proven in functional studies. The result fully explained proband's short stature and central hypothyroidism, but as the disease is inherited in the autosomal recessive way it did not give any information about the causes of short stature in the family.

Conclusion: Homozygous variants in the *TRHR* gene may cause CCH. As the associated symptoms are generally mild and the mental development normal, the diagnosis may be difficult. Short stature may be the only symptom leading to the correct diagnosis.

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P2-P271

Unexpected Growth Patterns in Branchio-Oto-Renal Syndrome

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Background: Branchio-oto-renal (BOR) syndrome is a rare inheritable condition affecting the ears, 2nd branchial arch structures and the urinary system. Recognised features include hearing loss, structural defects of the ear, branchial defects, and a variety of renal malformations. Causative genetic variants have been identified as SIX1 and EYA1, accounting for approximately 49% of all cases of BOR syndrome. Short stature has not commonly been described in BOR syndrome, but is associated with oculo-facial-cervical syndrome and oculoauriculovertebral syndrome, which have demonstrated allelism with BOR due to mutations involving the EYA1 gene.

Methods: We present growth data from two unrelated pedigrees with confirmed clinical diagnosis of branchio-oto-renal syndrome based on published criteria (Chang, 2004). The first pedigree consists of four siblings (one girl, three boys) and the second of three siblings (two girls, one boy), all aged between 7 to 24 years. Four of the cohort have reached a final height ranging from <3rd to 10th centile with a mid-parental height n prediction of the 25th centile in both families. Growth measurements available for the 7 children show normal pre-natal and post-natal growth, marked delay in bone age, and a definite fall off in height velocity from the mid childhood years. None have sufficient renal involvement (normal creatinine levels) to account for their poor growth. Two individuals, from separate families, have met the criteria for growth hormone deficiency and have shown a response to GH replacement. Growth factor measurements (IGF-1, IGFBP3) are non-discriminatory for growth in these pedigrees.

Discussion: Short stature and growth hormone deficiency are not recognised features of branchio-oto-renal syndrome but these two family cohorts show a similar pattern of growth, with low height velocity, falling below their centiles in later childhood and failure to reach the predicted mid-parental height suggestive of suboptimal late childhood and pubertal growth. The aetiology for this finding remains unclear. Genetic analysis is in process but the yield for positive mutations in BOR syndrome is low. As an extension of this review we are pursuing auxology data on other families with this rare syndrome to expand on this unusual phenotype in an effort to identify unelucidated factors contributing to reduced growth. Growth surveillance is advocated in children with this condition. Normal growth and centiles in the early childhood years do not guarantee final height attainment.

Reference

Chang, E. H. Branchio-oto-renal syndrome: The mutation spectrum in EYA1 and its phenotypic consequences. *Human Mutat* 2004;23: 582-589.

P2-P272

Mild Autistic Spectrum Disorder in a 33 Year-Old Male Japanese Patient with Temple Syndrome

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Introduction: Temple syndrome (TS14) caused by maternal uniparental disomy chromosome 14 (UPD(14)mat), paternal deletions and the imprinting defect affecting the 14q32.2 imprinted region is associated with non-specific symptoms such as growth failure, precocious puberty, obesity, and diabetes mellitus (DM). Some TS14 cases are misdiagnosed as having Prader–Willi syndrome (PWS). In TS14, patient's intelligence quotient (IQ) is usually normal, and autism spectrum disorder (ASD) is a rare comorbidity.

Case: A male patient was born at 39 weeks and was not small for his gestational age. He was clinically diagnosed with PWS owing to hypotonia during infancy. After infancy, he received no regular

follow up. He exhibited precocious puberty, transient obesity, and DM. His final height was within normal limits at 159 cm (-2.0 SD). At 33 years of age, he visited our hospital to receive a genetic diagnosis and social welfare. He showed the normal methylation levels of the *SNRPN*-DMR on chromosome 15 and hypomethylation of the IG-DMR and *MEG3*-DMR at the 14q32.2 imprinted region without UPD(14)mat and maternal microdeletion involving the 14q32.2 imprinted region, and was diagnosed with TS14. At age 33, his total IQ was 97; verbal IQ was 104, and performance IQ was 88 (Wechsler Adult Intelligence Scale-III). Although his scores of ASD assessment scales (Pervasive Developmental Disorders ASD Rating Scale-Text Revision and Autism Spectrum Quotient) were low, we clinically diagnosed with ASD, with both verbal and nonverbal communication impairments.

Conclusion: We report a patient who was diagnosed as TS14 at the age of 33, with post-natal growth failure, obesity and DM. Comorbidity of ASD was also diagnosed, which is the second case reported. This case also highlights the importance of genetic analysis for differentiating TS14 from PWS. Hypotonic infants with unknown etiology should be considered for genetic analysis of TS14. Additionally, long-term follow up is needed, not only to observe precocious puberty and DM, but also to identify problems associated with developmental disorders, such as ASD.

P2-P273

Seventeen-Year Observation in a Japanese Female Case of Tatton-Brown-Rahman Syndrome: An Overgrowth Syndrome with Intellectual Disability

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Background: Advances in genetic analysis techniques has greatly contributed to recent discovery of causative genes associated with overgrowth with intellectual disability (OGID). Tatton-Brown-Rahman syndrome (TBRS) (OMIM #615879) was one of them, characterized by tall stature, a distinctive facial appearance, and intellectual disability. This syndrome was first reported in 2014. Thus, long-term clinical courses are unknown. We present our Japanese case with OGID who was diagnosed TBRS by Whole Exome Sequencing supported by the IRUD (Initiative on Rare and Undiagnosed Diseases).

Case report: A 9-year-old Japanese girl first visited our outpatient clinic, complaining of tall stature and developmental delay. She was born from healthy nonconsanguineous parents (father 179cm, mother 168cm). She was born at 40 weeks' gestation with a birth height of 51cm, and body weight of 3604g. She had no history of prenatal abnormalities. At six years developmental delay was pointed out. She had a distinctive face (round face, heavy horizontal eyebrows, and narrow palpebral fissures) and intellectual disability (IQ 68). Physical findings at age 10 were the following; height 166.4cm (+3.9 SD), body weight 44.1kg (+1.25SD), arm span172cm, breast development Tanner 3-4, no menarche, arachnodactyly, Marfanoid habitus. No abnormalities were found in endoclinological, cardiac and ophthalmological analysis. Laboratory findings are listed below; IGF-1 325 ng/mL, LH 5.4 mIU/mL, FSH 8.2 mIU/mL, estradiol 63 pg/mL, G-banding 46, XX. Urinary homocysteine was not detected. Cranial MRI showed no abnormalities. Bone age was 11.1 yrs. She received estrogen therapy from 10.8 to 13.6 years old (175cm) to accelerate epiphyseal closures. At 26 years old her height was176 cm and body weight was 63kg. We performed a whole exome analysis for her excessive growth. It revealed de novo heterozygous mutation in the *DNMT3A* (DNA cytosine 5 methyltransferase 3A) gene (exon15, c.1761_1762del: p.G587fs. hetero), which was confirmed by Sanger Sequencing. No hematologic malignancy has been developed so far. She has spent her daily life without any special support and worked in disability employment.

Conclusion: TBRS resulted from constitutional mutations in the epigenetic regulation gene *DNMT3A*. Somatically acquired mutations in *DNMT3A* occur in hematological malignancies, but the association between OGID and malignancies has been veiled. Other epigenetic regulation genes such as *NSD1*, *EZH2* and *HIST1H1E* cause OGID. Features specific to mutations of each gene should be elucidated. Case reports of OGID may help to make differential diagnosis and reveal risk of malignancies in OGID.

P2-P274

KBG Syndrome: Our Experience and Unreported Clinical Features

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KBG syndrome (OMIM 148050) is a an emerging autosomal dominant disorder caused by heterozygous mutations in the ANKRD11 gene or deletions of 16q24.3, characterized by developmental delay, short stature, dysmorphic facial features and skeletal anomalies.

Patients and methods: We report 22 patients with dysmorphic features, learning disabilities, behavior problems and macrodontia, where a clinical diagnosis of KBG was suspected. An ANKRD11 defect was confirmed in 12 patients. In this group, 9 patients showed a point mutation in ANKRD11 gene and 3 patients carried a 16q24.3 deletion.

Results: All KBG patients presented facial dysmorphisms with typical nose-mouth appearances. Macrodontia is highly suggestive of this syndrome but not specific. Skeletal abnormalities were constant, in particular costo-vertebral abnormalities, and the majority of patients showed joint stiffness. Stature was <10th centile in 75% of the patients, 3 patients required GH treatment and 2 of these showed GH deficit. GH-therapy caused a significant increase of height velocity. Advanced puberty was reported in 28,5% males patients ANKRD11+ in peripubertal age. Due to its potential effect on growth, early signs of puberty must be carefully monitored in patients diagnosed at a young age. Cerebral structural abnormali-

ties were seen in 8 patients. Developmental delay was reported in 83.3% patients, especially speech delay (75%) and learning difficulties. Language delay and ID are not related with the degree of intellectual disability and are non specific for the condition. In agreement with previously reported cases, all patients showed behavioral abnormalities (hyperactivity, attention deficit, anxiety, lack of self-confidence, frustration intolerance, aggressiveness and depression). Two patients had hematological abnormalities.

Retrospectively, patients with negative genetic results had less typical clinical features. One patient showed a causative RAD21 mutation, confirming phenotypic overlap with cohesinopathies, and another one harbored a large de novo duplication of 12.q21.1-q21.33. The remaining eight patients are at present undiagnosed.

Conclusions: We emphasize that genetic analysis of ANKRD11 can easily reach a detection rate higher than 50% thanks to clinical phenotyping, particularly facial appearance. Joint stiffness was not reported previously but seems to be a common feature and can be helpful for the diagnosis. Hematological abnormalities could be present and warrant a specific follow-up. We recommend echocardiogram, renal ultrasonography, ophthalmic, and hearing assessments and good dental care along with formal developmental assessments and appropriate early intervention.

References

1 Herrmann J et al: The KBG syndrome-a syndrome of short stature, characteristic facies, mental retardation, macrodontia and skeletal anomalies. Birth Defects Orig Art Ser 11:7-18 (1975).

2 Low K et al: Clinical and Genetic Aspects of KBG syndrome. Am J Med Genet 170:2835-2846 (2016).

P2-P275

Growth of Infants Born by Intracytoplasmic Sperm Injection (ICSI) Technique

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Due to recent scientific progress in assisted reproductive techniques (ART), infertile couples can now become fertile. Thus, a number of infants in our country are the results of these costly interventions. This study has been undertaken to evaluate the physical growth of ART infants using standard growth charts from birth until 18 months of age.

Methods: We measured the anthropometric data of 100 infants newborns conceived through ART intracytoplasmic sperm injection (ICSI) at HMC. A sequential sampling method in a period of 2 years was used. Their birth size was assessed by measuring infants' weight, height and head circumference, and physical examination. The weight for age SDS (WSDS), length SDS (LSDS) and head circumference SDS (HCSDS) were calculated with reference to normal standard for gestational age and sex of the newborn. WHO growth charts (0: 2years) were used to assess these infants' growth during the study period.

Findings: In comparison with normal growth standards for gestational age and gender, the HCSDS was < 2SDS in 3/100 infants, the LSDS was < -2 in 6/100 infants, and WSDS was < -2 in 16 % of the infants. Low birth weight (LBW) infants were twice more in the ART group compared to infants of normal population. During the first 18 +/- 5 months postnatally linear growth was normal in the majority of infants with no significant change in the mean WtSDs, LSDS or HCSDS. Only 2 infants had LSDS <-2, 8 infants had WtSDS <-2, 2 infants had HCSDS <-2. (table)

Table 1. (for Abstract no P2-P275)

Age	Wt SDS	LSDS	HCSDS
Birth			
Mean	–0.85	–0.23	–0.36
SD	0.98	0.91	0.77
18 months			
Mean	–0.90	–0.34	–0.43
SD	0.84	0.88	0.79

Conclusion: Infants born with ART have normal intrauterine growth appropriate for their gestation age. However, they are more susceptible to be underweight at birth and during infancy compared to normal infants.

P2-P276

Earlier Mother's Age at Menarche Is a Risk Factor of Daughter's Early Menarche and Short Stature in Young Korean Female: Epidemiologic Study

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Objective: To investigate whether earlier mother's age at menarche is a risk factor of daughter's early menarche, obesity, and short stature in young Korean female.

Research design and methods: We tested associations between mother's age at menarche, mother's adult body size and her daughter's age at menarche, body size from the data of 6th Korea National Health and Nutrition Examination Survey (KNHANES VI) (2013-2015). We analyzed 999 pairs of mothers and daughters aged 15-30 years who had menarche age and anthropometrics data.

Results: In the mothers, earlier menarche was not associated with short adult height or obesity. In contrast, in her daughter, earlier mother's menarche predicted shorter height and greater BMI. Daughter of earlier mother's menarche had a higher prevalence of short stature (<152cm) than those of later menarche. The odds ratio (OR) of a short stature in daughter of earlier mother's menarche was 3.61 (95% CI, 1.90-6.88). In multivariate regression, the OR of a short stature remained 3.61 (95% CI, 1.90?6.88) after adjusting for age, mother's height, and household income.

Conclusions: Earlier age at menarche of mother increased the risk of early menarche and short stature of her daughter in young Korean female. Thus, knowledge of mother's menarche age is important in identifying female at risk for short stature.

P2-P277

Pulling the Brakes — 'Catch Down Growth': A Phenomenon for Achieving Mid-Parental Height Centile after Acquired, All-Cause, Brain Injury

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Introduction: Of any pituitary dysfunction following brain injury, growth hormone (GH) deficiency (GHD) is the most prevalent. The cut-point for defining GHD has been placed at 7 ng/mL representing optimum test performance. We hypothesised this cut-off may be set too low for genetically taller children with acquired brain injury, notably brain tumours, who demonstrate severe growth failure but repeatedly fail to meet diagnostic thresholds for GH replacement until several centiles have been crossed downward over time; this treatment delay may ultimately compromise metabolic status and post injury wellbeing. We reviewed the possibility this cut-off, and its undifferentiated applicability to a broad variety of taller children with clear longitudinal growth failure of different target heights, height predictions and BMIs, requires re-consideration for this cohort.

Methods: We reviewed retrospectively the parental heights, longitudinal growth records and charts of 50 children from diagnosis of a brain tumour (47) or traumatic (3) brain injury, and noted, at intervals, height, weight, Tanner stage and peak GH (pkGH) at first onset of growth failure and at any subsequent testing for persistent growth failure. BMI, BMI SDS, height SDS and midparental height SDS (MPHSDS) were calculated.

Results: After a period of Initial growth exceeding MPHSDS, 42/50 (≙84%) fell to the midparental centile and were assessed for GHD. 26/42 (≙ 61.9%) did not meet diagnostic criteria for GHD. Despite "persisting" growth failure and little change in BMISDS, a median 24.7 (range 11.0; 53.1) months later, 10/26 again failed to meet GH treatment criteria and one additionally failed a third GH assessment 11.8 months later. In total, patients took a median 10.7 (range 0; 57.7) months to meet GH treatment criteria from first onset of growth failure, with an overall median -0.14 (range -1.21; 0.96) decrement in HTSDS and little change in BMISDS.

Conclusion: Our pre treatment data do not suggest a MPHSDS above average or an increment of BMISDS impairs diagnostic validity of current pkGH and may be a physiological 'catch-down growth' towards MPHSDS, not requiring immediate GH treatment. Severe GHD may ensue which requires continuous monitoring after recanalisation into the mid-parental centile and at onset of puberty. Post treatment review is still required to ensure that these children achieve their innate growth potential without compromise.

P2-P278

Effects of Inhaled Corticosteroids and Montelukast on Growth and Body Mass Index in Children with Asthma

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Background: Inhaled corticosteroids (ICS) and montelukast are commonly prescribed drugs in asthma treatment. Several studies have investigated the adverse effects of ICS on growth and weight gain in children. However, the biosafety studies of montelukast are mostly focused on the neuropsychiatric side effects. The present study aimed at investigating the adverse effects of montelukast and ICS on anthropometric parameters in children.

Methods: The present study used a retrospective cohort design of 175 children with asthma in three treatment groups including budesonide, fluticasone propionate, and montelukast sodium. Children who were admitted to the outpatient department with allergic symptoms other than asthma were demarked as a control group. All subjects had at least two clinical visits within a 12-month interval. The daily steroid dosage was calculated individually for each patient. The skin prick test results, cumulative dose, and type of medication, anthropometric parameters including height, weight, body mass index (BMI) in both the visits, were obtained from medical records of the patients.

Results: There were no significant differences between the groups in terms of age, gender, atopy and rhinitis prevalence. In the first, as well as last visit, the height SDS, weight SDS and BMI SDS did not show the difference between the groups. These values did not vary during the study period also. There was found a negative correlation between the variations in height SDS and daily dosage of BUD.

Conclusions: Commonly prescribed doses of inhaled steroids and montelukast are safe and do not affect BMI and growth in asthmatic children.

P2-P280

Skeletal Disproportion and Growth Impairment in Glucocorticoid Treated Boys with Duchenne Muscular Dystrophy

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Introduction: Although short stature is common in boys with Duchenne Muscular Dystrophy (DMD), little information on body proportions and the GH/IGF-1 axis exists.

Methods: Total height (Ht), sitting height (SH), leg length (LL) and bone lengths (femur, tibia, humerus) in boys with DMD (n=30) and healthy boys (n=79) were measured using DXA digital images by 1 observer. Insulin growth factor-1 (IGF-1), IGF binding protein-3 (IGFBP-3) and acid labile subunit (ALS) were converted to sex and bone age adjusted SDS. Ht, SH, LL, SH:LL ratio and bone lengths in DMD were compared to healthy controls adjusted for age and puberty. Results expressed as median (range).

Results: Median age of boys with DMD and controls was 10.0 years (6.1,16.8) and 12.4 years (5.8,17.0), respectively [p=0.03]. All DMD boys were treated with glucocorticoids with a median duration of 7.1 years (1.3,15.2). 26 (87%) and 31 (39%) were prepubertal, respectively. 3 (10%) boys with DMD were on testosterone, 8 had vertebral fractures. None had significant scoliosis. Ht [β=-14.3 cm, 95% CI=-18.3,-10.4], SH [β=-5.0 cm, 95% CI -6.9,-3.1] and LL [β=-9.3 cm, 95% CI -11.7,-6.8] were significantly lower in DMD compared to controls. Femur [β=-3.6 cm, 95% CI-5.5,-2.2], tibia [β=-5.7 cm, 95% CI -6.9,-4.4] and humerus lengths [β=-1.4 cm, 95% CI -2.5,-0.5] were also significantly lower in DMD compared with controls. In a sub-analysis of 20 boys with no knee and hip contractures from joint angle measurements, SH:LL ratio [β= +0.10, 95% CI +0.04, +0.13] remained significantly higher in DMD compared with healthy controls. Median IGF-1, IGFBP3 and ALS Z-scores were +1.2 (-2.1,+3.7), +1.5 (+0.2,+3.7) and -0.5 (-1.5,+0.9) respectively. IGF-1 [β= -0.001, 95% CI -0.02,+0.014], IGFBP-3 [β= -1.8, 95% CI -4.5, +1.0] and ALS [β= +0.001, 95% CI -0.004,+0.005] showed no association with Ht after adjusting for bone age.

Conclusion: As glucocorticoid excess is not usually associated with disproportionate growth, the finding of disproportionate growth in boys with DMD raises the question whether there is an intrinsic and localized disorder of growth in this condition. Despite the growth impairment in these boys, abnormalities in GH/IGF-1 axis were not seen and were not associated with stature.

P2-P281

A Novel Mutation in the *SLC2A2* Gene in a 19-Year-Old Female with Diabetes Mellitus and Renal Tubular Acidosis: A Therapeutic Conundrum

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Background: Mutations in the *SLC2A2* gene are implicated in Fanconi-Bickel syndrome (FBS). This is a rare form of glycogen storage disease (GSD) inherited in an autosomal recessive manner characterized by hepato-renal glycogen accumulation, impaired glucose and galactose utilization, and proximal renal tubular dysfunction. The world-wide frequency of Fanconi-Bickel syndrome is not known, though the disease is considered to be rare in which a little more that 100 cases have been reported in the literature. Interestingly, there is no FBS cases described from Qatar.

Objective(s): To describe the clinical and genetic characteristics of a FBS patient with a novel mutation encoding the *SLC2A2* gene.

Case report: The patient presented with renal tubular acidosis, recurrent spontaneous pathological fractures and short stature. On examination, her weight was 23 kg (<5th percentile) and height of 100 cm (<5th percentile). She had thoracolumbar scoliosis and multiple deformities in the upper and lower limbs, leading to limited ambulation. Biochemically there was hypophosphatemia, hypocalcemia, elevated alkaline phosphatase and liver enzymes (ALT and AST). Fasting hypoglycemia and postprandial hyperglycemia were identified. Urine analysis was significant for phosphaturia, and evidence of proximal renal tubular acidosis (RTA) indicated by generalized aminoaciduria. The patient was diagnosed with diabetes mellitus at the age of 17 years and is currently on insulin.

Methods/Results: Using genomic DNA Whole Exome Sequencing (WES) analysis was performed. The exonic region and flanking splice junctions of the genome were captured and sequenced by NetGen sequencing on an Illumina system. Sequence and copy number variations were described according to the Human Genome Variation Society (HGVS) and International System for human Cytogenetic Nomenclature (ISCN) parameters, respectively. Whole Exome Sequencing showed c.613-7T>G: IVS5-7T>G in intron 5 in the *SLC2A2* gene. This variant reduces the quality of the splice acceptor site in intron 5 and creates a new cryptic splice acceptor site upstream of the natural splice site.

Conclusions: We report a novel mutation in the *SLC2A2* gene in a FBS patient. The molecular mechanism/s underlying some of the biochemical and clinical features of FBS are not well understood and currently there is no effective treatment for the underlying genetic defect. Further research is focusing on developing novel therapies for these patients with FBS.

P2-P282

Vesico-Ureteral Reflux and Effect on Growth Indices

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Background: Vesico-ureteral reflux (VUR) is the most common urologic abnormality seen in children. It represents the backflow of urine from bladder to upper urinary structures due to a defect in closure of uretero-vesical junction. This condition predisposes children to repetitive pyelonephritis associated with renal scarring.

Objective: Studies are continuously searching for the potential effect of VUR on growth. We aimed to assess growth indices: height z-score (HZ), Ideal body weight percent (IBWp) and percent of actual weight over median weight for age (MWAp) in children with VUR at presentation and at time of study and to compare them with those of children with pyelonephritis without VUR.

Materials and methods: We included children aged between 0 and 6 years old with a normal renal function admitted in our center

for pyelonephritis. However, children with chronic diseases affecting growth were excluded. The children who met above criteria (109 children) were divided into 3 groups according to voiding cystography results: G1(VUR grade 1-2), G2(VUR grade 3, 4, 5) and G3 (no VUR).

Results: Our data showed no significant difference between the 3 groups concerning sex, age groups, consanguinity, gestational age, height and weight at birth. However, we noted a strong association between VUR and ESBL infection (p=0.0001), and history of previous pyelonephritis (p=0.0357). Growth indices HZ and MWAp were significantly lower in G2 than in other groups at presentation and at time of study (p=0.0001 for both). In contrast, no significant change was detected in IBWp neither at presentation nor in at time of study. No significant association was found between reflux laterality and growth indices. We also noted a significant improvement in HZ (p=0.01) and in MWAp (p=0.0168) following surgical treatment, while no significant change was recorded in growth indices following antibiotic prophylaxis.

Conclusion: VUR might have a negative impact on growth depending on severity and surgical treatment was shown to improve growth indices. So, an early detection and surgical correction especially for severe cases of VUR might prevent growth retardation.

Key words: Vesico-ureteral reflux, pyelonephritis, growth indices.

P2-P283

A Novel in Frame Deletion Mutation in Exon11 in *BTK* Gene to X- Linked Agammaglobulinemia: Case Report and Function Analysis

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Objective: X- linked agammaglobulinemia (XLA) is a kind of primary immunodeficiency disease caused by mutations in the gene encoding Bruton agammaglobulinemia tyrosine kinase (*BTK*). This study, we identified a novel in frame deletion mutation in exon11, c.902 _ c.904 delAAG(p.e301 _ g302 delinsG) in *BTK* gene and evaluated the function of BTK.

Methods: A five- year-old boy presented with recurrent respiratory tract infections. His height was 110.3cm(M), his body weight was 17.5kg, white blood cell count, immunoglobulin (IgG,IgA,IgM), immunoglobulin subtypes(Ig G1,Ig G2, Ig G3, Ig G4) and CD3,CD4,CD8 were detected. *BTK* gene exons of the patient and his parents were sequenced. Mutation and wild type recombinant plasmid (pEGFP-N1 vector) were constructed respectively, 293T cell and COS7 cell line were transfected, qPCR and western blot were detected.

Results: agammaglobulinemia was detected as Ig G was 20.0 mg / dl (800 - 1800 mg / dl) and Ig G subtypes (G1,G2,G3,G4) were all very low. A novel in frame deletion mutation of *BTK* gene c.902 _ c.904 delAAG(p.E301 _ G302 delinsG) in a child was detected and no mutations of *BTK* in his parents were founded. In pEGFP-N1 vector, EGFP is the downstream gene of *BTK* gene. Fluorescence signal can be used to measure transcription level. The expression was no difference between *BTK* normal group and deletion group from the fluorescence intensity. By the result of western blot, The protein volume of normal type was higher than deletion type.

Conclusion: A novel in frame deletion mutation of *BTK* gene, c.902 _ c.904 delAAG (p.E301 _ G302 delinsG) of *BTK* gene was identified and it affects the protein stability after *BTK* translation, result to the typical clinical manifestation of XLA.

Growth & Syndromes P3

P3-P219

Is Growth Hormone Deficiency a Contributor to Short Stature in Cutis Laxa Syndrome?

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Autosomal dominant cutis laxa type 3 (ADCL3) is a genetic connective tissue disorder characterized by poor pre- and postnatal growth and, rarely, by systemic impairment. The aetiology of short stature is incompletely known, some of these patients reaching normal final height. Less than 50 cases were reported in the literature.

We report the case of a male patient 3.2 years old who presented for endocrinological evaluation of short stature. His medical history reveals congenital hypothyroidism treated with levothyroxine, congenital cataract, pseudophakia, hiatal hernia, micturition disorder. The patient was born small for gestation age (SGA), has facial dysmorphic features, lax, thin skin with vascular markings, severe short stature [-4,08 standard deviations (SD)], body weight at the upper normal range (BMI at the 80 percentile) and decreased growth velocity (-1,76 SD in the last year). The patient was also under genetic evaluation. Laboratory assessment shows normal IGF1 (111 ng/ml), peek growth hormone (GH) during two stimulation tests of 8,07 ng/ml and 2,98 ng/ml, bone age of 3 years and pituitary hypoplasia on MRI. The diagnosis of short stature due to SGA and growth hormone deficiency was established and somatropin treatment 0,035 mcg/kg body weight/day was started. After 12 months of treatment the height increased by 8.5 cm and the height SD score improved at -3.1. The treatment was well tolerated by the patient. The patient presented the results of the genetic tests which showed ADCL3.

This is the first case report of ADCL3 associated with GH deficiency treated with somatropin. Evolution under treatment will be closely followed in interdisciplinary collaboration to optimize the results.

P3-P220

Effect of Sickle Cell Disease on Growth and Puberty

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Background: Research has shown that some of the endocrine disorders in patients with sickle cell disease include delayed growth and pubertal development. No study has been done in Kenya to investigate whether this applies for the local children with sickle cell anaemia.

Objective: To describe growth and pubertal development in children and adolescents with Sickle cell disease

Methodology: This was a cross-sectional descriptive study involving 142 children with confirmed sickle cell disease who were being followed up at Kenyatta National Hospital's Paediatric Hematology clinic.

Demographic information including age, gender, tribe and socio-economic data were obtained by standard questionnaire while the clinical information including height, weight and BMI were obtained by actual measurements and plotted on the CDC charts for age and gender.

Pubertal status in girls was determined by assessing breast tanner stage while in boys it was assessed by measuring the testicular volume. Presence of pubic and axillary hair was assessed in both.

Results: The median age of patients was 7.0 years (IQR 5.5,9.5 years). Of these patients 86 (60.6%) were male and 56 (39.4%) were female with a male to female ratio of 43:28. Those with underweight were 16.3% male and 16.1% female (<-2 SD) while 11.1% male and 13.5% females were stunted (<-2SD).33.9% female and 30.2% male had BMI of less than -2SD. None of the differences in the anthropometry parameters between male and females were statistically significant.

Among boys aged > 9 years (n=29) 20 (69%) had testicular size tanner (< 3cc) while among girls aged >8 years (n=22) 18 (82.6%) had breast tanner <2 (pre-pubertal). Twenty girls (96.4%) and all the boys in their respective age groups had no axillary hair while 19 of the girls (85%) and 27 of the boys (93%) had no pubic hair.

Conclusion: A large proportion of these children were either underweight, stunted or had low BMI. There is need for longitudinal studies to determine whether this growth failure is due to the sickle cell condition or other environmental factors.

Most of the children with sickle cell disease had not initiated puberty at their expected respective ages. Follow up needs be done on these patients to determine at what age they will go into puberty and what effects this condition has on their fertility rate.

P3-P221

Two Siblings with Alström Syndrome

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Background: Alström syndrome is a rare genetic disorder characterized by retinal degeneration, hearing loss, early-onset obesity, type 2 diabetes, cardiomyopathy, systemic fibrosis and progressive multi-organ failure. Our aim is to present two siblings who were diagnosed in early childhood.

Case presentation: Three years five months old female and her two years one month old sister admitted to paediatric neurology department due to lack of eye contact and speech delay. There was no history of consanguinity. The older sister was born after an uncomplicated pregnancy, birth weight was 2700 grams and the neonatal period was uneventful. She could sit at 6 months and walk at 18 months of age. She never talked, her constant anxiousness could only be ameliorated by eating. On admission her height was 98.7 cm (-0.01 SDS), weight 24 kg (+3.5 SDS), BMI 24. 64 kg/m^2(+ 4.21 SDS), had craniofacial dysmorphism (round face, nystagmus, bitemporal flatting), photophobia, truncal obesity and hepatomegaly. There was no evidence of cardiac involvement, hypertension and polydactyly. The younger sister had learning difficulty, blindness and shortness of breath. Birth weight was 3000 grams, could sit at 6 months, walk at 16 months of age, she can currently talk 2-3 words. Her height was 98 cm (+2.78 SDS), weight 28 kg (+6.91 SDS), BMI 29.15 kg/m^2 (+5.45 SDS). She had round face, short neck, nystagmus, bitemporal flatting, and truncal obesity. Denver developmental screening test demonstrated moderate retardation in older and mild retardation in younger sister. Both sisters had low HDL levels, hypertriglyceridemia, and vitamin D deficiency. The older sister had slightly elevated transaminases, the younger sister had insulin resistance and subclinical hypothyroidism. The ophthalmologic examination was notable for retinal degeneration in both, echocardiography and abdominal ultrasounds were normal. Hearing test could not be applied due to incompatibility. The older sibling had bilateral serous otitis media, the younger sister had acute suppurative otitis media; auditory brain-stem response testing under general anaesthesia was planned after treatment of otitis. Appropriate nutrition was arranged. The genetic analysis revealed homozygous mutation in *ALMS1* gene (c.10563_10564del p.(His3521Glnfs*17).

Conclusion: Although Alström syndrome is a rare genetic disease, it should be kept in mind in patients with early onset obesity and speech delay. Awareness of this syndrome may prompt early genetic counseling.

P3-P222

Development of an Online Learn-Pro Module to Support Health Care Professionals Knowledge About Growth and Puberty

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Background: The Scottish Paediatric Endocrine Managed Clinical Network is committed to providing equity of care and education across Scotland.

A key role is the education of health care professionals and how this is delivered. An extensive survey using a Learning Needs Analysis Tool was completed to ascertain learning needs and their delivery across Scotland. This highlighted the desire to have online learning available to health professionals.

Objective: To design an online education program accessible to all Health Care Professionals.

Method: A small multidisciplinary paediatric endocrine focus group was formed all with previous experience at delivering education workshops to look at the development of an online tool using Learn-pro an existing online learning platform within Scotland and the UK.

Materials were adapted from previous workshops. A detailed programme was developed to enable users to better understand normal growth and puberty, understand what influences growth, variations of normal growth and puberty, to understand growth charts and their uses and to be able to measure children correctly and understand causes of abnormal growth. The module is accompanied by an interactive test that allows assessment of learning following completion of the module.

Results: As of 26/02/2018 139 people have enrolled to do the module and 44 have completed it.

Conclusion: The Learn-Pro Module has been developed and launched across Scotland as a useful evidence-based update for those working in paediatrics as well as endocrinology and can be recommended learning for all health care professionals working with children.

P3-P223

Coeliac Disease in Turner Syndrome More Frequent Than Expected

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The risk of developing coeliac disease (CD) is higher in Turner syndrome (TS) than the general population,and screening has been recommended in asymptomatic individuals known to have an increased risk of developing the disease. In light of this recommendation,the aim of the study was to assess prevalence of celiac disease in Turner syndrome.

Patients and methods: Serological screening of coeliac disease were performed in 85 children and adolescent with Turner syndrome during the last 3 years (since 2015). Serological investigations were repeated yearly, and the results of screening of new patients were completed.

Results: Positive serologic results were found in nineteen 19 of 85 patients (22%). Intestinal biopsy was applied in all cases. Coeliac disease was revealed by histologic analysis in 12 cases - 12/85 (14%).

Conclusion: The prevalence of celiac disease in Turner syndrome patients observed in the present study is quite high and seems to indicate that the connection between these disorders can not be coincidental. Their cases and the available data from the publications indicate that screening of coeliac disease in patients with Turner syndrome should be performed and intestinal biopsy is recommended in positive cases.

P3-P224

A 14-Year-Old Boy with Simpson-Golabi-Behmel Syndrome-Case Report

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Simpson-Golabi-Behmel syndrome is a condition which classified as an overgrowth syndrome and affects many parts of the body and occurs primarily in males. Infants have macrosomia at birth and continue to grow and gain weight at an unusual rate. The incidence of Simpson-Golabi-Behmel syndrome is unknown. Mutations in the GPC3 gene are the most common cause of Simpson-Golabi-Behmel syndrome. About 250 people worldwide have been diagnosed with this disorder. About 10 percent of people with Simpson-Golabi-Behmel syndrome develop tumors in early childhood, espacilly Willms tumor and neuroblastoma.

We present a 14-year boy, who was diagnosed in our Department because of overgrowth, and we observed clinical signs and symptoms of Simpson-Golabi-Behmel syndrome.

A 4380-gram male neonate in a good condition was born at term to a mother without diabetes. From birth his weight and height were greater than 90th percentile, but during development he had mental retardation. The boy had distinctive coarse facial features, widely spaced eyes (ocular hypertelorism), a large tongue (macroglossia), abnormal ears and abnormalities affecting the roof of the mouth (the palate). Furthermore he had a chest deformation with two extra nipples. Puberty was normal. The bone age was about 16yrs. We excluded pediatric and endocrinological causes connected with overgrowth. The maximum level of growth hormone during OGTT was 0,52ng/ml. IGF-1 level was normal. The kariotype was 46,XY with mutation in the GPC3 gene. During ultrasonography we exluded possible tumors in abdominal cavity.

In conclusion, Simpson-Golabi-Behmel syndrome is a very rare condition connected with overgrowth. We should think about this syndrome when we have the patient with some congenital defects, and it is necessary to distinguish from Beckwith-Widemann syndrome. Tumor follow-up should be performed.

P3-P225

Central Precocious Puberty in a Girl with Silver Russell Syndrome

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Introduction: Silver-Russell syndrome (SRS) is a rare, clinically and genetically heterogenous condition, and affects one in 100,000 born children. The most well-known genetic mutations in this syndrome are: 11p15 mutation (20-60% patients), and maternal uniparental chromosome 7 disomy (7%-15%). Children with SRS have severely impaired physical growth - intrauterine and after birth. They can be treated with growth hormone (GH).

Case report: 8 years old girl with SRS which manifested symptoms of premature puberty during treatment with growth hormone. The patient was born at term by caesarean section because of intrauterine growth retardation (IUGR) with fetal distress. Birth weight was 2670 g, length 51 cm, head circumference 30 cm. The pregnancy was not complicated. It was the first child of young healthy parents. (MPH 165 cm, 50 percentile). At the age of 3.5 short stature was diagnosed: her height was 89 cm (-3 SD) and weight 11.4 kg (-2.5 SD). Physical examination revealed SRS-like somatic features such as: triangular face, relative macrocephaly, micrognathia, subtle body assymetry with right side hemihypertrophy. Molecular study for hypomethylation of the H19 region of 11p15.5 chromosome was positive, and confirmed the diagnosis of SRS. At the age of 4.5 the girl started treatment with GH at the dosis 0.036 mg/kg. The growth velocity accelerated to 9.8 cm/year. At the age of 7 (hight 119 cm, 25 pc, weight 19 kg, 10 pc), breast enlargement (Tanner 2) and estrogenisation of mucous membrane of the external genitalia was noticed. The laboratory results were as follows: E2 23.9 pg/ml, basal LH 0.232 mIU/ml, basal FSH 2.47 mIU/ml, after GnRHa stimulation: LH 18.3 mIU/ml, FSH 17.7 mIU/ml. Bone age was 8 years. MRI of the pituitary gland was normal. The girl started combined therapy with GH and GnRHa (3,75 mg every 4 weeks). As the result pubertal signs disappeared, and growth velocity stabilized at the level of 6 cm/year

Conclusion: Acceleration of growth velocity during growth hormone treatment can be augmented by premature puberty in patients with SRS.

P3-P226

Etiologies of Short Stature in Pedaitric Endocrine Clinic in Northwest Region (Trakya) of Turkey

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Backround: Short stature (SS) is one of the common disorders referred for investigation of an endocrine disorder. The etiologies of SS vary and are commonly grouped into pathological and non-pathological disorders. Despite standard clinical and laboratory evaluation, a pathological diagnosis is not reached in 50-90% cases.

Aim: The aim of this study was to determine the etiologies and decribe the characteristic of short stature patients who were followed up by Pediatric Endocrinology Clinic and to compare factors between normal variant short stature (NVSS) and growth hormone deficiency (GHD).

Methods: The clinical and laboratory data of a total of 309 patients who were diagnosed as having SS during a six year period (2011-2017) were retrospectively analyzed based on the hospital records. Short stature was defined as height below – 2 standart deviation score (SDS) by gender and age based on population data of Turkish children.

Results: There were 169 (54.7%) boys and 140 girls (45.3%) with a mean age of 10.8 ±3.1 years. The proportion of boys to girls was 1.2:1. The age distrubition was categorized as 0-4 years: 8.4 % (26 cases; 11 M, 15 F),5-9 years: 25.6 % (79 cases; 38 M, 41 K) and 10-18 years : 66 % (204 cases; 120M, 84F). Of 309 patients, 65.1% (201 cases; 116M, 85F) were NVSS; that is familial short stature (16,2 %), constitutional delay of growth and puberty (CDGP) (29,8%) or combination of both (19,1%). Pathological short stature was found in 34,9 % of the cases, of which 4,5 % disproportional short stature (28,5 % of them achondroplasia). Endocrinological causes accounted for 18 % of short stature. GHD was found in 17,4 % of total cases and it comprises 96% among endocrinological causes. The common etiologies in severe SS (height SDS < -2.5) were CDGP (14,2 %) and CDGP-familial SS (13,2 %). In the moderate SS group (height SDS between -2and -2.5), CDGP was the most common etiology (15,5 %). Among the syndromic SS, Turner syndrome was the most common (3,6 %) followed by Noonan syndrome (1%). Celiac disease was found in 1% of total cases.

Conclusions: In this study, NVSS was the most common etiology of short stature, followed by growth hormone deficiency and syndromes in accordance with literature. NVSS was also the common cause of the severe SS.

P3-P227

Auditing Presentation, Investigations and Management of Turner's Syndrome

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Background: Turner's syndrome (TS) is the most common genetic disorder in females affecting approximately 1 in 2500 live female births as a result of partial or complete X chromosomal monosomy. TS mostly affect skeletal, cardiovascular, endocrine and reproductive systems. Girls with TS present with short stature and dysmorphic features such as webbed neck and delayed puberty. Age at diagnosis of children with TS is extremely important to start growth hormone at younger age to attain optimal adult height and then to decide on hormone replacement therapy to induce puberty and improve bone health.

Objectives: This audit evaluated trends in presentation, age at diagnosis and investigation findings of children with Turner syndrome at presentation and overall surveillance.

Method: Retrospective data analysis carried out on children diagnosed with Turner syndrome and followed up in Paediatric Endocrinology Clinic in Prime Tertiary care Hospital for Children in the country. Patient data (n=18) were analysed to evaluate trends in diagnosis and to audit clinical presentation, investigations and management.

Results: The most common age group at diagnosis was 11-15 years and only two cases were diagnosed at birth. Majority of them referred by General Paediatricians in peripheral hospitals and then by Paediatric Cardiologists. The commonest presentation is short stature (72%)and with congenital heart defects(16%) and other presentations were strabismus, dysmorphic features and neonatal lymphoedema.

The frequently observed genetic defect was 45, X0 nearly 44% followed by 46XX/45X0 which was 22%. Approximately 11% of them had SRY positive and rest of the others had variable chromosomal abnormalities including deletions, isochromosomes, ring chromosomes and translocations.

Regarding cardiovascular system 55% of them had cardiac lesions in Echocardiogram. Majority had small uterus and atretic ovaries but only two girls had renal anomalies. Currently, 72 % of them on growth hormone and 16% on hormone replacement therapy. Two of them underwent bilateral gonadectomy as they carry Y chromosome material. Abnormal thyroid functions found in 22% and currently on thyroxine. Screening for hearing detected 22% of girls with mild to moderate hearing impairment whereas assessment of vision found two girls with strabismus and two with refractory errors.

Conclusion: This study shows delay in diagnosing and referring patients with TS most commonly after 11 years of age which has resulted limited time period for growth hormone therapy and delay in detecting other system involvement.

P3-P228

Children Born Small for Gestational Age: Catch-Up Growth during the First Four Years of Life

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Children born small for gestational age (SGA) have a weight and/or heighth less than -2SD from the mean, the realization of an adequate catch-up or not during the first years is important and the growth assessment is required.

Objective: Analyze Catch-up on Growth of 52 SGA children during the first 4 years of life, compared 23 children who performed it properly(AC) with 19 who did not recover(NAC).

Methods: Retrospective study of SGA children with appropriate cath-up (height SDabove -2.5) 23 children comparing with not cath-up (height SDbelow -2.5) 18 children, it was analyzed, sex, preterm children, age of the mother, height of the mother, presence of maternal pathology, SD weight and height at birth and 1-2-4 years and diagnosis at birth. Statistical analysis SPSS v.24.

Results: Compared both groups, mean age of mother in AC 32,64±3,9 y NAC 32,06±5,5years, height of mother AC 156.74±5.3cm and NAC 153.3±5.3cm, in relation to sex 63% AC males versus NAC 37% while NAC 61.5% females versus AC 38,5%, preterm children 26%(6) AC were 100% males versus 28%(5) NAC were 60/40% females/males, placental pathology 66.7% NAC versus 33.3% AC and unknown etiology 64%AC versus 36%NAC, evolution of weight and height from birth to 4 years in SD(table 1) where a clear improvement is observed at 4 years in AC while in NAC did not improve their growth at any point in the follow-up.

The diagnosis in SGA was in relation to the height AC / NAC 72% versus 27.8%, SGA weight 60% versus 40% and SGA height and weight 35.3% versus 64.7%.

Conclusions: SGA children, especially females, born to mothers with short stature, placental pathology and height less than -2.5SD will not be able to recover and will require follow-up and treatment with GH to evolve satisfactorily.

Table 1. (for Abstract no P3-P228)

SD weight birth AC/NAC	SD height birth AC/NAC	SD weight 12 months AC/NAC	SD height 12months AC/NAC	SD weight 2 years AC/NAC	SD height 2 years AC/NAC	SD weight 4 years AC/NAC	SD height 4 years AC/NAC
-1.78±0.6	-2.44±0.6	-1.98±0.6	-2.22±0.8	-1.9±0.5	-2.34±0.6	-1.42±0.3	-1.99±0.3
-2.11±0.7	-2.76±0.7	-2.49±0.6	-3.16±0.8	-2.56±0.5	-3.42±0.6	-2.24±0.4	-3.33±0.5

P3-P229

A Novel Heterozygous Pathogenic Variant in *PORCN* Gene Causing Focal Dermal Hypoplasia with Short Stature: Case Report and Literature Review

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Objective: To explore the clinical features and the genetic cause of a multiple malformation patient with short stature.

Methods: The clinical data was collected in Beijing Children's Hospital in November 2017. The disease-causing variant was identified using exome sequencing and confirmed with Sanger sequencing. Related literature was searched from Wanfang and Pubmed databases using the key word of "PORCN gene" to identify the clinical features and gene mutation.

Results: The patient is a 10-year-old girl, she was referred to hospital because of short stature. She presented multiple deformities such as patchy skin hypoplasia, syndactyly and right ear malformation. In exon 2 of *PORCN* gene, genetic sequencing revealed a de novo heterozygous variant c.49_80delTGTCTCCTGCCTAC TGCCCAGCAGGGCCTTGA (p.C17fs*84). The variant is novel and classified as pathogenic. The patient was diagnosed with focal dermal hypoplasia (FDH).

Conclusion: FDH is a multi-system affected birth defect. In addition to typical skin damage and bone malformation, it can also cause short stature.

P3-P230

Endocrinological Evaluation of Girls with Turner Syndrome Attending Alexandria University Children's Hospital

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Introduction: Turner Syndrome (TS) is the consequence of complete or partial absence of one X chromosome in a phenotypic female. The genes involved in Turner phenotype are X-linked genes that escape inactivation. A major locus involved in the control of linear growth has been mapped within the Pseudo-Autosomal Region (PAR1) of the X chromosome.

Aim: To study some endocrine hormones with considerable effect on the presentation and prognosis of TS and their relation to the genotype of TS.

Methods: Thirty girls with Turner Syndrome attending Endocrine Clinic of Alexandria University Children's Hospital were subjected to detailed history, clinical examination, karyotyping, and hormonal investigation including luteinizing hormone (LH), follicle stimulating hormone (FSH), estrogen (E2), anti- mullerian hormone (AMH), insulin-like growth factor1 (IGF-1), growth hormone (GH) and thyroid function tests. Bone age & pelvic ultrasound were done.

Results: Age ranged from 3 to 18 years with a mean of 10.98± 4.85 years. Monosomy (45, XO) was the predominant genotype (40.0%) followed by mosaic genotype (36.7%), while isochromosome (46, Xi Xq) was the least (23.3%). Most cases (76.7%) presented with short stature which was significantly more common among mosaic genotype. (p =0.048). Monosomy (45, XO) was the predominant genotype (40.0%). Ultrasound of the ovaries revealed abnormalities in 70% of cases as streak gonads in and infantile ovary, while of the uterus showed hypoplastic form in 56.7% of cases. LH, FSH, AMH were high in 11 cases (73.3%). FT4 and TSH levels were normal in all studied patients while Anti –TPO (Thyriod peroxidase antibodies) was high in 8 cases (26.7%). No statistically significant differences were found between genotypes regarding hormonal assessment.

Conclusion: The most common genotypes of Turner Syndrome in the current study are monosomy 45 XO and the mosaicism. Majority of the cases have streak gonads or infantile ovaries with high levels of gonadotropins, AMH and Anti –TPO. Their thyroid functions were normal.

P3-P231

A Long Follow-Up in a Young Patient with Atypical Progeroid Syndrome

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The LMNA gene encodes lamin A/C, intermediate filament proteins associated with the inner nuclear membrane. Mutations in LMNA gene cause a wide range of human diseases sometimes called "laminopathies" that affect different organ systems depending upon the mutation [1,2]. Most laminopathies involve tissue of mesenchymal origins, resulting in such features as cardiac disorders and/or muscular dystrophy, lipodystrophy or progeroid syndromes. The group of progeroid syndromes includes: Hutchinson-Gilford progeria syndrome (HGPS), Mandibuloacral Dysplasia (MAD), atypical Werner syndrome (a-WS) and Atypical Progeroid Syndrome (APS).

HGPS is a rare, sporadic, dominant genetic disorder characterized by phenotypic features of accelerated aging and it is caused by de novo mutations in the LMNA gene.

APS is a new autosomal dominant disorder with heterogeneous phenotype, due to different LMNA mutations. Patients show different clinical signs referred to HGPS, MAD or atypical Werner's syndrome. The phenotype of APS has not been well characterized and patients have been reported to have variable progeroid features such as: short stature, beaked nose, premature graying, par-

tial alopecia, high-pitched voice and skin atrophy over the hands and feet, besides having diabetes, generalized lipodystrophy, skin pigmentation and mandibular hypoplasia.

The evolution of HGPS and MAD is generally well known, but the evolution of APS is not so clear and it probably depends on the mutation.

We report a female patient with APS followed-up for 10 years, who showed normal pubertal timing with reduced pubertal growth spurt, normal FH compared with Target height, lipodystrophy with acral loss of sc fatty tissue and excess fat accumulation in the face, neck, chest and abdomen. During the follow-up, she developed sclerodermatous skin, signs of insulin resistance, glucose intolerance and mild hepatic steatosis. No signs of acroosteolysis or osteoporosis were observed.

An adequate food survey with a personalized diet and a pharmacological approach with metformin improved the control the metabolic disease.

P3-P232

GH Treatment in Kabuki Syndrome: A Case Report

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Introduction: Kabuki syndrome (KS) is a rare genetic disorder (1 in 32,000 newborns) caused by mutations in the KMT2D gene (autosomal dominant pattern) or the KDM6A gene (X-linked dominant inheritance). KS is characterized by distinctive facial features including arched eyebrows, long eyelashes, long palpebral fissures with everted lower lids at the outside edges, flat, broadened tip of the nose and large protruding earlobes. The name of this disorder comes from the resemblance of its characteristic facial appearance to stage makeup used in traditional Japanese Kabuki theater. KS patients show also mild to severe developmental delay and intellectual disability. Other characteristic features of KS include seizures, microcephaly short stature, early puberty, skeletal abnormalities such as scoliosis and cleft palate, heart abnormalities, hearing loss and strabismus.

Case report: A patient affected by KS, diagnosed at the chronological age (CA) of 6 years was referred to our department for short stature at the CA of 11 years. She presented typical facial features including arched eyebrows, long eyelashes, long openings of the eyelids and large protruding earlobes; she also showed mild intellectual disability, microcephaly, bilateral renal ectopia, bowel malrotation, strabismus, fetal pads and cleft palate surgically corrected at the CA of 1 year. At the CA of 11.5 years patient was still prepubertal, height was 137.5 cm (-1.6 SDS), target height was 166 cm (0.58 SDS), bone age was 6.9 years, growth velocity was -4.6 SDS. After excluding other causes of growth retardation, we evaluated her growth hormone (GH) secretion, by performing 2 pharmacologic stimulation tests (arginine and L-Dopa) that showed GH deficiency. Brain MRI for evaluation of hypothalamus and hypophysis was negative. Idiopathic GH deficiency was diagnosed and GH replacement treatment was started at the usual dosage employed in idiopathic GH deficiency. During the first 6 months of treatment growth velocity markedly increased from -4.6 SDS to -1.5 SDS and no adverse events occurred.

Conclusion: The presence of GH deficiency has been reported in some KS patients. In a study conducted on 18 KS children, 28% of these patients resulted biochemically GH deficient and those treated with GH showed a marked catch-up growth during the first year of rhGH treatment. Our patient started replacement therapy few months ago, therefore we do not have a sufficient follow-up to evaluate the persistent beneficial GH effect, after the dramatic increase in growth velocity observed during the first 6 months.

P3-P233

GH Treatment in Oto-Spondylo-Megaepiphyseal Dysplasia: A Case Report

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Introduction: The oto-spondylo-megaepiphyseal dysplasia (OSMED) is a rare condition with autosomal recessive inheritance caused by congenital defect in the formation of cartilage collagen. OSMED is caused by mutations in the COL11A2 gene, which encodes the alpha2 chain of XI type collagen, a complex molecule that gives structure and strength to the connective tissues that support the body's joints and organs. OSMED is characterized by severe sensorineural hearing loss and skeletal abnormalities with distinctive facial dysmorphisms, enlargement of the epiphysis, disproportionately short limbs and platyspondyly. Patients often experience limited joint movement, back and joint pain and arthritis beginning early in life. The prevalence is unknown. Up to now only a few families with OSMED worldwide have been described in the literature. We describe the case of a girl affected by OSMED and growth hormone (GH) deficiency.

Case report: A 6 years old girl was initially referred to our department for evaluation of sensorineural deafness, language retardation and facial dysmorphisms, characterized by protruding eyes and upturned nose with flattened bridge, large and rounded tip. Genetic evaluation showed homozygous mutations in the COL11A2 gene (6p21.3), leading to the diagnosis of OSMED performed at the chronological age (CA) of 7.5 years.

Duo to the presence of short stature (-2.0 SD), with target height of 159 cm (-0.6 SD), after excluding other identifiable causes of short stature, we evaluated growth hormone (GH) secretion, spite bone age being advanced about 1 year compared to her CA.

We performed 2 pharmacologic stimulation tests that confirmed GH deficiency. The brain MRI was normal and therefore a diagnosis of idiopathic GH deficiency was made. The patient started GH replacement therapy and after 6 months on treatment her growth velocity markedly improved from 4cm/years to 6cm/years, even thought calculated over a period of only 6 months. No adverse events were reported.

Conclusion: To our knowledge, this is the first case of OSMED who presents also GH deficiency and is being treated with GH replacement therapy reported in the literature. In contrast to what generally happens in GHD, bone age in our patient was not retarded compared to CA, but we believe that this phenomenon could be due to the syndrome itself. Only the long-term follow-up of this patient will show whether the

beneficial effect of GH treatment on growth velocity observed during the first 6 months will be confirmed, without the occurrence of adverse events.

P3-P234

Hepatic Glycogen Synthasedeficiency Associated with Growth Hormone Deficiency: A Case Report

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Objective: Type 0 glycogen storage disease (GSD0) is caused by deficiency of the hepatic isoform of glycogen synthase. Growth hormone deficiency in this disorder has not been reported.

Case: A two-year old girl who had suffered from occasional morning convulsions was admitted to our clinic. Her length and body weight were measured as 80 cm (-2.4 SD) and 11.3 kg (-1.3 SD), respectively. Physical examination was unremarkable. Metabolic profile showed fasting hypoglycaemia, hypertriglyceridemia, hyperketonaemia, hyperlactatemia, and growth hormone deficiency. Hyperglycaemia, hypertriglyceridemia and hyperlactatemia were determined after meals and in an oral glucose tolerance test. GYS2 gene analysis revealed a homozygous mutation (c.1145 G>A (p.Gly382Glu) (p.G3822E). The patient was treated human growth hormone (hGH) and uncooked corn-starch. Her height growth rate after hGH therapy was calculated as 7 cm/yr.

Conclusion: This is the first case with hepatic glycogen synthase deficiency associated with growth hormone deficiency. The patients with GSD0 should be followed for growth hormone deficiency.

P3-P235

Analysis of Genetic Mutations in a Chinese Patient Affected with Noonan Syndrome

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Objective: The aim of this study was to detect potential gene mutation of Noonan Syndrome in a Chinese family. **Methods:** Patient with clinical diagnosis and parents were analyzed in this study. The analysis included medical histories, clinical analysis, and genetic tests. The PTPN11,KRAS,SOS1,RAF1,NRAS,BRAF,RIT1,SOS2,LZTR1,SHOC2,CBL,NF1 gene was sequenced to identify the pathogenic mutation responsible for the development of Noonan Syndrome by PCR and Sanger.

Results: A novel mutation c.2600A>G (p.N867S) of the SOS2 gene was found in the patient, but not in his parents. The same mutations were not found among 100 healthy controls.

Conclusion: A novel SOS2 c.2600A>G (p.N867S) mutation can be a cause of Noonan Syndrome in Chinese. We think that genetic studies to may assist in making Noonan Syndrome diagnosis and providing the consultant for their families.The novel mutations have enriched the mutation spectrum of the SOS2 gene.

P3-P236

A Novel Homozygous Mutation in ERCC8 Cause Cockayne Syndrome a in a Chinese Family

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Background: Short stature can be caused by mutations in a multitude of different genes. Cockayne Syndrome is a rare growth disorder marked by progressive growth failure, neurologic abnormality. The current report describes a patient with severe short stature and neurologic abnormality.

Methods: Patient with clinical diagnosis and parents were analyzed in this study. The analysis included medical histories, clinical analysis, and genetic tests. The gene was sequenced to identify the pathogenic mutation responsible for the development of Cockayne Syndrome by qPCR.

Results: Inherited disease panel identified a novel homozygous mutation c.394_398delTTACA in ERCC8 that had not been previously reported. qPCR analysis revealed c.394_398delTTACA was maternal and his father was heterozygous.

Conclusion: A novel homozygous mutation c.394_398del TTACA in ERCC8 gene can be a cause of Cockayne Syndrome in Chinese. The novel mutations have enriched the mutation spectrum of the ERCC8 gene.

P3-P237

Growth Hormon Deficiency in Identical Twins with Gitelman Syndrome Due to Compound Heterozygous Mutation (p.R80fs*35/p.K957X) of the SLC12A3 Gene and the Evaluation of the Response to Growth Hormone Replacement Therapy

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Background: Gitelmann syndrome, a rare autosomal recessive disorder, is characterised with hypokalemic metabolic alkalosis, hypomagnesemia and hypocalciuria. Mutations in the SLC12A3

Table 1. (for Abstract no P3-P237)

	Case 1	Case 2
Weight (kg)	32.7	35.5
Height (cm)	145.5 (-2.88SD)	149.2 (-2.39SD)
Testicular volume (ml)	4/4	4/6
Bone age (year)	10	13
IGF1 (ng/ml)	80.7 (-2.41SD)	110.7 (-2.06SD)
IGFBP3 (ng/ml)	2219 (-2.31SD)	2124 (-2.37SD)
Growth rate (cm/year)	1.6	3.2
L-dopa test peak GH (ng/ml)	4.6	0.09
Clonidine test peak GH (ng/ml)	4.32	0.716
GH dose (mg/kg/day)	0.033	0.033
Growth rate with GH therapy (cm/year)	5.3	7.7
IGF1 (Under GH therapy) (ng/ml)	293.4	296.0
Mutation	p.R80fs*35/p.K957X	p.R80fs*35/p.K957X

gene, which encodes for "Thiazid sensitive sodium chloride co-transporter channels" located at the renal distal convoluted tubules account for the underlying molecular mechanism of Gitelmann syndrome. Although, is less frequent than those seen in "Bartter Syndrome", the exact mechanism of growth retardation in Gitelmann syndrome has not been elucidated.

Case reports: Male identical twins presented at the age of 14.4 years-old with complaints of short stature which was recognised about the age of 8-10 years. Both patients was on magnesium and potassium replacement therapy for hypomagnesemia and hypokalemia. The antropometric measurements, bone age and pubertal findings at presentation are shown in Table 1. Serum IGF1 and IGFBP3 levels were low, both cases had low growth rates and inadequate peak growth hormon(GH) response to the GH stimulation tests (Table 1). A diagnosis of Gitelmann Syndrome and GH deficiency was considered and GH replacement therapy was added to the therapy. Pituitary MRI and other pitutary hormones were normal for both cases. Assessment of the GH therapy at 9th month revealed an increase in IGF1 levels and growth rates, with accompanying progression of puberty; though the response to GH therapy was not satisfactory, particularly in case 1. Unsatisfactory response to GH replacement therapy was attributed to the poor compliance to the therapy and frequent hospital admissions due to recurrent episodes of electrolyte imbalance. In the mutation analysis a compound heterozygous mutation (p.R80fs*35/p.K957X) was detected in the *SLC12A3* gene, which confirmed the diagnosis of Gitelmann syndrome.

Conclusion: Gitelmann syndrome patients with short stature should be investigated for GH-IGF-1 axis disturbances. For optimal growth, in addition to correcting serum potassium, GH replacement may be considered. However, in order to further assess the response to GH replacement therapy, more experiences are required.

P3-P238

Hypothyroidism and Growth Hormone (GH) Deficiency, a Spotlight on De Novo Chromosomal 20p11.2 Deletion

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Background: There are few reports describing proximal deletions of chromosome 20p, making it difficult to predict the likely consequences of the deletion in this area. One report has described a proximal 20p11.2 deletion associated with panhypopituitarism, craniofacial dysmorphism, a small phallus with a semi bifid scrotum, and bilateral widely separated first and second toes. The only other report has demonstrated neurodevelopmental abnormalities associated with band 20p11.2 haploinsufficiency.

Objective(s): To report a child with dysmorphic features, GH deficiency and central hypothyroidism associated with a complex chromosomal rearrangement involving the short arm of chromosome 20.

Case report: The patient presented at the age of 4 years with short stature and was noted previously to have multiple dysmorphic features. Investigations confirmed GH deficiency and central hypothyroidism.

Methods/Results: G-banding chromosome analysis of 12 cells from a peripheral blood sample revealed a male chromosome complement with a reciprocal translocation between the short arm of chromosome 6 and 20 (karyotype: 46 XY, t (6; 20)(p11.2; p11.2)). The patient carries a deletion of around 914-kb of the short arm of chromosome 20 within cytogenetic band 20p11. The parents had normal chromosomes. The deleted region harbors several candidate genes involved in regulating GH secretion.

Conclusion: Our patient carries a reciprocal translocation with a cytogenetic band 20p11.2, which is involved in the translocation

and deletion of around 914-kb. The patient exhibited features related GH deficiency and hypothyroidism. Understanding the role of the deleted genes might provide further insights into the regulation of GH and thyroid hormone secretion. Therefore, our patient expands the spectrum of phenotypes associated with proximal deletions of chromosome 20.

P3-P239

Pharmacoeconomic and Adherence Analysis in Growth Hormone According to Galenic Presentation: In Vivo Study versus In Vitro

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Currently in Spain, treatment with GH is approved for hospital use with different formulations (JM), multidose vials (VM) and systems with electronic self-injection devices (DE).

The long-term treatments, involves the lack of adherence to GH in pediatric patients, it has been estimated a lack of adherence between 5 and 82%.

The main objective of this study is to perform a comparative analysis of costs and product loss among the different GH presentations approved in Spain in pediatric patients. The secondary objective is to observe differences in efficacy in GH treatment, based on the differences in the prescribed and dispensed doses detected according to presentation. It is compared with the in vitro study of the ISCIII (IPE Report 2013/70).

A retrospective, observational study in which a comparative analysis of the doses and costs of GH prescribed by the endocrinologist and that dispensed in the pharmacy service was carried out over 12 months. Variables: sex, age pathology levels of IGF-1. IMMULITE 2000 IGF-1. PIL2KGF-17 The economic impact of administering the total mg prescribed using exclusively each of the GH presentations was estimated. test (X2) for paired samples (n <30).

Difference between the dose of GH prescribed and that dispensed in the pharmacy service according to (1A) the GH presentations used and according to (1B) the pathology for which the treatment is prescribed.

The presentation of GH with which the prescribed mgs are closer to those dispensed is that of JM (Genotonorm®), followed very closely by the DE (Saizen ®). The one with which a greater difference is obtained with the VM formulations. Adherence data according to indication and galenic formula are also presented.

Estimated loss of mgrs dispensed from 7,536 euros / year (economic impact) considering the exclusive use of each of the GH presentations with less loss. The study coincides with in vitro results IPE Report 2013/70.

P3-P240

The Expression of Cytokines in SGA Children Throughout Lactation Allows to Characterize Early the Type of Cath-Up

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Up to 50% of children born SGA at 2 years have not made a correct catch up (by excess or defect), with repercussions on size, metabolic and cardiovascular alterations, DM, etc. The Project has developed a prospective cohort of SGA and seeks to study phenotypic, BQ and genetic differences that explain their different behavior.

Material and methods: We study live births of single pregnancies in our Hospital during 2012-2014, and are classified according to EG and weight / height (Spanish Tables 2010). N estimated: 110. Visits are made at 0, 3, 6, 9, 12, 15, 18 and 24 months, with measurements of weight, height and perimeters. Blood samples are obtained at times 3.12 and 24

Results at the end of the initial selection: 103 SGA recruited in 24 months (♂56, 55%) Data of the children at birth: average weight -2.7 SD [-3,5-1,8], average size -2, 4 SD [-3.2-1.9], for sex and EG.

Exclusive breastfeeding: 77/103 (74%) during the 3rd month of life.

Differentiation is carried out according to spontaneous catheter type with assessment at 12 and 24 months. Comparative variables P /TΔ+/- 0.5 SDS vs. TE2010

NOV, vaspina, omentina, adiponeptina, leptin and chemerina were studied as metabolic markers. Mann-Whitney's Study U / Student's t test.

Conclusions: We characterized significant changes in NOV, Imentin, Adiponectin and leptin. It has also been allowed to characterize that compared to the CONTROL group (normal cathup), there are differences in the different variables, which would allow defining the evolution of a PEG from 3 months.

Table 1. (for Abstract no P3-P240)

Ctchup	SLOW	Normal	RAPID	Differences
NOV ng / ml	141.77 (45.70)	114.93 (18.54)	91.11 (20.06)	p <0.05a
Vaspin ng / ml	0.14 (0.07)	0.20 (0.10)	0.17 (0.07)	p <0.05b
Omentin ng / ml	434.98 (117.37)	312.80 (113.81)	305.95 (81.77)	P <0.1ab
Adiponectin µg / ml	81.96 (42.27)	56.61 (36.78)	31.51 (13.62)	p <0.05a
Leptin ng / ml	3.41 (1.15)	5.77 (2.69)	4.52 (3.19)	P <0.1b
Chemerin ng / ml	207.78 (35.46)	191.00 (19.68)	201.03 (22.06)	P <0.1b

Table 2. (for Abstract no P3-P240)

	Visit 1	Visit 2	Visit 3	Differences
NOV ng / ml	120.17 (37.39)	88.03 (24.56)	73.15 (17.74)	p <0.01a, b
Vaspin ng / ml	0.17 (0.08)	0.16 (0.07)	0.19 (0.08)	DK
Omentin ng / ml	363.13 (119.94)	394.77 (102.43)	423.51 (116.01)	p <0.05a, b
Adiponectin µg / ml	61.12 (39.21)	54.65 (28.10)	91.39 (72.85)	p <0.05b
Leptin ng / ml	4.47 (2.40)	3.39 (1.60)	3.09 (1.87)	p <0.05b, p <0.1a
Chemerin ng / ml	205.38 (29.20)	201.95 (19.33)	192.58 (24.72)	HL

P3-P241

Small Stature: A Singular Difference for Accessing to Job

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The pathological low stature is considered to be one that does not conform to normality (<2 SDS), that with a pathological growth rate. An obvious element is the conditioning that can generate in their professional outings, both in public and private activity. This seems to be evident in the female sex than in the male sex.

The health system considers the treatment (with Ghrh) in pathological size without considering sexual dimorphism.

Goals: To study the differences of requirements in question of height in diverse public and private professions comparing it between sexes and in relation to the different somatometric tables of habitual use in Spain

Material and methods: I study current legislation. Comparisons Orbegozo 2004, 2011 and Spain 2010. Statistical study SPSS 11.0 X2 for paired samples nonparametric (SE p <0.05). Size and sex. Spanish / regional legislation 2017

Results: 16 professions of public and private service

Selection criteria consider adult height according to patterns (normality graphs) with evident differences by sex. 13 consider size as a limiting element (82%) of access to selection tests.

The average size requested for MAN was 166.41 [165-175] compared to the WOMAN of 162.08 [160-170].

Table 1. Reference regarding p50 to 18 years old / adult Man (for Abstract no P3-P241)

Difference in cm. P50 vs required to which percentile corresponds	Difference in SDS Woman Difference in cm. P50 vs required To which percentile corresponds	Difference in SDS
Talle Orbegozo 2004 LONGITUDINAL	7.68 15	-1.6 -1.30 55 0.1
Talle Orbegozo 2004 TRANSVERSAL	10.27 5	-1.9 1.74 25 -0.5
Talle Orbegozo 2011 TRANSVERSAL	9.85 5	-1.9 2.01 25 -0.5
Size SPANISH 2010 TRANSVERSAL to 18a	9.79 5	-1.9 1.89 25 -0.5
Size SPANISH 2010 TRANSVERSAL to adult	11.03 5	-1.9 2.01 25 -0.5

There are significant differences in the difference of cm between women and men (P: 0.001) and the SDS in stature that supposes (P. 0.0001).

Conclusions: There are significant differences more unfavorable for the female sex, limiting access to 25-40% of women according to profession and normality tables compared to only 5% of male people.

The size can not be an argument to assess the physical capacity, existing others as BMI, lean mass; adding that within these professional bodies there are administrative, scientific, command or other positions where height is not a determining factor.

P3-P242

A Case of Hutchinson-Gilford Progeria Syndrome (HGPS) Due to a Pathogenic LMNA Variant c.433G>A (p.Glu145Lys): Growth Hormone Administration Failed to Improve Growth and Long-Term Outcome

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Hutchinson-Gilford Progeria Syndrome (HGPS) is an extremely rare condition (estimated incidence 1:4-8 million), caused by mutations in LMNA gene, which leads to premature aging. Median life expectancy is shortened to 13 years due to vascular complications such as stroke or myocardial infarction. We present below the history of a child born with a pathogenic LMNA variant c.433G>A (p.Glu145Lys).

A male patient was referred due to failure to thrive and low growth velocity at age 18 months. He was born SGA (39th GW, BW 3270g, BL 46 cm), had feeding problems and runny stools since early life. His motor development was slightly delayed. He underwent detailed paediatric check-up that failed to elucidate the underlying condition. Due to severe short stature (height -2.38 SD) and low IGF-I (39 ug/l; -1.45 SD) he was tested and finally diagnosed with growth hormone (GH) deficiency (peak GH 2.43 ug/l after clonidine stimulation). The subsequent MR revealed partial empty sella. GH therapy was initiated when 23 months old. Unfortunately, GH failed to improve growth velocity, despite a transient increase of IGF-I to 135 ug/l (-0.15 SD). The treatment was stopped at age 4.4 years (height -3.93 SD).

His phenotype became suggestive of progeria when 2.5 years old, with partial hair loss, visible veins on his forehead, pinched nose and small recessed jaw. HGPS was confirmed by genetic testing.

His first ischemic complication manifested via transient hemiparesis at age 4.2 years. MRI revealed severe ischemia of basal ganglia, subcortical ischemic changes in the right frontal lobe and severely reduced flow in the right internal carotid artery. Several subsequent episodes of transitory ischemic attacks developed despite combined anticoagulation and antiplatelet therapy. When 7 years old, he presented with seizures and unconsciousness due to a massive haemorrhagic stroke which led to a fatal outcome.

LMNA provides instructions for making intermediate filament proteins known as lamin A and C. Their role is to support and provide stability to the nuclear membrane. The c.433G>A (p.Glu145Lys) variant is known to disable lamins to form dimers and higher structures. No causal therapy is available, however some data in animal models proposed a positive effect of IGF-I administration (Ugalde AP et al. Aging, 2010;2:1017-1022).

Our single-case observation revealed failure of GH therapy, not only to improve growth, but to prevent or postpone vascular complications in HGPS as well, despite increased IGF-I levels.

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P3-P243

Increased Serum Activity of Liver Aminotransferases in Young Patients with Turner Syndrome

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Background: Liver tests abnormalities are common in adult patients with Turner Syndrome (TS). The data regarding liver tests in children and adolescents with TS remain lacking.

Design and patients: A cross-sectional review of liver function of 100 girls with TS (age range 4-16, the mean BMI SDS 0.63 [-1,86 -6,78]); 56 receiving rhGH therapy (9 obese, 47 normal weight), and 44 receiving rhGH therapy and estrogen or estrogen/progesterone hormone replacement therapy (HRT)(8 obese and 36 normal weight). A longitudinal study included 81 patients (mean follow-up period: 3-5 years).

Measurements: Activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured in fresh serum samples using dry chemistry (Vitros).

Results: When compared to reference ranges, 34 % of girls with TS demonstrated increased AST and ALT activity (32% without HRT, 36% on HRT), with not significant yearly increase of the incidence ($p<0.05$). During follow-up period no patient developed serious liver disease. Ultrasound examination revealed liver steatosis in 11% patients without HRT and in 9 % of patients with HRT. The difference was not significant. No architectural changes, nor bile duct alterations have been noticed. There was no significant correlation between AST and BMI SDS R=0.09; $p>0.05$, ALT and age (R=0.02, $p>0.05$), nor AST and age (R=-0.01, $p>0.05$). Although there was significant correlation between ALT and BMI SDS (R=0.23 $p<0.05$), the relative risk of increased ALT and AST activity was not higher in obese patients (OR 0.2; 95%CI 0.1-0.36; p=0.38, and OR 0.16; 95%CI 0.08-0.3, p=0.1 respectively). HRT did not increase the risk of higher ALT and AST activity in girls with TS (OR 0.8; 95%CI 0.5-1.2; p=0.37, and OR 0.7; 95%CI 0.4-1.1, p=0.27 respectively).

Conclusions: Presence of obesity and HRT do not increase the relative the risk of higher ALT and AST activity. To explain clinical signficance of this phenomenon further longitudinal investigations are needed.

P3-P244

Terner Syndrome: Epidemiological Study in Uzbekistan

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Turner syndrome is linked to the absence or abnormality of one of the X chromosome leading to haplo-insufficiency of genes involved in the development and maintenance of the ovarian stock in women. The purpose of this study was to establish the clinical, hormonal, cytogenetic and evolutive pattern of Uzbek population with Turner syndrome and to search for correlations between genotype and phenotype. We examined 149 Uzbek girls with Shereshevsky-Turner syndrome aged from 3 month to 44 years at the time of this analysis. Eighteen percent of them were diagnosed in adulthood (greater or equal to 20years). Homogeneous karyotype 45,X was prevalent 54,4%, where as the mosaicism was found in only 41,6% of the patients; structural anomalies were found in 4%. Irrespective to chromosomal aberrations in Uzbek girls with Shereshevsky-Turner syndrome 100% growth delay was found, 93.5% having gonadal dysgenesis. The dysmorphic syndrome was observed in 89,9% of cases; it was significantly more frequent in monosomics. The loss of ovarian function was more severe in case of monosomia compared to other forms. The most pronounced manifestations of phenotypic signs and variants of dysembryogenesis were found in girls with monosomy. Percentage of disturbances in hearing system (39,6%) and kidneys (26,8%) was the highest. We have managed to reveal the following variants of dysembryogenesis. Congenital hearing loss and otopyosis were found in 39,6% of examinees with hearing problems; 2% of girls having congenital heart disease (aortic stenosis, patent ductus arteriosus). 26,8% of examinees had kidney pathologies, such as, kidney salt masses and solitary kidney.

P3-P245

SHOX Haploinsufficiency in Short and Not Short Children: A Sigle Italian Cetre Data

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SHOX haploinsufficiency (SHOX-D) is a cause of disharmonic short stature and a possible genetic cause of idiopathic short stature also in familial cases.

We describe clinical, hormonal and genetic characteristics of patients with SHOX-D haploinsufficiency, followed and treated in the period 2014-2017, in a single Italian centre. The Rappold score was used to screen short children, to select those who needed a genetic analysis of SHOX gene by MLPA and sequencing.

We selected 6 patients (5 females; 1 male; age: 1.2-11 years), with documented mutations of the SHOX gene or of the promoter. One patient was already treated with low doses of GH for GHD, documented by 2 tests.

One patient had type 1 DM; GH treatment in a first phase worsened glycaemic control, otherwise corrected by an increased insulin dose.

One patient was first diagnosed in another centre as GHD and was treated with substitutive doses of GH. She came to our centre for the follow up and we noted the disharmonic short stature. The genetic study confirmed SHOX-D. Hence, she progressively increased GH dose, for the low improvement in growth.

Two patients born SGA: one for length; the other for weight.

One patient was studied for the SHOX-D relieved in the short sister and in the mother.

Rappold score was >7 in 50% of the patients. Younger children did not show radiologic signs of SHOX-D, well documented in 2 with Madelung deformity, radiographic lucency of the distal radius on the ulnar side, carpal pyramidalization.

The male patient had a duplication of the regulatory region of the gene; 3 patients had a deletion of the regulatory region of SHOX gene; 2 patients had a punctiform mutation of SHOX gene.

All the patients were treated with GH, at different dosages in relation to the first diagnosis and to the drug response in growth velocity, and significantly improved height velocity and the best results were obtained in patients who started earlier GH.

P3-P246

Microduplication of 3p25.3 and 4p23 Regions in a Patient with Multiple Congenital Anomalies, Congenital Hypothyroidism and Adrenogenital Syndrome

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We report the case of a seven-year-old boy, unicogenised child, born at 33w, PN 1,540 Kg, (APGAR 8-10), hospitalized in neonatology unit for 30 days, invasive respiratory assistance was not necessary. At birth evidence of hypospadias with penile incurvation, oval fossa pervia, corpus callosum agenesis. Normal male karyotype. For positivity to screening for IC (in-situ normal thyroid), started L-Thyroxine therapy.When he was six the phenotype showed broad forehead, down-slant eyelid, bulbous nose tip with long filter, malarial hypoplasia, large auricles, no supplants, adrenarche, normal testicular volume, acceleration of growth rate, normal IQ. We started diagnostic procedure with confirmation of adrenogenital syndrome (double heterozygous V281L - R26W). At seven-year CMA test was performed with detection of microduplication region 3p25.3 about 546 Kb which partially involves the OMIM Diseasde gene causing ATP2B2 and a paternal segregation microduplication of the chromosome long arm 4, of the 4p23 region, extended about 181 Kb not involving OMIM Desease Causing genes. Both mutations to date are not associated with syndromic frameworks or clinics highlighted in the patient, however it is not possible to predict the phenotype of the child and a monitoring follow-up over time is required.

P3-P247

A Rare Chromosomal Disorder, Trisomy 4p

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Background: 4p duplication syndrome is a very rare chromosomal disorder. In the literature; dysmorphic facial features, learning disability, speech retardation, overgrowth, musculoskeletal abnormalities, attention deficit hyperactivity disorder and autism syndrome have been reported to be associated with 4p16.3 duplication. Here we present a patient who admitted to our clinic with complaints of growth in hands and feet along with delayed speech and mental retardation. The genetic analyses revealed the diagnosis of 4p duplication syndrome.

Case presentation: A 15-year-old male patient admitted to our clinic with complaints of growth in hands and feet which that have been noticed for the last 2 to 3 years. He had also delayed speech and psychistric analyses was consistent with attention deficit hyperactivity disorder since he was 4 years old. Based on the history his parents were third degree relatives and he has a cousin who was followed up with the diagnosis of autism. On physical examination, his body weight was 76.9 kg (75-90p) and height was 163.4 cm (10p). A high arched palate, an adenoid face and bilateral clinodactyly of fifth finger were also noticed.

In laboratory work-up, basal GH (growth hormone) and IGF-1 (insulin-like-growth factor-1) levels were within normal limits. GH suppression was provided with OGTT (oral glucose tolerance test). Insulin resistance was not detected in clinical and laboratory findings. The IQ test was delayed. The patient's pituitary MRI and visual field examination were also normal. A genetic review revealed a duplication of 4p16.3p16.1.

Discussion: Duplication of 4p16.3 is a rarely described chromosomal disease, also known as trisomy 4p syndrome in the literature. Genetic examination should be performed in patients with significant dysmorphic facial features along with speech and cognitive deficits, overgrowth syndrome and attention deficit hyperactivity disorder.

P3-P248

Prediction of Response to Growth Hormone Treatment in Korean Girls with Turner Syndrome

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Purpose: Growth hormone (GH) treatment has become common practice in Turner syndrome (TS) to improve final adult height. However, there are only a few studies on the analysis of good responders to GH treatment in TS. The aim of this study is to predict the responsiveness to growth hormone therapy in Turner syndrome.

Methods: Among 197 TS patients registered in LG Growth study, 92 patients were excluded because of systemic illness or hypothyroidism. The clinical and biochemical parameters of 105 girls with TS patients were retrospectively reviewed. Patients were divided into subgroups (minimal, intermediate, good responders) according to the increment of height standard deviation score (SDS) during the first year of GH treatment, and the prognostic factors for good responders were identified.

Results: In good responders, chronologic age (CA) and bone age (BA) at the start of GH treatment were significantly earlier than the other groups ($P < 0.001$). They were not significantly associated with initial height SDS, GH dose, midparental height (MPH), predicted adult height (PAH). Accordingly, height response was significantly related with earlier CA and BA at start of GH treatment ($P < 0.001$). Especially, patients who started GH treatment before 7 years showed significantly higher height SDS increment than patients treated after 7 years ($P < 0.001$). Additionally, the starting age of estrogen therapy was not significantly correlated with height SDS increment in estrogen treatment group.

Conclusion: This study suggests that CA and BA at the start of GH treatment are significant factors in good responders in TS patients. Early intervention with growth hormone treatment is needed in TS patients.

P3-P249

A Rare Case of Turner Syndrome with the Presence of the Y Chromosome Genetic Material

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Turner syndrome (TS) is the most common genetic disease associated with the X-chromosome abnormality. Sex chromosome monosomy (45,X) occurs in 40-50% of the cases. 5% of patients with TS, in addition to cells lacking the genetic material of the X-chromosome, have a cell line with Y-chromosome, whether complete or not, which can be clinically manifested by virilization and mixed gonadal dysgenesis. Early identification of the Y-chromosome genetic material in patients with TS is of great clinical importance because of the increased risk of germ cell tumors, especially if growth hormone is used.

Case report: A 6 year-old girls was consulted to endocrinology department for decrease in the growth velocity from the age of two years and clitoromegalia. Considering the presence of clinical features of TS, short stature (height - 102.5 cm (- 2 SDS), parental height - 171.0 cm (+2 SDS)), small size of the uterus and ovaries according to ultrasound, clitoromegalia, hirsutism girl was carried out molecular cytogenetic FISH study. Cytogenetic study revealed besides a cell line with 45,X a second cell line where the short arm of the Y-chromosome was translocated onto the short arm of a chromosome 7, karyotype: 45,X,add(7)(p21).ish(SRY+)[97]/45,X.ish(SRY-)[40]. Diagnostic laparoscopy with gonadectomy was performed. Histological examination of the left gonad revealed a stroma of the ovary without follicles and a tissue of the rudimentary testicle, the right gonad - fragments of the ovarian stroma without follicles. Growth hormone treatment was initiated at the age of 6.5 years, due to significant growth retardation. At the age of 15 years 9 months treatment with somatropin was canceled because of little growth potential (height velocity 2.6 cm/year, bone age > 14 years). The achieved height was 154.5 cm (-2 SDS). Estrogen replacement was started at the age of 11.5 years (estradiol valerat 0.5 mg/day). The dose of estrogens increased gradually, and was 1 mg/day, which allowed to reach the Tanner 3 stage of sexual development 1.5 years after the onset of estrogen therapy. It is planned to administer cyclic therapy with the addition of progesterone to prevent endometrial cancer associated with prolonged estrogen monotherapy.

Conclusion: Molecular techniques such as FISH or PCR for identifying Y-chromosome-specific sequences are recommended to be used in patients with TS and signs of virilization and/or when there is a marker chromosome not identified by classical cytogenetics.

P3-P250

Prader-Willi Patient with Rectal Bleeding – Experience in Center for Rare Endocrine Disordesrs in Varna, Bulagria

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Prader-Willi syndrome (PWS) is a genetic condition (frequency from 1:8000 up to 1:30 000), which is associated with deletions of chromosome 15 (region 15q11.2), maternal uniparental disomy and impring defects. It is characterized by muscle hypotonia in the early postnatal period, excessive weight gain after 2 years of age, lack of satiety, short stature, hypogonadism and compulsive-like behavior. Every patient has his/her own specific needs that change with age and individualized approach is mandatory for providing them with better quality of life. PWS patients sometimes present with peculiar signs and complaints, and it is extremely important that experienced multidisciplinary team cares for them.

We present a typical PWS patient with tendency of self-scratching of the rectum, that caused a lot of non contributing laboratory tests. The patient is a 16 year old girl, born from first pathological pregnancy and delivery. Her postpartal care was complicated and she had delayed motor and mental development. The girl has late diagnosis, genetically confirmed by methylation test (B.I.R.D. Foundation, Mauro Baschirotto Institute for Rare Diseases, Italy), at 11 years of age. She was started with GH therapy immediately, and achieved good results without safety concerns. The girl and her family achieved satisfactory control of weight for the syndrome (BMI 30 kg/m^2), losing 15 kg for 1 year after proper counselling. She was doing well until a year ago her parents noticed that there is a large amount of blood and mucus in girl's faeces. She was admitted at another clinic, where a lot of tests were performed (blood and faeces samples, abdominal ultrasonography, contrast colon radiography and colonoscopy with biopsy under anesthesia). She was misdiagnosed with mild form of chronic nonspecific colitis and rectal ulcer. A high-dose anti-inflammatory treatment (Mesalazine) was prescribed together with probiotics and high-carbohydrate dietary regimen was recommended. Three months later the girl was admitted for routine endocrine tests. The nature and possible etiology of the bleeding problem were discussed and recommendations for detailed observation of the child were given, after which the mother was able to observe self scratching of the rectal area. All unnecessary medications were stopped.

In conclusion, the self-scratching of rectum is common in PWS patients due to constipation, itching and high pain threshold. Revealing the nature of connected bleedings could spare a lot of unnecessary tests and treatments to patients, and counseling of parents could prevent further episodes.

P3-P251

Mosaicism 47XXX/45X0, A Case Report

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Background and aims: Turner Syndrome (TS), 45X0, is the most common chromosomal pathology affecting females, occurring in 1:2500 to 1:5000 female infants. The typical phenotype includes short stature, gonadal dysgenesis leading to sexual infantilism, low-set ears, low rear hairlin, mamary hypertelorism, neck webbing, gothic palate, irregular rotation of the elbows, shield chest, shortening of the 4th metacarpal, low hairline, shortening of lower extremities, renal disorders and heart defects (cardiovascular malformations such as bicuspid aortic valve, aortic coarctation, aortic aneurysm, and mitral valve prolapse are found in approximately 20% of TS females).

47XXX syndrome may be asymptomatic or present with tall stature, microcephaly, epicanthal folds, language learning disabilities and muscular dystonia.

Mosaicism is observed in approximately 30% of all TS cases, 1% representing the 45X/47XXX karyotype. Such rare cases can present with different phenotypes. The presence of the 47XXX cell-line makes them more prone to spontaneous menarche and more fertile, as compared to 45X.

Case Report: We report a case of a girl with 45X/47XXX karyotype.

ALM, third daughter of a non-consanguineous couple, was reffered to the pediatric endocrinology service due to a decrease in growth velocity. Child without chronic diseases, proper nutrition and normal neuro-psychomotor development.

Estimated target height was 167,5cm (75th Percentile). Birth length was 47 cm, height at 8,7 years was 122cm (5th Percentile). Physical examination showed epicanthal folds and mamary hypertelorism. Laboratory investigation rulled out hipotyroidism, renal or cardiac defects.

Conventional cytogenetic examination showed a mosaic karyotype with 66% of cells with X trisomy (47XXX) and 34% with X monossomy (45X0).

Growth Hormone therapy was iniciated.

Conclusion: 45X/47XXX females have no typical phenotype, and may present with various degrees of ovarian function, starting from normal to absent of hormonal secretion, with mono or bilateral streak gonads.

Prognostic counseling in Turner Syndrome is in growing demand, especially in the case of mosaics, uncommon karyotypes, and in prenatal detection of the sex chromosome aneuploidy. There is special interest, because of the possibility of ovarian tissue preservation in such patients.

P3-P252

Factors Influencing the Selection of Injection Areas During Self-Therapy for Growth Hormone Therapy Among Patients 10-15 Years Old

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Background: It is known that consistency in growth hormone therapy has major influence on long term linear growth. Many studies have researched the connections between varied growth hormone preparations, ease of use and adherence to treatment. No research was found on preference of specific injection areas and reasons for such.

Every year over 180 children begin growth hormone therapy at the institute. Training and monitoring them is a major part of the staff's daily work. The institute aims to optimize and personalize growth hormone self-therapy training, to improve self-therapy adherence.

Objective: Investigate the preferred injection areas for children aged 10-15

Investigate variables that influence the selection of preferred injection areas

Methods: 51 children between the ages of 10-15, in treatment for over 6 weeks, took part in a questionnaire study. The questionnaire examined several factors and their effect on the choice of injection areas: knowledge, patient environment (training staff, acquaintances also in treatment), pain, and personal factors (age, weight, BMI, previous experience, superstition).

(These are preliminary results for the full study which aims to cover 100 children).

Results: The study population consisted of 27 boys and 24 girls 51 aged 10-15 (mean 12.64), who were treated with growth hormone between 2 month and 10 years (mean 3 years).

Preference of injection areas (descending order) was: arms, buttocks, thighs and abdomen, with no prominent side preference.

Boys reported more subjective pain than girls (NS).

Children reporting a fear of injection in the abdomen also reported severe pain (mean of 6.9 vs. 2.66 for those that reported no fear of injection in abdomen: $p<0.005$). Those children were treated longer with growth hormone (mean of 3.7 years vs 2.1 years for those who reported no fear of injection in the abdomen, $p<0.011$)

11% of the children received a recommendation for a preferred injection area from another patient.

Sex, age, and familiarity with recommended injection areas were not found to impact choice of preferred injection area.

There was no concern among children regarding whether or the injection will leave visible marks that can be seen by others.

Conclusions: Pain and fear of pain are the main factors influencing the selection preferred injection sites. Time does not constitute a mitigating factor, and sometimes fear increases as the treatment continues.

P3-P253

Tall Stature: A Diagnosis Is Somtimes Difficult

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Background: Tall stature is defined as height > 02 standard deviations (SD) above the population mean. The most common cause is normal familial tall stature, but some cases are pathological and require special attention.

Observations: We report four clinical cases corresponding to four diagnostic categories. We describe the diagnostic approach and difficulties encountered through these cases.

Case 1: A boy aged 25 months was referred for large size, He had a history of repeated hypoglycaemia. Examination revealed: weight: 19kg (2+ DS), Height :101 cm (+ 4.5DS), Tanner:G2P3A1, testicles volume : 04 ml and a bone age of 04 years. Hormonal status: FSH : 5,5 mui/ml (< 4,6), LH: 3,9 mui/ml (< 3,6), testosterone:03 ng/ml (2,8-8), Abdominal ultrasound showed bilateral adrenal hyperplasia. A diagnosis of Beckwith Wiedemann syndrome with central precocious puberty was made.

Case: 02 A 13-year-old patient from a consanguineous family was referred with tall stature, Hight : 170 cm (> +2.5 SD), weight 80 kg > + 3 SD),BMI : 27,6 kg/m², facial dysmorphism associated with mental retardation, gynecomastia and micropenis, Karyotype showed a 47 XXY.

Case: 03 A 16 year old girl 46XX,was referred for delayed puberty. On examination, Height:176 cm (>+2 SD), weight :64 kg (M), BMI: 20.66 kg/m2.Tanner B1P5.Pelvic ultrasonography showed multicystic ovaries with a small uterus. The hormonal profile showed plasma 17β-estradiol level of 9035 pmol/L (normal 120 to 300 pmol/L during early follicular phase), (LH: 24 IU/L [N: 2 to 8 IU/L], FSH: 13 IU/L [N: 2 to 10 IU/L]), suggesting an estrogen resistance syndrome confirmed by genetic studies which showed a c.1181G>A mutation at 394 (Arg 394His) of the ESR1 ligand-binding domain

Case: 04 A 16-year-old girl from a 2nd degree consanguineous family and a history of epilepsy, was referred for delayed puberty. Clinical examination showed : Height: 175 cm > + 2DS), mental retardation, hypoplastic labia minor, Tanner: B2P2. Hormonal profile revealed primary gonadal failure with LH : 0,12 mui/ml (N : 2,4 – 12,5 FP) FSH : 0,29 mui/ml (N: 3.5 – 12,5 PF), estradiol : 3.5 ng / ml (N :12.5 – 166 PF). The Karyotype was 47 XXX, indicating triple X syndrome.

Discussion and conclusion: Physicians should always search for a pathological cause of tall stature. A systematic approach allows an early diagnostic of these pathologies and thus better screening for complications.

P3-P254

Woodhouse-Sakati Syndrome: Clinical and Molecular Study on a Qatari Family with C2orf37 Gene Mutation

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Background: Woodhouse-Sakati syndrome (WSS) is rare autosomal recessive condition characterized by progressive extrapyramidal signs, mental retardation, hypogonadism, alopecia, and diabetes mellitus. The age at disease onset, manifestation and severity of specific symptoms differs significantly among individuals with this syndrome and even among affected members of the same family. The gene C2orf37, which is responsible for WSS, located on chromosome 2q22.3-q35.

Objective(s): To describe the clinical and genetic characteristics of Woodhouse-Sakati Syndrome diagnosed in three siblings from the state of Qatar.

Clinical history/methods: The phenotype of the three siblings included hypogonadism, alopecia, diabetes mellitus, and different degrees of mental retardation ranging from mild to severe. Whole Exome Sequencing (WES) analysis was performed in the index patient and her parents. Using genomic DNA, the exonic region and flanking splice junctions of the genome were captured and sequenced by NetGen sequencing on an Illumina system. Sequence variants were analyzed using Xome Analyzer. Capillary sequencing was used to confirm all possibly pathogenic variants. Sequence and copy number alterations were reported according to the Human Genome Variation Society (HGVS) and International System for human Cytogenetic Nomenclature (ISCN) guideline, respectively

Results: Homozygous mutation c.436delC in exon 4 in the *DCAF17* gene was identified in all the three siblings. Both parents were heterozygous for the mutations. C2orf37 codes for DCAF17 (DDB1 and CUL4 associated factor 17) a transmembrane protein that localizes to the nuclear envelop of unknown function but that may be associated with the ubiquitin system. C2orf17 codes for a protein of 520 aa. The c.436DelC mutation causes a frame shift and a predicted truncated protein of 147 aa.

Conclusion: Mutations in *DCAF17* account for the features of Woodhouse-Sakati syndrome, however, the exact mechanisms of the hormonal abnormalities and the other signs and symptoms remain unclear. Understanding the molecular basis of WSS will provide novel insights into the role of the C2orf37 gene in normal physiology. In relation to the endocrine manifestations, understanding the role of C2orf37 gene in diabetes mellitus, hypogonadism and hypothyroidism will provide insights into the function of the pancreas, gonads and the thyroid gland respectively. The translational implications of this are that we might be able to develop novel therapies for this disorder if we know how mutations in C2orf37 gene lead to the multiple endocrine manifestations.

P3-P255

Factors Affecting Height Velocity in Normal Prepubertal Children

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Purpose: To analyze the effects of clinical and laboratory factors, including insulin-like growth factor (IGF) levels, on the height velocity of normal prepubertal children.

Methods: Ninety-five healthy prepubertal children (33 boys, 62 girls) were enrolled. The mean chronological age of the participants was 6.3±1.4 years, with a height standard deviation score (SDS) of -0.88±0.70. IGF-1, IGF binding protein-3 (IGFBP-3), SDS for anthropometric measurements, and changes in SDS for anthropometric measurements were analyzed for one year, and their associations with one-year height velocity were investigated.

Results: The group of children with a one-year height velocity of ≥6 cm were chronologically younger than the group with a one-year height velocity of <6 cm (5.9±1.3 vs. 6.7±1.3 years, P=0.004), with a lesser increase of SDS for body mass index (BMI) over one year (-0.18±0.68 vs 0.13±0.53, P=0.014). There were no differences between the two groups in IGF-1 SDS and IGFBP-3 SDS. Multiple linear regression showed that baseline chronological age (r=0.243, P=0.026) and height SDS (r=0.236, P=0.030) were positively associated with IGF-1 SDS. Binomial logistic regression showed that an increase in chronological age (odds ratio [OR], 0.68; 95% CI, 0.47-0.99) and an increase of BMI SDS over one year (OR, 0.41; 95% CI, 0.18-0.89) were associated with a decreased growth possibility of an above-average height velocity (≥6 cm/year).

Conclusion: Height velocity of normal prepubertal children is affected by an increase of BMI SDS and chronological age. Prepubertal IGF-1 SDS reflects height SDS at the time of measurement but is not associated with subsequent height velocity.

P3-P256

Low Dose Growth Hormone Using IGF1 Dose Titration Is Associated with Sustained Optimal Growth in a Child with Both Turner and Down Syndrome

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Background: Short stature occurs in both Trisomy 21 and Turner syndrome. This unusual case has a de novo mutation of 47,X,del(X)(p22.3),+21 with clinical features of both syndromes. Growth assessment data and investigations was previously discussed in ESPE2016.

Case: Following growth assessment due to parental concern that her short stature was too short for either syndrome and a falling height velocity of 3.5 cm/year at 2.8 years, the decision was made to start growth hormone (GH) treatment. Low dose GH was started with the aim of reaching Turner syndrome (TS) dose(9.8mg/m^2/week). IGF1 levels were closely monitored. Excellent growth response is seen with TS HtSDS -2.08, <5th centile Down's chart improving to TS HtSDS -0.09, just beneath 25th centile Down's chart despite a reduction in GH dose. IGF1 levels pre treatment were good at 171 ng/ml (51-303). Higher IGF1 levels during treatment lead to dose reduction of GH. Unfortunately not all monitoring blood tests were successful and not all blood samples reached the GH reference laboratory. Results have been tabulated.

Conclusion: Dose titration of GH with IGF1 monitoring is necessary in this case to use a lower dose of GH for optimal growth. Parents were pleased with the other non linear growth-related benefits of treatment like improved appetite and weight gain. You can see with increased BMI and age and possible physiological increased GH resistance that GH dosage could be increased again with IGF1 levels in range.

P3-P257

Growth Response in Noonan Syndrome in Indian Children

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Objective: To evaluate the growth response in children with Noonan syndrome (NS) treated with growth hormone (rGH).

Table 1. (for Abstract no P3-P256)

	3.12.10	31.10.11	12.11.12	11.11.13	13.08.14	15.06.15	6.05.16	3.11.17
TS HtSDS	-2.08	-1.29	-1.0	-0.57	-0.54	-0.44	-0.32	-0.09
non TS HtSDS	-3.95	-2.2	-2.2	-2.59	-2.6	-2.59	-2.57	-2.59
BMI SDS	+0.31	+1	+1.07	+0.95	+1.32	+1.41	+1.44	+1.75
IGF1	171 ng/ml (51-303)	327 ng/ml (49-289)		49.7 nmol/L (3.3-31.7)	57.9 nmol/L (5.1-48.2)	48.2 nmol/L (5.1-48.2)	50.2 nmol/L (5.1-48.2)	60.9 nmol/L (6.4-71.9)
GH (mg/m^2/wk)		8.4	9.2	9.5	5.8	4.4	4.8	6.3

Methods: We retrospectively collected data from 2007 of prepubertal children with NS, their baseline auxological parameters were recorded pre and post treatment.

Results: A total 1134 were treated with growth hormone for short stature of which there were 6 cases of NS, constituting 0.5% of the short stature. There were 5 males and 1 females, mean age of presentation was 10.8yrs + 1.78. The mean height at the start of treatment was 128.75cm and improved to 138.13cm after 12 months of rGH. The average height velocity was 9.38cm/year.

Conclusion: the prevalence of NS is very limited in Indian population but timely diagnosis and treatment can result in improved final height.

P3-P258

Late Referral of Siblings with Combined Pituitary Hormone Deficiency (PROP1)

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Background: PROP1 (Prophet of POUF1) mutations are the most frequent genetic cause of combined anterior pituitary hormone deficiency. The PROP1 gene encodes a transcription factor of synthesis: somatotrophs, lactotrophs, thyreotrops and gonadothrops. These mutations are characterized by great clinical variability, including time of onset of hormonal deficiencies, hypophyseal dimensions and secretion of cortisol.

Objective and hypothesis: Referral of children with growth hormone deficiency (GHD) is beside all checkpoints during childhood rather late. High genetic potential and living in countryside could be additional difficulties for GHD and additional hormone deficiencies detection.

Method: we present brother and sister addmited for tests; boy's (age 16y 3/12) Dg: Delayed puberty and girl's (age 12 y 11/12) Dg: Short stature and Obesity. Final height for both was according genetic potential (GP) at p 90. Boy's height was on p50, BMI 28,3 (p95), volume of both testis were 1,5 ml (Prader), without secondary sexual characteristics, -5 to -7 SD delayed bone maturation, MRI scan of pituitary-enlarged. Girl was 29 cm smaller than GP height (p 90), obese: BMI 27,2 (p95). Laboratory tests for both showed central hypothyreosis, GHD, low gonadotropins and low prolactine. Later done cortisol and ACTH were low (Synachen test) in both. Girl's bone age was -2 to -3 SD, without secondary sexual characteristics, regular size of pituitary gland with contrast opacifications. Treatment- substitution of lacking hormones: thyroid, GH, later hydrocortisone, depot testosterone injections monthly (boy) - secondary sexual characteristics developed, and in girl estrogen substitution – secondary sexual characteristics developed and later had spontaneous periods without hormone substitution. Additional treatment for both: Metformin (serious insulin resistance) and supplementation with vitamin D.

Results: The genetic study was performed by polymerase chain reaction confirmed homozygous mutation in the PROP1 gene with a 2-bp deletion (c.301–302delAG). At the age of 18 years boy's height was on p75 with BMI 24,4, developed male secondary sex characteristics (monthly substitution), and girl's height was on p 90, BMI 28, sexual development completed, regular periods. Both had continuous substitution with thyroid hormones, hydrocortisone, and metformin treatment.

Conclusion: Although first referral of brother and sister with combined pituitary hormone deficiency (PROP 1) was very late they gained height almost near GP, they stayed no to moderately obese and gained normal secondary sexual characteristics with continuous thyroid and suprarenal substitution.

P3-P259

17p13.1 Microduplication Syndrome in a Child with Familial Short Stature and Growth Hormone Deficiency: A Short Case Report

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Background: To date, 6 cases of 17p13.1 microduplications have been described in the literature. Intellectual disability is the core feature, together with minor facial dysmorphisms and obesity later in life, but a characteristic phenotype for 17p13.1 microduplication has not been delineated.

Objective and hypothesis: We describe a young patient with a 422 Kb microduplication maternally inherited in 17p13.1, affected by mild intellectual disability and growth hormone deficiency. To our knowledge this is the first case reported presenting growth hormone deficiency.

Patient and methods: A toddler boy was examined at the age of 3.5 yrs for growth retardation (Weight: 12.8Kg, 3rd percentile, Height: 89.1cm, <3rd percentile). He is the only child of healthy unrelated parents of Caucasian ancestry. His mother is short (Height: 148.5cm, <3rd percentile) and was diagnosed with intellectual disabilities in her school age. His father is also short (Height: 154,5cm, <3rd percentile) but no other family history of intellectual disability or endocrine disorder was reported. He was born at 40 weeks' gestation after an uneventful pregnancy (weight: 3070 gm, 25th percentile, length: 47 cm, 3rd percentile and head circumference: 34 cm, 25th percentile). During infancy and early childhood, the boy presented mild psychomotor developmental delay. At 7 yrs he was underweight (18Kg, <3rd percentile) but his height was more severely compromised (120cm, <<3rd percentile). Besides minor facial dysmorphism, he had normal physical examination. He was prepubertal and no asymmetry was appreciated. Neurological examination was normal except for motor dyspraxia.

Results: EEG recordings showed slow background activity without paroxysmal features. Basic blood tests were normal and endocrine investigation revealed normal thyroid and cortisol levels but IGF1 levels were low for his age. Growth hormone response to two different stimulation tests was below 10 ng/ml, consistent with growth hormone deficiency. Hypothalamic pitu-

itary MRI was normal. A chromosome analysis revealed a normal male karyotype 46 XY. Array-CGH analysis detected a 422 Kb gain of the copy numbers in the spanning region 17p13.1. The breakpoint was mapped between genomic coordinates chr17: 6,902,072-7,324,005 (Genomic coordinates are listed according to genomic build GRCh37/hg19). No additional aberrations were detected. Both parents were found to have normal karyotype but the mother's array-CGH analysis was identical to her son. Array-CGH analysis in the father was normal.

Conclusion: Although familial short stature is considered a „normal" variation of growth retardation hormonal and genetic investigation is indispensable for the etiological diagnosis.

P3-P260

Prader Willi Syndrome: Clinical Profile

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Prader Willi Syndrome (PWS) is characterized by hypotonia, developmental delay, short stature, small extremities, characteirstic facies, hyperphagia, obesity, hypogonadism, obstructive sleep apnea and other behavioral problems.

We report twelve cases of PWS (4 females, 8 males) in the age group of 1-18 years being treated at Sir Ganga Ram Hospital, a tertiary care center in Northern India. In males, seven (87%) had cryptorchidism; in females, one (25%) had labia minora hypoplasia. 9 children (75%) were diagnosed during infancy, two between 3-5years and one at 9years of age. DNA methylation analysis for PWS was positive in all children, three of them had deletion of 15q11-13 (FISH) & one had uniparental disomy (DNA polymorphism analysis). Among 10 children in the 5- 18year age group, 9 are obese and one is overweight. Five of these twelve patients presented with increased daytime sleepiness and polysomnogram showed mild to moderate degree of Obstructive Sleep Apnea in four while one had a normal study. Except one child, rest of them had delayed motor milestones. Three developed hypothyroidism, one had scoliosis, and one developed Type 2 Diabetes. Four children were started on growth hormone replacement at 9-12years of age for growth failure.

Early diagnosis of PWS is important for effective long-term management, and a precocious multidisciplinary approach is fundamental to improve quality of life, prevent complications, and prolong life expectancy.

P3-P261

Leri-Weill Syndrome Phenotype with Atypical Cytogenetic Finding

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Introduction: Leri-Weill dyschondrosteosis (LWD) is caused by haploinsufficiency of the SHOX gene, located in the pseudoautosomal region (PAR 1) of the short arm of the X and Y chromosomes. The gene is expressed in highest levels in bone tissue and its product likely controls the chondrocyte apoptosis. Deletions and duplications are most frequent, point mutations are responsible for minority of the cases. The main clinical symptoms of LWD include disproportionate short stature, mesomelic shortening of the limbs, Madelung deformity of the forearm and limited wrist movement. Patients with LWD seem to benefit from growth hormone treatment.

Case description: A 16 years old boy attended the clinic because of short stature. He was born after 3rd uncomplicated pregnancy and delivery, full term, weight 2950 g, lenght 49 cm. Neonatal period was normal. His first steps and first tooth eruption were at 1 year of age, his first words at 2 years of age. He had frequent respiratory infections. There was no familly history of inherited diseases and cosanguinity. On examination: W 69 kg, H 150.5 cm, SDS -2.97. Disproportionate short stature was noted with mesomelic shortening of the limbs and Madelung deformity of the forearms. Other findings were micrognathia, thoracic scoliosis, high-arched palate, unilateral cryptorchidism and relatively small testes volume (12 ml at Tanner V). Investigations (biochemistry, thyroid function, gonadotropins, testosterone, IGF-1) were normal. Radiographic changes typical for Madelung deformity were found, the bone age was adequate. US confirmed left-sided inguinal cryptorchidism. MRI of pituitary region was normal. Karyotype was 45,X[2]/46,X,del(Y)(q11.22)[28].

Discussion: We present a patient with typical LWD phenotype but with karyotype corresponding to mixed gonadal dysgenesis. Probably SHOX deletion even in small percentage of cellular lines is sufficient to cause the typical features of LWD. Also, the cytogenetic result shows the distribution of the cellular lines in the lymphocytes but in other tissues (bones) the percentage of 45,X line could be greater. Microdeletion in Yp11.2 is also possible but its detection is beyond the potential of the conventional cytogenetic testing. A point mutation is another possibility and a targeted genetic testing is required. Though our patient is well virilized he has unilateral inguinal cryptorchidism and smaller testes which is suspicious of some form of gonadal dysgenesis. He will undergo orchidopexy and testicular biopsy. Because of the limited remaining growth potential treatment with growth hormone will not be of benefit.

P3-P262

Deletion of 12q12 Increases the Risk of Growth Retardation and Intellectual Disability

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Single-nucleotide polymorphism (SNP) arrays have been widely used to identify novel genomic imbalances. Many of these genomic imbalances have been confirmed to interact with developmental delays, intellectual disabilities and congenital defects. Here, we identified a Chinese girl with a 3.18 Mb deletion at 12q12 (human genome build 19: 43,418,911-46,601,627). Deletions at 12q12 are extremely rare chromosomal imbalances; only five cases involving a deletion of this type have previously been reported. In these six sporadic cases, all of the patients exhibited developmental issues accompanied by different degrees of intellectual disability. A review of DECIPHER patient data revealed an additional 10 cases involving genomic deletion at 12q12. Many of the patients in these cases exhibited developmental delay and intellectual disability. When these patients were included, 88% and 69% of individuals with a deletion in this chromosomal region presented with developmental retardation and intellectual defects, respectively. Database searches indicated that this copy number variant (CNV) has not been found in normal humans. Therefore, we suggest that a CNV in this region is a risk factor for developmental retardation and intellectual disability.

P3-P263

A Patient with Turner Syndrome(45X/46XX) and Congenital Adrenal Hyperplasia

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An association between Turner syndrome (TS) and Congenital Adrenal Hyperplasia(CAH) due to 21-hydroxylase deficiency is rare. TS is caused by partial or complete loss of the second sexual chromosome which leads to genital system malformation and infertility. 21-hydroxylase deficiency is a well-known cause of disorder of sexual development in genotypic female neonates.The aim of our study is to report this patient and stress this rare possibility. A 8-month-old patient suffering from both 45,X/46,XX Turner's syndrome and virilization form of CAH was referred to our hospital. She was born spontaneously at full-term with normal birth measurement:weight 3750g(+1.21SD), length 51cm (+0.76SD). After birth, she showed normal in growth and development until her mom found ambiguous genitalia when she was 8-month-old. Genital examination revealed a 3cm phallus, normal external urethral orifice and incomplete fusion of labia. Laboratory investigations showed the normal levels of blood electrolytes, hyperandrogen, decreased levels of cortisol, and increased adrenocorticotropic hormone (ACTH) and 17-hydroxyprogesterone (17-OHP). 21-hydroxylase deficiency were cofirmed with the diagnosis of CAH owing to the mutation of *CYP21A2* gene. Meanwhile, she could also be diagnosed with Turner syndrome by her karyotype showing a 45X/46XX pattern. Besides, the Sanger sequencing showed a negative sex-determining region Y. She is receiving hydrocotisone in a dose of 10mg/m^2/day. Our recent follow-up revealed that the patient's adrenocorticotropic hormone level were normal and her cltoris did not increase or even seemed a bit shorter. Her length was 81cm (+2.17SD) and weight was 10.75kg (+1.22SD) when she was 1-year-old. The report suggests that it is necessary to cofirm karyotyping during investigation of patients with disorder of sexual development due to 21-hydroxylase deficiency. Additionally, TS accompanied with CAH and virilization should analyze *SRY* gene to exclude the possibility of hidden Y-segment. A long term follow-up about reproductive system, stature and treatment of this patient is needed.

P3-P264

Congenital Tufting Enteropathy Caused by Mutation of Epcam Gene: A Case Report and Review of Literature

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Objective: To explore the clinical characteristics of diagnosis and treatment in patients with congenital tufting enteropathy.

Method: A rare case of congenital tufting enteropathy was diagnosed at West China Second University Hospital, Sichuan University in July 2016, the clinical data of congenital tufting enteropathy was analyzed retrospectively, and the related literature were reviewed. Original papers on congenital tufting enteropathy published until Oct 2017 were retrieved at PubMed, CNKI databases and Wangfan databases by the use of the key words „ EPCAM „, „ congenital tufting enteropathy".

Results: A 2-year and 2-month old girl began to develop intractable chronic diarrhea soon after birth, accompanied with growth restriction, repeated infections, anemia and so on. Next-generation DNA sequencing revealed a homozygous C>A substitution at exon 3 in EPCAM of the affected patient(c.412C>T, p. R138X), and she was finally diagnosed as congenital tufting enteropathy. A total of 60 cases of congenital tufting enteropathy caused by EPCAM gene mutation were found in 14 papers, all of which were published abroad, and 34 EPCAM gene mutations were reported. 11 of them were located in exon 3.

Conclusion: A case of congenital tufting enteropathy caused by EPCAM gene mutation was reported for the second time in China. Congenital tufting enteropathy is rare and difficult to diagnosis. Chronic intractable diarrhea associated with growth retardation in infants should be highly alert to the possibility of congenital tufting enteropathy.

Key words: EPCAM, congenital tufting enteropathy, intractable diarrhea

P3-P401

Is Using a Specific Growth Charts a Chance to Be More Precise in Evaluation the Growth of the Children and Adolescence with Down Syndrome? Comparison of the Down's Syndrome Growth Charts with the Growth Charts for Polish Population

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Introduction: Down syndrome (DS) is a chromosomal disorder. Children with DS have different height and weight patterns compared to children without DS. The aim of our study was to compare anthropometric parameters (expressed in standard deviation score-SDS) of people with DS using charts for DS and population (P) charts.

Materials and methods: The study group consisted of 114 patients with DS (64 girls), aged 4 months – 36 years (average age: 8.2 years) from Poland. Body weight, height, and BMI were expressed in the SDS values using growth charts for children with DS and for population. We assessed whether there were any differences in the studied parameters. For data analysis we assumed that: values <3pc [<-1.88], 10-90pc [≥-1.66,≤1.66], >97pc [>1.88]. In addition, an online survey was conducted. The study group consisted of 183 parents of children with DS. The questionnaire consisted of four questions and concerned the topic of centile grids.

Results: There are significant differences between average values of SDS for DS charts and P charts for the examined group. Differences in SDS ranges were: height 2.75±0.79 (p=0.00); weight 0.94±0.80 (p=0.00); and BMI 0.2±1.73 (p=0.20 - not statistically significant). According to the P height charts, the prevalence of growth deficiency (<3pc) was higher than that based on the DS charts (69% vs. 4%). The amount of records within the norm was lower for P charts (32% vs. 77%). According to weight charts, prevalence of records <3pc were higher for P than DS charts (33% vs. 5%); records within the norm were lower for P than DS charts (55% vs. 79%); and records >97pc were lower for P (5% vs. 7%). According to population BMI charts, the prevalence of obesity is higher for P than DS charts (12% vs. 1%); normal body weight is lower for P than DS charts (39% vs. 61%); and underweight is higher for P than DS charts (42% vs. 31%).

Conclusions: The differences between DS charts and P charts were identificated. Growth charts for children with DS are essential for guiding clinicians and families in monitoring the growth of people with DS. The DS charts can be used as tools to provide indications of how growth of a child compares with peers of the same age and sex without DS. Most parents are aware of existance of specific charts, unfortunately most clinicians do not use them.

P3-P406

Two Siblings with Prader-Willi Syndrome Caused by Microdeletion Derived from the Paternal Grandmother

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Prader-Willi syndrome (PWS) is a complex neurobehavioral disorder characterized by infantile significant hypotonia and feeding difficulties, followed by morbid obesity secondary to hyperphagia, short stature, functionally deficient gonads, intellectual disabilities and behavioral problems. It is caused by lack of expression of imprinting genes on the paternally inherited chromosome 15q11.2-q13 region. The genetic mechanism responsible for Prader-Willi syndrome can rarely be inherited. Here we report a highly unique case of two siblings who share this condition by describing a case of two siblings with PWS. And methylation-specific multiplex ligation-dependent probe amplification (MS-MLPA) and single nucleotide polymorphism array (SNP array) demonstrate a 417 kbp microdeletion within 15q11.2 region derived from the paternal grandmother. To the best of our knowledge, the present case is the first to report a familial PWS case in China. In addition to previous studies, the present study contributes to consensus regarding imprinting defects results from a failure to erase the maternal imprinting during spermatogenesis.

P3-P412

Novel Mutation of CHD7 in a Chinese Boy with Kallmann Syndrome

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Kallmann syndrome (KS) is a rare heterogeneous disease with hypogonadotropic hypogonadism and anosmia or hyposmia. The aim of this study is to highlight the clinical features and diagnosis of this rare event by reporting a 13-year-old Chinese boy with a novel mutation of *CHD7*. He presented because of short stature (-2.0 SD) for 11 years. He was born at term with a birth weight of 2.95 kg. Cryptorchidism operation was undertaken at 5 years old. He suffered from absent pubertal development with 2 ml of testicles bilaterally, 1.5 cm of phallus, stage I pubic hair and lower basic sex hormone. He had a history of hyposmia that was ignored. Brain MRI showed hypoplastic left and aplastic right olfactory bulb. A novel heterozygous mutation c.2442+1G>A at the intron of *CHD7* was found, which may significantly affects mRNA splicing. Hence, in patients with short stature or deficiency of secondary sexual development, olfactory bulb image and function should be evaluated carefully. Genotyping may be helpful for confirming the clinic diagnosis, estimating prognosis and genetic counseling.

Key words: Kallmann syndrome; Short stature; Mutation; CHD7.

P3-P413

Conversion of Hypothyroidism to Hyperthyroidism in Children

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Objective: To highlight conversion of hypothyroidism to hyperthyroidism by case reported and literatures reviewed.

Methods: Case report and literature review.

Results: Two children diagnosed as Hashimoto's thyroiditis with hypothyroidism and treated with levothyrocine primary. During the following, hyperthyroidism was noted even the stop the administration of levothyrocine. thyroid receptor antibody (TRAb) was positive during the hyperthyroidism stage and antithyroid drugs was administer till now. Literature reviewed showed only 75 cases with conversion of hypothyroidism to hyperthyroidism were reported previously. Among 77 cases, 8 was children and 69 was adults aged from 5.3 to 66 years with a median age of 41.5 years. The duration from hypothyroidism to hyperthyroidism ranged from 0.1 to 18 years with a median of 2 years. The primary disease is autoimmune thyroiditis except one case of congenital hypothyroidism. Among these patients, TRAb and thyroid stimulating antibody (TSAb) have increased tendency while TSH-binding antibody (TBAb) have decreased tendency during the conversion.

Conclusion: Although the conversion from hypothyroidism to hyperthyroidism is a rare condition, more attention should pay to hypothyroidism patients. As the mechanism maybe involve TSAb to TBAb switch, monitoring the TSAb and TBAb in early stage may be helpful for early diagnose and further therapy.

Key words: Hyperthyroidism; Hypothyroidism; Hashimoto's thyroiditis; Graves' disease; Hashitoxicosis; TSAb; TBAb

P3-P415

Case Report: Novel *ACAN* Mutation in a SGA Short Stature Without Accelerated Skeletal Maturation

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Heterozygous mutations in the *ACAN*, encoding for aggrecan or cartilage-specific proteoglycan protein, are associated with short stature with advanced skeletal maturation and skeletal dysplasia.

A 2 years 7 month-old girl born small for gestational age presented with proportionate short stature (height 79.9cm, SDS, -3.23) and bone age was delayed about 1year less than her chronologic age. She was born as small for gestational age.(38 weeks and 5 days of gestational age, birth weight of 2.3 kg (SDS, -2.25), birth length of 44.6 cm (SDS, -2.44) and head circumference of 30.4cm(SDS -2.94)). Her father's height SDS was -1.57 and that of mother was -0.63. Karyotype test showed normal 46,XX. Exome sequencing, confirmed by Sanger sequencing, identified a novel missense mutation in ACAN (c.1927T>C), predicted to be deleterious by both SIFT and PolyPhen-2 analysis. Genetic tests for her family are in processing.

Multisystem Endocrine Disorders P1

P1-P189

Clinical Features and Assessment of the Pathway-Care Proposed by ISPED-Gsa Study Group in an Pediatric Italian Cohort with Pseudohypoparathyroidism

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Background and objective: Pseudohypoparathyroidism (PHP) refers to a heterogeneous group of rare endocrine disorders caused by genetic or epigenetic abnormalities affecting the GNAS locus. It is mainly characterized by resistance to PTH and TSH and a complete or partial Albright Hereditary Osteodistrophy (AHO) phenotype. Few data so far exist on LH/FSH, calcitonin and glucose-lipid metabolism involvement, as well as on neurocognitive aspects. The aim of this multicentre study is to explore prevalence and management of these less studied PHP features, according to the recently published pathway care proposed by the Italian Society of Pediatric Endocrinology and Diabetology (ISPED).

Methods: Twenty-three PHP patients followed by 4 Italian Pediatric Endocrine Centres were enrolled, 14 of which have genetic/epigenetically been characterized. Data on auxological variables, calcium-phosphorus metabolism, thyroid function, FSH/LH, calcitonin, glucose-lipid metabolism, ossifications and neurocognitive development were collected through a common standardized chart.

Results: The average age of the considered population was 12 yrs (6 yrs at diagnosis); 60.8% of patients displays overweight or obesity (average BMI 23.32, +1.44 SDS) and 23.8% show height <-2SDS (average 138.25 cm, -1.14SDS), 60% of which also had IGF1 <0 SDS; 3 patients have performed GH-stimulation tests, with low GH response resulting eligible for hrGH-therapy. At diagnosis, 90.5% of patients show increased PTH, 47.6% hypocalcemia and 66.7% hyperphosphatemia; after oral supplementation with 1,25-VitD alone or associated with calcium, the prevalence of these alterations decreases to 76.2%, 0% and 33.3% respectively; bone mineralization was appropriate in all patients. Clinical hypothyroidism was present in 8 patients (61.5%) at diagnosis; after substitutive therapy a subclinical form remained in 23.1%. FSH/LH resistance has been found in 30.8%, Calcitonin increased levels in 50% of the whole cohort. Glucose metabolism was normal in most patients (euglycemia in 94.7% and normal glucose tolerance in 5/6 patients, with 1 case only with type1-diabetes); 22.2% showed hypercholesterolemia, 11.1% hypertriglyceridemia and 77.8% reduced HDL-cholesterol levels. Heterotopic ossification was described in 45.5% of patients, delayed verbal-motor skills acquisition and/or intellectual disability in 63.2%, psychological support needs in 23.5%.

Conclusions: A standardized approach to the PHP patients, according to ISPED-Care pathway, seems a valid instrument to detect and manage the clinical features of this heterogeneous disorder, aimed to guarantee the same and best assistance to all patients.

P1-P190

Overview of Leading Causes of Death Among French Patients with Prader-Willi Syndrome, 2004–2014

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Introduction: Prader-Willi Syndrome (PWS) is a complex neurodevelopmental genetic disease comprising multiples cognitive, behavioural and endocrine abnormalities. This rare syndrome is one of the most common known reasons of syndromic obesity, a major cause of morbimortality among this population. In the last 20 years, substantial improvements have been made regarding the diagnosis, treatment and management of patients with PWS. Along those progresses, national policies were developed. The French Reference Centre for PWS (FRC-PWS) was created in 2004 with the aim to structure the care of people with associating scientific and medical expertise.

In this analysis, we target to report leading causes of mortality among the French patients with Prader-Willi Syndrome over ten years of the nationwide FRC-PWS.

Methods: This study relied on two sources of mortality information at national level between 2004 and 2014: The French Epidemiological Centre for the Medical Causes of Death (CépiDc) Registry and the FRC-PWS database.

Leading causes of death were classified into 7 categories: respiratory, cardiovascular, non-respiratory infection, accidents, sudden/unexplained death, other causes of death and unspecified/unknown. Descriptive statistics were calculated separately for children (<18 years-old) and adults (18 years-old).

Results: One hundred four deaths were identified in France from 2004 to 2014. Their median age at death was 30 years ranging from a few months to 58 years-old. Seventeen deaths occurred in <18 years-old patients, 70% of them were ≤2 years-old. Respiratory causes accounted for more than 50% of deaths in patients with Prader-Willi syndrome. Among adults most of deaths were triggered by a respiratory failure while the main cause of death was respiratory infection among children. Sudden or unexplained death was reported as a cause of death for 4 children and 16 adults emerging as the second predominant cause of death among this population.

No significant differences were found by gender or genetic subtype regarding the reasons of death. Mean age at death does not differ according to gender or genetic subtype.

Conclusions: PWS is per se a condition that can result in premature death. These findings highlight the respiratory vulnerability in PWS patients. The principal causes of death are respiratory-related for all ages and, in most adults secondary to the complications of obesity. Thus, obesity prevention and adequate management of respiratory problems are the two most important ways to lower the mortality rate in this population.

P1-P191

SGPL1 Missense Mutation in an Infant with Primary Adrenal Insufficiency (PAI), Congenital Nephrotic Syndrome, Primary Hypothyroidism and Gonadal Failure

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Background: Loss of function mutations in *SGPL1* have previously been described by our group in association with a multisystemic disorder encompassing PAI and nephrotic syndrome. *SGPL1* encodes, sphingosine 1-phosphate lyase (SGPL1), which irreversibly binds sphingosine 1-phosphate (S1P) and commits it to the final degradative step in sphingolipid metabolism. SGPL1 is therefore a major modulator of S1P signalling. Several sphingolipid intermediates such as ceramide, sphingosine and S1P have been purported to act as modulators of the steroidogenic pathway, as second messengers altering downstream expression of steroid responsive transcriptional elements. Under normal physiological conditions, S1P is largely pro-proliferative, suppressing the pro-apoptotic actions of ceramide. However, loss of function mutations in *SGPL1* result in a pathological accumulation of both S1P and ceramide leading to induction of apoptosis.

Objective and hypotheses: Assessment of the genetic cause of PAI and congenital nephrotic syndrome in a Pakistani male (46,XY) infant who presented in early life with failure to thrive. Urinalysis revealed massive nephrotic range albuminuria. The patient was noted to be hyperpigmented with primary adrenal disease, with a low serum cortisol (61 nmol/L), markedly elevated ACTH (999 ng/L) and low normal aldosterone (190 pmol/L).

Method: Sanger sequencing of the entire coding region of *SGPL1*.

Results: Analysis of patient genomic DNA revealed a very rare homozygous missense mutation in SGPL1 (p.N171D, c.511A>G; gnoMAD MAF = 9.86e-6 with no homozygotes), which was heterozygous in his consanguineous parents. In silico prediction tools, SIFT (score 0) and PolyPHEN (score 0.948) predicted this change to be deleterious.

The patient had a wider endocrine phenotype with gonadal and thyroid disease with raised basal gonadotrophins (FSH 71 IU/L, LH 27 IU/L), an elevated TSH (25mU/L) and low fT4 (10.7 pmol/L). Treatment included hydrocortisone, fludrocortisone, L-thyroxine and captopril. Renal function continued to deteriorate and secondary hyperparathyroidism addressed with alfacalcidol initiation. Other systemic manifestations included persistent lymphopenia, ichthyosis and motor developmental delay. Aged 9 months the patient presented with end stage renal failure and pulmonary oedema after a brief diarrhoeal illness and subsequently died.

Conclusion: The case further highlights the extent of endocrinopathy associated with this form of PAI and supports the emerging multisystemic phenotype of patients with loss of function *SGPL1* mutations. Given the multisystemic and progressive nature of this form of PAI, a genetic diagnosis is crucial to accurate management and screening for comorbidities in these patients.

P1-P192

Final Adult Height, Insulin-Like Growth Factor 1 (IGF-I) Concentration in Adolescents and Young Adults with B-Thalassemia Major (BTM) with and Without Growth Hormone Deficiency

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Background: Relatively little is known about endocrine function, bone mineral health, and growth during oral iron chelation therapy (OIC) in β-thalassemia major patients (BMT) on treatment with deferasirox.

Aims of the study: To measure the final adult standing height (FA-Ht) and the frequency of endocrine complications in relation to their liver iron content (LIC) and insulin-like growth factor 1 (IGF-I) concentration. Patients were grouped into two groups according to their iron chelation therapy.

Patients and methods: The first group (Group A; 15 patients, 6 females and 9 males) received oral iron chelation therapy (OIC) with deferasirox for 6 years before puberty; the second group (Group B; 40 patients) attained the FA-Ht before the use of OIC (iron chelation therapy with deferoxamine (DFO) given subcutaneously, since the age of 2 years). In both groups LIC was measured using FerriScan ® R2-MRI method.

Results: Patients with BTM who received OIC for 6 years or more before their end of growth were significantly taller and had lower LIC assessed by FerriScan® R2-MRI, and lower fasting glucose level (FBG) and liver enzymes (ALT and AST) concentration, and higher IGF-1 SDS versus those who did not receive OIC before attaining FA-Ht. The prevalence of endocrinopathies, including hypothyroidism, impaired fasting glucose and hypogonadism were significantly lower in Group A versus Group B. The IGF-1-SDS did not differ between the two groups. Neither ferritin level nor IGF-1 concentrations were correlated with the Ht-SDS.

Conclusions: The use of OIC years before the end of puberty was associated with a significantly lower prevalence of endocrinopathies, lower LIC and higher FA-Ht. Proper blood transfusion and early use of intensive oral chelation can improve the final height of patients with thalassemia major.

Table 1. Growth and endocrine function in adults who received oral iron chelation (OIC) vs those who did not receive OIC before attaining final adult height (for Abstract no P1-P192)

	Group A: OIC	Group B: No OIC
Number of patients	15	40
DM	6.6%	2.5%
IFG	6.6%	17.5%*
Hypothyroid	0.0%	10.0%*
IGF-1 <-2	20.0%	87.5%*
HtSDS < -2	6.6%	52.5%*
Hypogonadism	13.3%	40.0%*

DM: Diabetes mellitus, IFG: Impaired fasting glucose, IGF-1: insulin growth factor-1; SDS: standard deviation score; (*p<0.05).

P1-P193

McCune-Albright-Syndrome: Clinical and Genetic Study in a Large Cohort of Pediatric Patients

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Background: McCune-Albright-Syndrome (MAS) is an extremely rare multisystem disorder that affects bones (fibrous dysplasia), skin (cafe-au-lait spots) and endocrine organs (hyperfunctioning endocrinopathies) and is caused by somatic mutations in *GNAS* gene.

Materials and methods: We have evaluated 55 pediatric patients (44 girls (G) and 11 boys (B)) diagnosed in the period of 20 years. Mutation analyses using competitive allele-specific TaqMan® PCR (CAST-PCR) and next-generation sequencing (NGS) techniques were performed to search for *GNAS* mutations in DNA from peripheral leukocytes from 39 MAS patients.

Results: The first clinical manifestation was peripheral precocious puberty in 75% of patients (41/55, G), fibrous dysplasia (FD) - in 20% (11/55, 2G, 9 B) and Cushing's syndrome (CS) in 3 patients (5%, 3/55, 1 G and 2 B). Peripheral precocious puberty, fibrous dysplasia and Cushing's syndrome were seen in very young patients in the first months of life. *GNAS* mutations p.R201C and p.R201H were found in 41% (16/39) of patients with MAS. The prevalence and age of clinical manifestations are shown in table 1.

Conclusion: MAS can manifest in children at the age less than 1 year with precocious puberty in girls, fibrous dysplasia and Cushing's syndrome. CAST- PCR and NGS methods are not reliable for identifying patients with clinically uncertain MAS.

Table 1. (for Abstract no P1-P193)

Clinical manifestations of MAS	% of patients (n=55, 44 G + 11 B)	The age at the time of revealing a clinical finding, y.o.
Fibrous dysplasia	78% (43/55)	0,9 - 13
Cafe-au-lait spots	84% (46/55)	0-3
Girls: peripheral precocious puberty	98% (43/44)	0,2 – 4,2
Boys: macroorchidism	64 % (7/11)	1,7 - 13
Boys: peripheral precocious puberty	36% (4/11)	3,7 - 6
Thyropathies (ultrasound)	35% (19/55)	1,5 - 13
Hyperthyroidism	13% (7/55)	1,5 - 13
Hypophosphatemia	33% (18/55)	2 - 13
Growth hormone (GH) excess	26% (14/55)	4 - 13
Growth hormone-secreting pituitary adenoma	7% (4/55)	11,7 - 13
Cushing's syndrome	9% (5/55)	0,4 - 1
Tachycardia not associated with hyperthyroidism	20% (11/55)	2,5 - 13

Multisystem Endocrine Disorders P2

P2-P284

Endocrine and Metabolic Complications in Children and Adolescents with Sickle Cell Disease: An Italian Cohort Study

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Background: Children with Sickle Cell Disease (SCD) show endocrine complications and metabolic alterations. The physiopathology of these conditions is not completely understood: iron overload due to chronic transfusions, ischemic damage, and inflammatory state related to vaso-occlusive crises may be involved. Aims of this study were to evaluate the growth pattern and the endocrine and metabolic alterations in a cohort of children with SCD and to detect the relationship between these conditions and the SCD severity.

Methods: Fifty-two children and adolescents with SCD [38 homozygous sickle hemoglobin (HbSS) and 14 heterozygous sickle hemoglobin (HbSC); age range 3-18 years] were recruited. Anthropometric [height, body mass index (BMI), arm span, sitting height, target height (TH), and pubertal status] and laboratory [blood cell counts, hemolysis indices, metabolic and nutritional status indices and hormonal blood levels] data were evaluated. The SCD severity was defined according to hematological and clinical parameters.

Results: Height-SDS adjusted for TH and z-score-BMI were significantly higher in HbSC children than in HbSS ones. The 92% (48/52) of the population show at least one metabolic and/or endocrine alteration: insufficiency/deficiency of vitamin D (84.7%), insulin resistance (11.5%), growth hormone deficiency (3.8%), subclinical hypothyroidism (3.8%), and hypogonadism (1.9%). Levels of 25-hydroxy-vitamin D were negatively correlated with clinical indicators of the SCD severity. Subjects with HbSS genotype show significant lower levels of both insulin-like growth factor-I (IGF-1) and insulin-like growth factor binding protein 3 than children with HbSC. In the study group IGF-1 values were positively related with Hb and negatively related with lactate dehydrogenase.

Conclusions: Metabolic and endocrine alterations are very common in children and adolescents with SCD. A regular follow-up is necessary to identify subjects at risk for complications, to precociously initiate an appropriate treatment, and to improve the quality of life of SCD patients.

P2-P285

Bone Marrow Failure in McCune Albright Syndrome

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Background: A somatic activating GNAS mutation leads to the triad of café au lait macules, fibrous dysplasia and precocious puberty known as Mc Cune Albright Syndrome (MAS). We present a patient with bone marrow failure as a rare non-endocrine complication of MAS.

Clinical case: A 2-year-old girl with neonatal giant cell hepatitis, a large right sided café au lait spot and fibrous dysplasia was diagnosed with MAS. The severe polyostotoc fibrous dysplasia lead to a total of 12 fractures, 18 operations, short stature and wheel chair dependency. Over the following years, the patient developed gonadotropin-independent precocious puberty, hyperthyroidism,

FGF-23 mediated phosphate wasting and a breast duct papilloma which were treated accordingly.

At the age of 14 years the patient felt fatigued and the blood count showed pancytopenia. No signs of infection, haemolysis or malignancy were found in the hematologic work up. Her spleen was enlarged to 166 mm. A bone marrow biopsy of the iliac crest revealed fibrous dysplasia without bone marrow cells.

In bone and breast tissue a mutation of the GNAS Locus: (c.601C>T,p.R201C) with activation of the MAPK pathway (pERK positive) was detected. Monthly transfusions had to be initiated 6 months after the onset of pancytopenia. The splenomegaly progressed, causing increasing abdominal pain and respiratory distress. Therefore, a splenectomy had to be performed 1 year after the onset of pancytopenia. Histology confirmed extramedullary haematopoiesis in the spleen. After splenectomy pancytopenia resolved. The patient has now been without blood transfusion for 1 year.

Conclusion: Though fibrous dysplasia is a hallmark of patients with MAS, bone marrow failure is rarely observed. It is still unknown, whether the grade of fibrous dysplasia, the extent of bone reconstruction surgery, the presence of endocrinopathies or a different pathogenetic mechanism trigger the onset of bone marrow failure. Treatment of the extramedullary haematopoiesis with splenectomy is therapeutic and leads to remission of pancytopenia.

P2-P286

Final Adult Height, Insulin-Like Growth Factor 1 (IGF-I) Concentration and Endocrine Complications in Adolescents and Young Adults with B-Thalassemia Major (BTM) Who Received Oral Iron Chelation (OIC) in Comparison with Those Who Did Not Use OIC

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Background: Relatively little is known about endocrine function, bone mineral health, and growth during oral iron chelation therapy (OIC) in β-thalassemia major patients (BMT) on treatment with deferasirox.

Table 1. Growth and endocrine function in adults who received oral iron chelation (OIC) vs those who did not receive OIC before attaining final adult height (for Abstract no P2-P286)

	Group A: OIC	Group B: No OIC
Number of patients	15	40
DM	6.6%	2.5%
IFG	6.6%	17.5%*
Hypothyroid	0.0%	10.0%*
IGF-1 <-2	20.0%	87.5%*
HtSDS < -2	6.6%	52.5%*
Hypogonadism	13.3%	40.0%*

DM: Diabetes mellitus, IFG: Impaired fasting glucose, IGF-1: insulin growth factor-1; SDS: standard deviation score; (*p<0.05).

Aims of the study: To measure the final adult standing height (FA-Ht) and the frequency of endocrine complications in relation to their liver iron content (LIC) and insulin-like growth factor 1 (IGF-I) concentration. Patients were grouped into two groups according to their iron chelation therapy.

Patients and methods: The first group (Group A; 15 patients, 6 females and 9 males) received oral iron chelation therapy (OIC) with deferasirox for 6 years before puberty; the second group (Group B; 40 patients) attained the FA-Ht before the use of OIC (iron chelation therapy with deferoxamine (DFO) given subcutaneously, since the age of 2 years). In both groups LIC was measured using FerriScan ® R2-MRI method.

Results: Patients with BTM who received OIC for 6 years or more before their end of growth were significantly taller and had lower LIC assessed by FerriScan® R2-MRI, and lower fasting glucose level (FBG) and liver enzymes (ALT and AST) concentration, and higher IGF-1 SDS versus those who did not receive OIC before attaining FA-Ht. The prevalence of endocrinopathies, including hypothyroidism, impaired fasting glucose and hypogonadism were significantly lower in Group A versus Group B. The IGF-1-SDS did not differ between the two groups. Neither ferritin level nor IGF-1 concentrations were correlated with the Ht-SDS.

Conclusions: The use of OIC years before the end of puberty was associated with a significantly lower prevalence of endocrinopathies, lower LIC and higher FA-Ht. Proper blood transfusion and early use of intensive oral chelation can improve the final height of patients with thalassemia major.

P2-P287

Endocrine Challenges in Patients with Thalassemia

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Introduction: Beta-thalassaemia is caused by point mutations leading to decreased production of beta-globin, which results in defective red blood cells and ineffective erythropoiesis. Complications are microcytic hypochromic anaemia, extramedullary haematopoiesis and increased intestinal iron absorption due to compensation mechanisms. The resulting iron overload can be aggravated by recurrent blood transfusions necessary for treatment of anaemia and may cause several endocrine complications such as pituitary dysfunction, diabetes, hypoparathyroidism and hypothyroidism. Beta-thalassaemia intermedia/major may only be cured by haematopoietic allogenic stem cell transplantation. In developed countries and with optimal treatment possibilities, patients with severe complications are rarely seen. But unfortunately this is not reality for all children.

Methods: Three refugees from the Middle East came to our institution for treatment late. They all suffered from beta-thalassaemia and had severe complications due to inadequate therapy in their past.

Results: Patient 1, a 14 year old girl was wheel chair bound at admission because of long bone fractures, and was in a very bad health situation with severe cardiac and liver dysfunction and diabetes. Furthermore she suffered from delay of growth and puberty, severe hypothyroidism, vitamin D deficiency and hypoparathyroidism. Patient 2 (sister of patient 1) was 17 year old and presented with delay of growth and puberty and vitamin D deficiency. Patient 3, a 15 year old boy suffered from diabetes, delay of growth and puberty and vitamin D deficiency. Two years of optimal treatment improved his health status tremendously. Thus complications like delay of growth and puberty and vitamin D deficiency were found in all three, diabetes in two, and hypothyroidism and hypoparathyroidism in only one.

We started treatment for all endocrine complications including vitamin D and calcium supplementation, thyroid hormone replacement and functional insulin treatment in patient 1, vitamin D supplementation in patient 2, and functional insulin treatment, vitamin D supplementation, growth hormone treatment and puberty induction in patient 3. The latter was postponed in patients 1 und 2. Treatment of the underlying disease included blood transfusions aiming at suppression of ineffective erythropoiesis as well as chelation therapy to reduce iron overload.

Conclusion: There are special medical challenges in suboptimal treated thalassaemia patients, which include severe endocrine complications. These are seen in refugee children in our units as a result of war and lack of medical care. An interdisciplinary and individual approach is important to improve the health situation of these patients, in whom some permanent damage is unfortunately irreversible.

P2-P288

Can Oral Iron Chelation Therapies Reduce Endocrine Complications in β-Thalassemia Major Patients?

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Objective: β-thalassemia major is an autosomal recessive hemoglobinopathy that needs to blood transfusion for the survival of patients with β-thalassemia. Iron overload as a side effect of transfusion causes some endocrine deficiency in these patients. The injectable iron chelators as an only treatment in the past lead to painful among patients. At present, use of oral iron chelator and increase in patients 'compliance has been successful.

Methods: 72 patients with β-thalassemia major from April 1997 to August 2017 at the Children's Medical Center Hospital in Tehran, Iran, contributed to this research. Depending on the type of iron chelator, individuals were divided into two groups. Group one (39 patients) were receiving oral iron chelator and the group two (33 patients) were taking the injectable once.

Findings: 72 patients, 49% male and 51% female were assessed. The average age of patients was 20.4±5.9 years. Prevalence of IGT, DM and clinical and subclinical hypothyroidism were 17.94%, 5.1%, 17.4%, and 25.64% in group 1 and 18.1%, 9.02%, 24.5% and 24.3% in group 2 respectively. Hypoparathyroidism was not seen in any case and twenty patients had no endocrine deficiency.

Conclusion: The lack of any difference in the incidence of endocrine deficiency between the injectable iron chelator and oral one, suggested use of oral iron chelator as an acceptable treatment among the patients.

P2-P289

Statural Growth and Endocrinopathies in Relation to Liver Iron Content (LIC) and Insulin-Like Growth Factor 1 (IGF-I) Concentration in Adolescents with Beta Thalassemia Major (BTM) and Sickle Cell Disease (SCD)

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We evaluated growth parameters and endocrine disorders in relation to the quantity of liver iron (LIC) measured by the Ferriscan method and insulin-like growth factor 1 (IGF-I) level in a cohort of adolescents with sickle cell disease (SCD) (n =40) and beta thalassemia major (BTM) (n = 52) receiving nearly the same protocol of transfusion and iron chelation therapy since early childhood. Before transfusion, hemoglobin concentration had not been less than 9 g/dl in the past 12 years; subcutaneous daily desferrioxamine was administered for all of them since early childhood (2- 5 years of age). All patients were shifted to oral therapy with Deferasirox iron chelation, 20 mg oral daily for the past 5 years.

Results: BTM patients with severe hepatic iron overload had significantly shorter stature, lower IGFISDS and higher ALT and AST and ferritin concentration compared to thalassemic patients with lower LIC. Patients with SCD with significantly higher LIC had significantly shorter stature, lower IGFISDS and higher ALT compared to SCD patients with lower LIC. Linear regression studies showed significant correlation between LIC and ferritin level in SCD and BTM. LIC and serum ferritin level were correlated

Table 1. Prevalence of Endocrinopathies in adults with SCD and BTM (for Abstract no P2-P289)

	SCD	BTM	p
HtSDS <-2	20%	29%	0.3
IGF-I SDS < -2	27.5%	40.4%	0.2
Hypothyroidism	2.5%	25%	0.0012
DM	10%	30.7%	0.017
IFG	37.5%	15.4%	0.016
Hypogonadism	7.5%	61.5%	<0.001

SCD= Sickle cell disease, BTM = beta thalassemia major, IGF-ISDS = insulin-like growth factor 1 SDS, DM = diabetes mellitus, IFG= impaired fasting glucose.

significantly with IGF-I level in patients with BTM. LIC was correlated significantly with ALT in patients with BTM and serum ferritin was correlated significantly with ALT in both groups. Patients with BTM had significantly lower HtSDS, IGF-I SDS and FT4 level compared to patients with SCD. LIC and mean FBG were significantly higher in patients with BTM compared to those with SCD. Serum Ferritin and hepatic enzyme concentrations did not differ between the 2 groups of patients. (table)

Conclusion: The Prevalence of endocrinopathies especially hypothyroidism, DM, and hypogonadism were significantly higher in BTM patients versus SCD patients and higher in patients with higher LIC versus those with lower LIC.

P2-P290

Successful Treatment of Severe Atopic Dermatitis with Calcitriol and Paricalcitol in an 8-Year Old Girl

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Atopic dermatitis (AD) is a chronic inflammatory disease affecting children and adolescence. The traditional therapeutic options for AD, including emollients topically and immune modulatory agents systemically focusing on reducing skin inflammation and restoring the function of the epidermal barrier, are proven ineffective in many cases. Several studies have linked vitamin D supplementation with either a decreased risk to develop AD or a clinical improvement of the symptoms of AD patients. In this report we present a girl with severe AD who - under adequate supplementation with cholecalciferol, was treated with calcitriol and subsequently with paricalcitol. She had significant improvement – almost healing of her skin lesions within 2 months, a result sustained for 3 years now. Because of hypercalciuria as a side effect from calcitriol therapy, therapy was continued with paricalcitol, a Vitamin D analogue used in secondary hyperparathyroidism in chronic kidney disease. Calcitriol therapy may be considered as a safe and efficacious treatment option for patients with severe AD, particularly for those with refractory AD, under monitoring for possible side effects. Treatment with paricalcitol resolves hypercalciuria, is safe and should be further investigated as an alternative treatment of atopic dermatitis and possibly other diseases of autoimmune origin.

P2-P291

Hypoglycemia in Adolescence as the Presenting Sign of Familial MEN1

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Multiple Endocrine Neoplasia Type 1 (MEN1) is an inherited autosomal dominant disorder caused by mutations in the MEN1 tumor suppressor gene. Penetrance increases with age. It combines mainly hyperparathyroidism, adenomas of the pancreas and pituitary gland. The prevalence is about 2/100 000. Diagnosis in children is rare except in the case of family screening. We report the diagnosis of a familial MEN1 whose index case was an adolescent girl investigated because of hypoglycaemia.

A 13-year-old girl presented with several episodes of immediate postprandial confusion. Blood glucose at the time of confusion was 21 mg/dL and insulin level was 18.2 µU/mL, diagnosing hyperinsulinism. Pancreatic MRI showed a 15-mm nodular lesion likely corresponding to an insulinoma. The systematic search for possible MEN1 involvement in the girl led to the diagnosis of asymptomatic primary hyperparathyroidism (Ca 2.84 mmol/L, PTH 45 pg/mL).

Family history showed renal lithiasis in the father, which prompted the search for primary hyperparathyroidism (Ca 2.75 mmol/L, PTH 108 pg/mL).

A c.136del mutation of MEN1 was identified in the girl.

Surgery allowed for the removal of the insulinoma, and found a second 10 mm-adenoma which was removed at the same time, corresponding to an asymptomatic glucagonoma.

The diagnosis of familial MEN1 can originate from a pediatric index case. In children, the occurrence of pancreatic adenomas, pituitary adenomas, or primary hyperparathyroidism must lead to the careful record of the familial history, and the screening of MEN1 gene mutation.

P2-P292

Aldosterone, Renin, Sodium and Potassium Excretion in Normotensive Prepubertal Children

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Introduction: Previous studies have demonstrated that hypertension may begin early in the life. Under physiological conditions, the Renin-Angiotensin-Aldosterone System (RAAS) is highly variable due to variations in salt intake and other factors, making it difficult to interpret results. We measured aldosterone and renin, and compared them with sodium and potassium excretion in a normotensive pre-pubertal population.

Methods: A cross-sectional study was performed in 40 healthy normotensive children (23 females; 5.2 to 8.9 years old). Office blood pressure (BP) was measured in a seated position using an oscillometric device, according to international recommendations. Normal BP was defined as the mean of 3 determinations lower than the 90th percentile using international references. Systolic and diastolic BP indexes (SBPi and DBPi) are expressed as observed BP/50th percentile BP.

Morning plasma aldosterone and renin were measured by immunoassay (DiaSorin), also electrolytes in serum as well in urine collected after discarding the first morning sample were obtained. Sodium and potassium excretion was assessed by calculating: FENa (100 x (urinary sodium × serum creatinine) ÷ (serum sodium × urinary creatinine)), TTKG (urinary potassium / plasma osmolality ÷ serum potassium / urinary osmolality) and SUSPPUP (serum sodium / urinary sodium ÷ serum potassium2 / urinary potassium).

Results (median [3rd to 97th percentile]): The median age was 7.0 [5.2-8.8] years, and SBPi and DBPi were 1.02 [0.87-1.10] and 1.02 [0.82-1.20], respectively. Concentrations of aldosterone were 12.6 [3.3-48.1] ng/dL and for renin 35.1 [12.6-125.2] µUI/mL. As calculated, aldosterone/renin ratio was 0.38 [0.08-1.19] ng*mL/µUI*dl, FENa 0.34 [0.08-0.95] %, TTKG 8.28 [2.96-16.55], NaU/KU 1.15 [0.19-5.05] and SUSPPUP 6.37 [1.49-37.09] ((mmol L (-1))(-1).

Pearson correlation (r) of aldosterone and renin to electrolytes derived ratios and their statistical significance (* = $p < 0.05$, ** = $p<0.01$) are presented in the table.

Conclusion: In a normotensive pediatric population, renin and aldosterone concentrations were highly associated with SUSPPUP, an equation where small changes in potassium levels are better represented. SUSPPUP could be a complement for an adequate interpretation of RAAS. It is necessary to demonstrate if SUSPPUP in pediatrics subjects is also useful in RAAS related diseases.

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Table 1. (for Abstract no P2-P292)

Pearson correlation (r)	FENa	TTKG	NaU/KU	SUSPPUP
Aldosterone	-0.491**	0.643**	-0.557**	0.811**
Renin	-0.254	0.459**	-0.344*	0.495**

Linear regression analysis showed the following results for SUSPPUP: Aldosterone = SUSPPUP * 1.092 + 6.7 (R2 = 0.66; $p<0.001$) and renin = SUSPPUP * 1.764 + 28.6 (R2 = 0.25; $p= 0.001$).

P2-P293

What is the Impact of a Structured Healthcare Pathway Dedicated to Patients in Transition on their Long-term Follow-up?

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Management of patients presenting a chronic endocrine or metabolic disease during transition period is a challenge for multiple reasons. The department of Adult Endocrinology and Reproductive Medicine in Pitie Salpêtrière Hospital, Paris has been involved in the management of such patients for many years. However, in our own experience, 81% of patients are still followed-up after 1 year, 71% after 3 years and only 49% after 5 years.

Based on such experience, we decided to set up a structured healtcacare pathway dedicated to patients in transition. We built up this program with the Department of Nutrition, the Department of Diabetology and the Department of Endocrinology and Metabolism, all located in the same building in Pitie Salpêtrière Hospital. We associated to this program among others nurses,

dieteticians, psychologists and more recently a coordinator dedicated to this healthcare pathway.

Since september 2016, 273 patients have been included at a mean age of 19 yrs. These patients were mostly referred from Necker Hospital, Robert Debré and Trousseau Hospitals located in Paris and managing children with endocrine disorders. The most frequent chronic diseases were brain tumours (15%), obesity (14%), DSD (11%), Diabetes (10%) and Pituitary deficiencies (9%). Among this population we studied the follow-up pf patients included between September 2016 and February 2017 and analyzed their management after one year, by the end of march 2018. Seventy-none patients were followed-up during this one-year period; seventy-four patients (93.6%) have been currently managed in in-door or out-door clinics. Even if this appears as a very important number of patients, we have to notice that such result depends on the strong involvement of the educative team dedicated to this pathway.

In conclusion, this structured healthcare pathway appears potentially helpful for the management of young adults during transition period. The benefits and the limits of this program will be discussed.

P2-P294

British Society for Paediatric Endocrinology and Diabetes Peer Review of Specialised Paediatric Endocrinology Services in the UK – Evaluation of the Process

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Introduction: The BSPED Peer review programme was developed to provide a regular cycle of independent impartial professional assessment, against agreed quality standards for Specialised Paediatric Endocrine Services (SPES) in the UK.[1] The aim is to continuously promote best quality of care for children and young people with endocrine disorders requiring National Health Service treatment at a SPES. We present here an evaluation of the process during this first review cycle.

Methods: We examined:

1. the format, process and documentation of the review process
2. SPES experiences from questionnaires immediately and at least 6 months after the review.

Results: A Peer Review Officer was appointed by the BSPED to oversee the planning and delivery of this programme. SPES were assessed against the BSPED Quality Standards[1], which comprise 54 criteria, categorised as essential and desirable, in 5 domains: 1.Access to SPES; 2.Resources of SPES; 3.Environment and facilities, care of the child and family/patient experience; 4.Communication; 5.Clinical governance, professional education and training, and evidence base. Information about the SPES to assess against these criteria was obtained from the following:

1. a self-assessment questionnaire (SAQ) completed by the SPES lead
2. SAQ completed by paediatricians in linked secondary care hospitals
3. a one-day SPES visit by a BSPED review team consisting of a senior paediatric endocrinologist, a general paediatrician with special interest in endocrinology and a specialist paediatric endocrine nurse. The SPES visit date was mutually planned at least 6months in advance, comprised interviews with key professionals, trainees and patients, inspection of facilities and review of documents (e.g. medical records, protocols, patient information). Conclusions and recommendations of the assessment were conveyed to the SPES professionals and senior managers face-to-face at the end of the visit and in a written report within 4 weeks.

Twenty BSPED members were designated to undertake the reviews. All 22 SPES (England 18, Scotland 2, Wales 1, Northern Ireland 1) participated. All reviews were completed between 2011 to 2017. All SPES reported that the quality standards were appropriate, the assessment from the review process was fair and it motivated engagement in quality improvements.

Conclusion: This BSPED activity aimed at promoting the quality of SPES in the UK demonstrates the feasibility and acceptability of establishing a nationwide Peer Review programme. The model could also be used by international professional societies such as ESPE or European Reference Networks such as Endo-ERN.

Reference

1 BSPED. UK Standards for Paediatric Endocrinology, 2010. https://www.bsped.org.uk/media/1370/bspedpaediatricendocrinestandards-vs130710.pdf

P2-P295

Paediatric Endocrinology Mapping and Services in Nigeria: A Decade After

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Background: With the inception of the Paediatric endocrinology training centre for Africa and West Africa a decade ago, several endocrinologists have been trained and are practicing in various part of Africa and Nigeria. The services and challenges faced are articulated in this survey.

Objective and hypothesis: To determine the service delivery and challenges faced by paediatric endocrinology units in Nigeria.

Method: A self-administered structured questionnaire survey was given to paediatric endocrinologists practicing in Nigeria during the annual Paediatric endocrinology meeting and also emailed to those who could not attend between November 2017 and February 2018. Questionnaire contained practice setting, patient strengths, equipment availability, drug availability and research capabilities.

Results: There are 37 paediatric endocrinologists practicing in Nigeria and 10 paediatric endocrinology units completed and returned the survey. Most units had standard inexpensive equipment and tools for testing and managing endocrine conditions, but some equipment had to be outsourced and these were expensive. Diabetes remained the commonest condition and most children

are still using mixtard insulin. No center could do iodine uptake studies but drugs for thyroid disorders are readily available. Research capabilities are still rudimentary but basic clinical audit and collaborative studies are being undertaken in various units.

Conclusion:

While so much has been achieved in improving the services for paediatric endocrinology in Nigeria, it is like a flash in the pan considering the population of children that need to be covered.

P2-P296

The Impact of Military Conflict in The East of Ukraine on The Physical Development of Children and Adolescents

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Background: The negative effect of military conflicts on the health of the child population is a proven fact. The consequences of modern military conflicts for the physical development of children are practically not studied.

The aim - of the study is to assess the nature of the physical development of children affected by the military conflict in the East of Ukraine.

Materials and methods: At the 179 girls and 128 boys aged 6-18 years who were in the zone of armed conflict in the East of Ukraine and applied for medical assistance in the SI «Institute for Children and Adolescents Health Care of the NAMS of Ukraine» in 2015-2017 studied the nature of physical development. Mathematical processing of the results obtained was carried out using the SPSS Statistics 17,0 and Excel software packages.

Results: Disharmonic physical development was defined by 41.0% of children (46.0% of boys and 37.3% of girls). Overweight was detected in 23.0% of children, high growth in 10.0%, low growth and insufficient body weight was detected at a frequency of 7.0%. A relationship between the nature of physical development, the sex of the child and his age at the time of the outbreak of hostilities in the East of Ukraine (April 2014) is established. Violation of physical development was most often determined in children whose age in 2014 was less than 7 years (66.7%). Among boys more often detected a low growth, among girls - overweight. In boys, who were 9-10 years old in 2014, on the contrary, twice the age of girls of the same age, excess body weight was determined (42.9% and 27.6%, respectively). It was in this age group in the dynamics of observation more often diagnosed severe form of obesity. It should be noted that overweight was the most common form of physical development disorder in adolescents of both sexes. Deficiency of body weight was detected much less often, mainly in boys, who in 2014 were 11-13 years old (14.6%).

Conclusions: Young children and adolescents at the beginning of puberty, who at this time were in the zone of military conflict in the East of Ukraine, are at risk of developing physical development disorders. In the structure of disharmonious physical development excessive body weight prevails.

Key words: children, adolescents, physical development, military conflicts.

P2-P297

Polycystic Ovary syndrome Metabolic Syndrome Predisposition in Puberty

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This case control study aims at investigating the cardiovascular profile of Greek adolescents suffering from polycystic ovary syndrome (PCOS) by comparing them with age- and body mass index (BMI)- matched non-PCOS controls. Nineteen PCOS patients and eighteen non-PCOS controls (aged 13 to 23 years) were studied for: (i) bioreflex sensitivity (BRS), as a marker of cardiac function, (ii) carotid pulse pressure (PP) and subendocardial viability ratio (SEVR), as markers of arterial stiffness, and, (iii) intima medial thickness (IMT), as a marker of arterial thickness. Non- parametric statistical analysis showed significant differences between PCOS patients and controls in arterial stiffness measured by pulse pressure PP (p=0.006) and SEVR (p=0.0042). No differences were detected in BRS or IMT. As expected, a strong correlation of PP and IMT showed relations between cyclic stress and arterial remodeling (Spearman's Rho coefficient is - 0.603 p=0.023) in carotid (elastic) artery. The arterial stiffness results illustrate early onset of vascular dysfunction, predisposition to hypertension and metabolic syndrome in adolescents with PCOS.

P2-P298

Fanconi-Bickel Syndrome in Sudanese Children, Case Series

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Introduction: Fanconi-Bickel syndrome (FBS), is a rare autosomal recessive disorder of carbohydrate metabolism (FBS, OMIM 227810), caused by defects in the facilitative glucose transporter glut-2, which transports glucose in and out of hepatocytes, pancreatic β cells and basolateral membranes of intestinal and renal epithelial cells. Characteristic features include growth failure, hepatomegaly, glucose and galactose intolerance, fasting hypoglycemia, and renal tubular nephropathy.

Cases: Six patients from different unrelated Sudanese families presented to us with features of FBS. Mean age of presentation was 4.6 months. Male: female ratio was 1:1. All affected children presented in infancy with growth failure and features of rickets. Polyuria was the first symptom to be noticed by the family. Recurrent tachypnea and dehydration wrongly diagnosed as pneumonia or gastroenteritis. Many siblings died undiagnosed with a similar

clinical picture. Features of rickets were prominent on examination as well as abdominal distention and liver enlargement. Investigation confirmed presence of proximal renal tubular acidosis and hypophosphatemic rickets. All cases had fasting hypoglycemia and postprandial hyperglycemia. Clinical diagnosis for most cases were confirmed by liver biopsy, while molecular genetics confirmed presence of SLC2A2 mutation in others.

Conclusion: We are adding more cases of Fanconi Bickel syndrome to the case which we published before to show that Fanconi Bickel syndrome is not uncommon in Sudan where there is a high consanguinity rate. This is the largest series from sub-Saharan Africa. Cases can be missed as the clinical picture at presentation can mimic some of the common local problems such as gastroenteritis and pneumonia. Increase in awareness among paediatricians and easy accessibility to molecular genetics through help from international institutes have helped in diagnosing these cases.

P2-P299

The N309K Pro-Protein Convertase Type 1 (PCSK1) Gene Mutation Causes Lack of Spontaneous Puberty and Primary Amenorrhea

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Introduction: PCSK1/3 gene mutations are known as a cause for congenital diarrhea and various endocrinopathies. Hypogonadotrophic hypogonadism and aberrant pubertal development due to pro-convertase dysfunction was not characterized yet. This study aimed to characterize the pubertal development in a family carrying the novel N309K mutation in the PCSK1 gene.

Methods and Results: We Identified 2 siblings who presented with severe congenital diarrhea followed by overweight and endocrinopathies during early childhood to have a novel homozygous N309K PCSK1 gene-mutation.

The female developed severe congenital malabsorptive diarrhea and was kept on parenteral nutrition for 5 years. L- thyroxin replacement was administered for central hypothyroidism diagnosed at 2 years of age. Poor growth rate and low GH response in stimulation tests lead to GH therapy. Severe obesity was noticed since the age of 6 years with BMI -21.6.

Pubertal development started late at 12 years with breast developing only up to Tanner stage 2. No menarche occurred by the age of 14 years. Basal and LHRH stimulated LH levels were low. Estradiol levels were undetected.

Gradual replacement therapy with Estrogen at 14 years of age resulted in pubertal progression with secondary sexual signs, addition of progesterone achieved menarche and regular periods.

Conclusions: This case illustrates the crucial role of the prohormone convertase 1/3 PCSK in processing of LHRH, LH and FSH and enabling normal pubertal development in females. The novel homozygous N309K mutation causes severe obesity associated with hypogonadotrophic hypogonadism and primary amenorrhea that fully respond to hormonal replacement therapy.

P2-P300

Somatostatin experiment in Prohormone Convertase Deficiency

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Introduction: Prohormone convertase (PC) is a calcium-dependent serine endoprotease.

PC 1/3 is responsible for converting hormones and neuropeptitids which has role on energy homeostasis, food intake,glucose metabolism (a-MSH,CART, NPY, AgRP, Orexin, Hypocretin, Ghrelin, insulin, cholecystokinin,GLP-1, GHRH, GnRH, ACTH,TRH) from proforms to active form.

PC 1/3 deficiency's clinical signs are diarrhea that started in the newborn period, obesity, hypoglycemia, multiple pituitary hormone insufficiency in the infant stage is observed.

Case: A 4-month-old male patient was admitted to our hospital with diarrhea, dehydration, metabolic acidosis. It was learnt that the diarrhea began when he was 12 days old. The patient was consulted to our department because he had hypoglycemia while receiving intravenous fluid and total parenteral nutrition therapy. In the family history of the patient, the mother and father were first degree cousins. In his physical examination his weight was: 4590 gr (-2.93 SD), height :58.5cm (-2.13 SD), BMI: 13.1 kg/m² (-2.78 SD), blood pressure: 55/pulse, thyroid stage 0, tanner stage 1, penis length 2cm (<10p), calibration was fine. While the patient's serum glucose level was 44 mg/dl, blood ketone negative, cortisol and insulin levels were normal but growth hormone was detected to be low. As a result of the laboratory (Table 1), central hypothyroidism was detected and LT4 therapy was initiated. The patient's proinsulin: 1300 (3-20pmol/L), Insulin: 12.7 (2.6-25 uIU/mL) were detected. In the genetic analysis of the patient who was diagnosed with Prohormone convertase deficiency, a new mutation of IVS4-2A> G (C.544-2A> G) homozygote was detected. Central hypothyroidism, central adrenal insufficiency and diabetes insipitus were included in the follow up observation of the patient. Somatostatin therapy was started after the catheter was removed from the patient with hypoglycemia due to catheter infection. The patient's hypoglycemia was put under control with somatostatin therapy.

Conclusion: Hypoglycemia due to proinsulin elevation is seen in cases with Prohormone convertase 1/3 deficiency. Although there are cases of postprandial hypoglycemia in the literature, the corresponding treatment is not shared. Our case hypoglycaemia was prevented by somatostatin therapy. This case is shared because

Table 1. Laboratory values of Prohormone Convertase Deficiency (for Abstract no P2-P300)

fT4	0.66	0.92-1.99 ng/dl
TSH	4.37	0.73-8.35 uIU
ACTH	12.9	0-46 pg/ml
Cortisol	16.2	6.2-19.4 ug/dl
FSH	1.85	0.16-4.1 IU/L
LH	<0.1	0.02-0.3 IU/L
T. Testosteron	<0.025	0.003-0.010 ng/mL

of a new mutation being identified in Prohormone Convertase Deficiency and the first somatostatin experience in the treatment of hypoglycemia.

Multisystem Endocrine Disorders P3

P3-P265

Insulinoma as Initial Presentation of Multiple Endocrine Neoplasia Type 1

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Background: Multiple Endocrine Neoplasia type 1 (MEN1) is a disorder with autosomal dominant inheritance pattern. It is characterized by the occurance of parathyroid, pituitary and pancreatic tumors. MEN1 presented by insulinoma as first presentation in children is very rare. On the other hand insulinoma affects 10% patients with MEN1 and occurs usually in young patients.

Case: Eleven years and eight months old girl was admitted, after a syncopal episode due to neuroglycopenia. For the previous 2 months she had experienced headaches, subsiding after a meal. Her fasting tolerance was limited to 2 hours. Her father was diagnosed with MEN1 manifested with insulinoma at the age of 20 and subsequently with hyperparathyroidism.

Laboratory results revealed hyperinsulinemic hypoglycemia. Abdominal MRI scan showed pancreatic lesion 11x8,5x3,5 mm localized in uncinate process. ^{68}Ga-DOTATATE PET/CT scan confirmed pancreatic nodule with high SSTR expression. No other lesions were found. Serum calcium level and PTH level were normal.

She was referred for pancreatic surgery. Before surgery she was treated with diazoxide (4mg/kg/d) with a good response. After pancreatic tumour enucleation, hypoglycemia resolved. The diagnosis of insulinoma was confirmed by histological examination.

The patient is under continuous endocrine control. In 7 months of follow up she remained euglycemic and without symptoms of other pathologies connected with MEN1 syndrome.

Conclusions: Insulinoma is a rare initial manifestation of MEN1, especially in children. In presented case positive family history of MEN1 helped to establish diagnosis and begin proper treatment.

Genetic examination in offsprings should be the mandatory element of medical care of adult patients with potentially life threatening inherited diseases.

P3-P266

Assessment of Ovarian Reserve in Young Women with Hashimoto Disease - The Pilot Study

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Introduction: Human ovary is commonly the target of an autoimmune attack in cases of organ- or non-organ-specific autoimmune disorders. Hashimoto's thyroiditis (HT) is likely to be associated with ovarian dysfunction and diminished ovarian reserve. The classical hormonal test assessing ovarian reserve as early follicular phase serum levels of *follicle-stimulating hormone* (FSH), inhibin B and estradiol (E2), which are interdependent, and the calculation of the number of antral follicles by transvaginal ultrasonography have some inconvenience in very young girls. Anti-Muellerian Hormone (AMH), a relatively new marker of the ovarian reserve. Serum AMH levels increase during the first two decades of female live and then decrease gradually with age, and the levels become undetectable after menopause.

The aim: The aim of the study was to assess the ovarian reserve in young women with HT using the evaluation as well classical hormone methods (FSH, E2, Inibin B) as a measurement of AMH.

Material and methods: There were 21 patients treated due to Hashimoto disease, median age 15.6 yrs, and 17 healthy age-matched controls included to the study. In the group of patients with HT, 8 patients have additional T1DM diagnosed, so they presented with type 3 autoimmune poliendocrinopathy (APS 3). In all participants FSH, LH, estrogens, PRL, SHBG, TSH, fT4, anti-TPO, AMH, and Inhibin-B, if possibly in 3-5th day of the menstruation cycle were measured.

Results: As well FSH, E2, and Inhibin-B, as AMH levels did not differ statistically between group of patients with HT and healthy controls. Moreover we did not find any differences regarding parameters assessing ovarian function and reserve between patients with only HT and those with APS 3. Moreover levels of LH, SHBG, PRL, and fT4 did not differ in patients with HT, including APS 3 than in controls. Only TSH levels were significantly higher in HT group than in the control group ($p = 0.02$). Body mass index (BMI) of HT patients did not differ statistically from BMI of healthy controls.

Conclusion: The results of our study did not indicate that young patients with HT, including those with APS 3 have impaired ovarian reserve or function.

P3-P267

Unusual Clinical Presentation of Autoimmune Polyendocrinopathy Type 1

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Background: Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) or autoimmune polyendocrinopathy type 1 (APS-1) is a rare monogenic autosomal recessive disease due to pathogenic variants in the *AIRE* gene. APECED usually begins during early childhood with chronic mucocutaneous candidiasis (CMC), followed by hypopathyroidism (HP) and Addison's disease (AD); however, other endocrine and non-endocrine components may occur with a different prevalence.

Case Presentation: We report on a boy affected by APS-1 who presented with cutaneous vasculitis followed by psychomotor delay interpreted as autism spectrum disorder when he was 10 and 26 months old, respectively. He was referred to our clinic for the first time at 3,1 years of age, for hypocalcemic seizures. The autoantibody profile (OS and NOS) performed at that time was negative as it was Catch 22 analysis and array CGH. A congenital hypoparathyroidism was suspected and treatment was started with alfa1 calcidiol, Ca, Mg and Teriparatide supplementation. During subsequent follow up, anti TPO antibodies (Abs) appeared and raised progressively with anti adrenal Abs positive only once and no other Abs positivities until now. Clinical signs of gastrointestinal (episodes of recurrent diarrhea) and cutaneous autoimmune involvement (vitiligo) occurred later. No mucocutaneous candidiasis, hypothyroidism or adrenal insufficiency are clinically present until now. The *AIRE* gene analysis showed a compound heterozigosis with a frameshift and a potential causative missense mutations inherited from non consanguineous parents.

Conclusion: The clinical picture of APS-1 may be characterized by rare or atypical isolated or immune-mediated autoimmune manifestations, even years before the beginning of the classical components of the disease. Among these uncommon features there may be rashes of variable shape and duration, with the histological characteristics of vasculitis. At our knowledge, this is the first case with a presentation characterized by neurological alterations interpreted as autism spectrum disorders. Although it is not easy to discriminate between neurological symptoms due to a separate disease and neurological manifestations due to unrevealed hypocalcemic levels, we outline the heterogeneity of presentation of APS-1 and the need to think to this clinical entity, even when very unusual symptoms are present. After the substitutive treatment the patient did not repeat hypocalcemic seizures and showed a significant improvement of his neuromotor and behavior development.

P3-P268

Glycemic Abnormalities and Normal Thyroid Function in Adolescent Survivors of Childhood Acute Lymphocytic Leukemia Who Required Repeated Packed Red Cell Transfusion During Treatment

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Introduction: Packed red blood cell (PRBC) transfusions are an essential component of leukemia treatment regimens. Transfusion-induced iron overload can be seen after approximately 10 to 20 transfusions. Very little is known about transfusion-related iron burden in oncology populations and its possible effect on endocrine function and glycemia.

Patients and Methods: We evaluated growth parameters and endocrine disorders in relation to the iron overload status measured by serum ferritin concentration and the quantity of liver iron (LIC) measured by the Ferriscan method in 7 adolescents aged 16 +/- 1.5 years treated with conventional chemotherapy for acute lymphocytic leukemia (ALL) between 2-4 years post diagnosis, who received more than 10 packed red cells transfusions (PCT) during their treatment. Anthropometric measurements were recorded and height SDS and BMI were calculated. Lab investigations included measuring hepatic enzymes (ALT, AST, and ALP), fasting blood glucose (FBG) and thyroid function (free T4 and TSH).

Results: The mean HtSDS of patients = -1.25 +/- 0.53, and their mean BMI = 24 +/- 5.2 kg/m2. None had HtSDS < -2 and 1 had BMI > 30 (Obese). They all had normal hepatic enzyme concentrations (ALT, AST and ALP) and renal function. Their mean serum ferritin = 853 +/- 480 ug/L and their LIC ranged between 1.2 and 5.6mg Fe/g dry liver (mild iron liver iron overload). All had normal FT4 and TSH levels. 1 had diabetes (BMI = 24, FBG = 7.4 mmol/L, ferritin level = 1600 ug/L and LIC = 3.3 mg Fe/g dry liver) and another one had impaired fasting glucose (BMI = 20.4, FBG= 6.5 mmol/L, ferritin level 1250 ug/L and LIC = 3.4 mg Fe/g dry liver).

Conclusion: Adolescent survivors of childhood ALL with a history of repeated PCT and serum ferritin >1000 ug/L had a higher risk for developing glycemic abnormalities and they may need iron chelation and follow up of their glycemic status.

P3-P269

Graves' Disease in Children With T1DM: A Report of Three Cases

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Objectives: Type one diabetes mellitus (T1DM) is an autoimmune disorder that is yet the most common type of diabetes in children and adolescents. Therefore, children and adolescents with T1DM are at increased risk for developing other autoim-

mune diseases including Graves' disease. Detection of thyroid abnormalities in children is crucial since thyroid dysfunction can affect growth, pubertal maturation, insulin metabolism and gastrointestinal function. Herein, we reported three T1DM cases with Graves' disease.

Methods: This is case series report to describle clinical features and laboratory manifestations of patients with diabetes and Graves' disease.

Results: Three girls with onset age were at 7.5 ± 4.9 years. All cases admitted with the features of polydipsia, polyuria and weight loss. On admission, they presented with tachycardia, exophthalmus, diffuse goiter grade 3 and low weight with BMI of 13.7, 11.6 and 8.9 kg/m^2 respectively. They had not diabetes ketoacidosis and history of diabetes in her family. Laboratories showed that blood glucose levels of 21.7± 2.8 mmol/l; HbA1C of 9.99 ± 1.26 %; C-peptide 1.17 ± 0.22 nmol/l; T_3 4.6 ± 0.5 nmol/l, T_4 151.4 ±32 nmol/l, TSH <0.01 mUI/l, Trab 15 ± 4.9 UI/ml (normal range 1-1,58), anti TG 1176.3 ± 870.8 UI/l (normal range <115), anti TPO 1024 ± 946 UI/ml (normal range <34). All cases have been treated with insulin, thyrozol and propranolon.

Conclusions: All patients with T1D should be screened for hyperthyroidism to have early diagnosis and treatment.

P3-P270

Case Report: Neonatal McCune-Albright Syndrome with Juvenile Ovarian Granulosa Cell Tumor in a 4 Months Old Girl

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Introduction: McCune-Albright syndrome (MAS) is a rare disease resulting from a somatic activating mutation of GNAS1 encoding the Gs-alfa subunit of the G-protein coupled membrane receptor responsible for multiple hormonal signaling cascades leading to the classical trias: polyostotic fibrous dysplasia, café-au-lait hyperpigmentation and GnRh independent precocious puberty. Early manifestation is accompanied with multiple organ involvement and may lead to ACTH-independent hypercortisolism, hyperthyroidism, cardiac alterations, hepatopathy and GH-Excess in addition to the classical trias.

Case report: We report a case of neonatal MAS in a girl with apparent manifestation at the age of 6 weeks with ACTH-independent Cushing syndrome, HOCM, hyperthyroidism, hepatopathy, bilateral nephrocalcinosis and autonomous ovarian cysts besides the café-au-lait hyperpigmentation. We describe the clinical course with initial metyrapone therapy to control hypercortisolism. Side effects as hypertension and hyperandrogenemia were observed. The girl developed hypercalcemia at the age of 3 month with the need of bisphosphonate therapy. The course was complicated by appearance of acute abdomen at the age of 4 months, caused by a ruptured large juvenile ovarian granulosa cell tumor. Tumor cells contained highly expressed androgen receptors. It can be assumed that high androgen levels as side effect of metyrapone therapy have caused rapid growth of ovarian tumor cells. Bilateral adrenalectomy was performed to stop hyperandrogenemia at the age of 5 month in head of the tumor. Activating mutation in the GNAS-Gen (c.602G>A; p.R201H) was found in the ovarian tumor cells and in the adrenal glands.

Conclusion: Early manifestation of MAS is accompanied by multiple organ involvement. Juvenile granulosa cell tumor (JGCT) is a rare tumor. Activating GNAS mutation can be found in JGCT cells. JGCT has not been described in MAS. Metyrapone is effective to control hypercortisolism but leads to high androgen levels. It has to be taken into account that high androgen levels under metyrapone can cause rapid growth of existing tumor cells as observed in this case.

P3-P271

Polyostotic Fibrous Dysplasia of McCune Albright Syndrome Responding to Intravenous Zoledronate Therapy

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Introduction: McCune Albright Syndrome consists of at least 2 of the following 3 features: (1) polyostotic fibrous dysplasia (PFD), (2) Café au lait macules and (3) autonomous endocrine hyperfunction (eg, gonadotropin-independent precocious puberty). Other endocrine syndromes include hyperthyroidism, acromegaly, and Cushing syndrome.

Case: 2 year old girl presented with severe hip pain, inability to walk and progressive deformity of right lower limb. Basic workup suggested a hip lesion suspicious for fibrous dysplasia. She was referred to us for further evaluation. On examination she had extensive Café au lait macules over the back. Further inestigations showed thyrotoxicosis (T4: 10.92 mcg/dl and TSH 0.01 mcIU/ml). Technitium scan of the thyroid showed large toxic nodule in the right lobe. CT brain showed craniofacial fibrous dysplasia. Hence the diagnosis of "McCune Albright Syndrome" (Polyostotic fibrous dysplsia, Café au lait macules and thyrotoxicosis) was made.

She had severe pain in the right lower limb. Hence it was decided to give bisphosphonates. She was started on I.V. Zoledronate 0.0125 mg/kg dosage. She was also started on Carbimazole 5 mg/day. Her pains reduced significantly in the follow up visit (>3 months) and she was able to walk. She was given I.V. Zoledronate 0.025 mg/kg once in every 3 months. Carbimazole was continued at 5 mg/day. Her phosphate excretion (TmP/GFR) was normal.

After 6 months, she had an episode of vaginal bleeding (FSH: 1.27 IU/l, LH: 0.13IU/l). She was given Letrozole 2.5 mg/day, after which she didn't have any vaginal bleed. Her T4 levels increased and TSH suppressed on follow up. We had to uptitrate the Carbimazole dosage for that..

With three monthly Zoledronate injection she is pain free now and able to walk.

Conclusion: I V Zoledronate is a good option in the management of painful fibrous dysplasias. Letrozole is very effective in controlling peripheral precocious puberty in McCune Albright syndrome.

P3-P272

Two Cases of Costello Syndrome and literatures Review

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Objective: To investigate the clinical features and genetic characteristics of HRAS-associated Costello Syndrome. **Method:** Characteristics of clinical data and gene mutation of two cases Costello Syndrome in XX hospital were retrospectively analyzed. The related literature was searched by using search terms"HRAS"or"Costello Syndrome".

Result: Both patients were presented with mental retardation, growth retardation,postnatal feeding difficulties and characteristic facial appearance,and carried the same HRAS gene mutation site Exon2 c.34g>a P. (Gly12Ser).Moreover,the patient 1 had seizure at toddler age, and patient 2 had neonatal intractable hypoglycemia.A total of 18 articles in English and 2 articles in Chinese were retrieved. The main clinical features of 20 patients included feeding difficulties, characteristic facial appearance, mental retardation, growth retardation,and accompanied with cardiovascular, skeletal muscle or central nervous system abnormalities.

Conclusion: Costello syndrome is a rare multisystem disorder accompanied by tumor predisposition.It is vital to comfirm the diagnosis through the identifcation of a specifc germline mutation in the HRAS. In addition,early intervention treatment and tumor monitoring are necessary.

P3-P273

Endocrine Complications in Beta-Thalassaemia Major Children

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Introduction: Beta-thalassaemia major is an inherited anemia which requires chronic transfusions and is frequently associated with endocrine dysfunctions secondary to iron overload.

The aim of this study was to identify the prevalence of various endocrine complications in beta-thalassaemia major children over a period of 14 years and the factors associated with them.

Materials and methods: 61 children with BTM (mean age 12.23 years) registered at the Endocrinology Department of Elias University Clinical Hospital from February 2004 to March 2017 were evaluated and data related to chelation and transfusion treatment were collected.

Results: From 61 children, 33 (54.1%) were girls and 28 (45.9 %) were boys. Seventeen (27.9 %) had short stature. Eight of the patients (13.1%) were diagnosed with hypothyroidism. Hypogonadotropic hypogonadism was the diagnosis in 12 children (34.3 %) aged 12 years and more. The most prevalent type of hypogonadism was delayed puberty, documented in 6 (17.1 %) children. Ferritin levels were significantly higher in patients with short stature compared with those with normal stature (2457.67 ng/ml vs 1296.47 ng/ml, p=0.001). However, no association between serum ferritin concentration and the presence of hypothyroidism or hypogonadism was found. The presence of either hepatitis B or C was not associated with short stature, hypogonadism or hypothyroidism. Children with hypogonadism started the transfusion treatment at a younger age compared with eugonadic ones (8 months vs 33 months, p=0.05).

Conclusion: Endocrine complications occur with a high prevalence in Romanian beta-thalassaemic children, hypogonadism being the most frequent. High levels of serum ferritin were associated with the presence of short stature. Transfusional treatment started at a younger age was more prevalent in children with hypogonadotropic hypogonadism.

Key-words: thalassaemia, endocrinopathies, iron overload.

P3-P274

The Case of Combination of Multinodular Goiter and Sertoli-Leydig Cell Ovarian Tumor Due to Mutation in *DICER1* Gene

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Background: Pathogenic germline DICER1 variants cause a hereditary cancer predisposition syndrome with a variety of manifestation. In addition to conferring increased cancer risks for pleuropulmonary blastoma (PPB) and ovarian sex cord-stromal tumors, particularly Sertoli–Leydig cell tumor, individuals with pathogenic germline DICER1 variants could also have lung cysts, cystic nephroma, multinodular goiter, ciliary body medulloepithelioma, genitourinary embryonal rhabdomyosarcoma and brain tumors including pineoblastoma and pituitary blastoma.

Objective: The girl presenting at 16 years with complains of voice coarsening, irregular menstruation, clitoral hypertophy, pulling pains in the lower abdomen and about the multinodular goiter diagnosed during clinical examination.

Anamnesis: Menarche was at the age of 11, regular menstrual cycle was until the age of 13, after irregular. The last menstruation at the age of 15. Voice coarsening was revealed from the age of 14. A multinodular goiter was identified at the age of 16 (histologically – colloid goitre). At the same time, a hormonal examination was performed: LH 17.2 IU / L (2.4-5.4), FSH 2.59 IU / L (1.9-3.7), estradiol 18.35 pmol / l (143-264), testosterone 8.85 nmol / l (0.6-2.3), DHEA-S 6.13 μmol / L (0.9-11.7), androstenedione 30.2 nmol / l (1-12, 2), TSH 1.25 mIU / L (1.3-4.9), f.T4 15.3 pmol / L (10-25).

Pelvic Ultrasound: a tumor (11.0 x 7.5 x 11.0 cm) with a dense capsule, inhomogeneous with multiple cystic components was detected in the right ovary.

Oncomarkers (CA19-9, HE-4, alpha fetoprotein) were negative.

The patient underwent the resection of the right ovary. Histological examination: Sertoli-Leydig cell ovarian tumor with areas of hemorrhage and decay.

The hereditary history: a multinodular goiter in the mother.

Methods: 'Pituitary adenomas panal' genes were sequenced using a custom Ion Ampliseq gene panel and PGM semiconductor sequencer (Ion Torrent).

Results: A heterozygous mutation p.A969CfsX5 was found in DICER1 gene.

P3-P275

Unusual case of Autoimmune Polyglandular Syndrome

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Background/Aims: Incidence of Autoimmune disease dramatically increases in children and adolescents in the past decades. But in other hand case of APS is rare. Signs and symptoms appear with different combination during the lifespan in different patients. Here we report case of APS syndrome with unusual presentation.

Case presentation: Patient 16,4 years old boy with diabetes mellitus since the age of 2,6 years. Mother died at age 40, when boy had 5 years, with gastric cancer, after that he had psychological problems. At the age of 12,6 years were diagnosed hypothyroidism-autoimmune thyroiditis, after that he received L-thyroxine. At the age of 14 appears problems with the skin, that at first was diagnosed as Psoriasis. Last hospitalization - at the age of 16,4 years with clinical features of severe anemia. Based on clinical and paraclinical data analyses and catamnestic observation (The child had the same anemia at the age of 13 years, which was cut with appropriate treatment), this case was diagnosed with megaloblastic anemia caused by a B-12 deficiency. The situation was stabilized after therapy of vitamin B12, without glucocorticoids. After that, the boy was consulted with the dermatologist and diagnoses of psoriasis were changed with cutaneous candidiasis after diagnostic test. A physical examination shows retardation of growth (since 11 years) weight -32kg-(-4,91SDS), height-147cm(-3,3SDS), Tanner stage 2 pubic hair development, testes<4ml, penile length-5cm. His bone age was 13 years by the standards of Greulich and Pyle at a chronological age of 16 years. Insulin daily requirement- 1,1U/kg, L-thyroxine-100mcg/day. Electrolytes: K, Na, Ca, P-were normal. Complete blood count: Hb-5,2g/dl, Ht-16%, anaemia is macrocytic(MCV>105fL), reticulocyts count is low, tr-52, Ieik-2,4(Pancytopenia). Bone marrow: hypercellular with large erythroblasts, giant and abnormally shaped metamyelocytes. Serum B12 is low<51ng/l. In ultrasound liver is always enlarged since 11 years by 2-4cm, ALT-65U/L, AST-36U/L, Cortisol-531,48ng/ml, Mean HbA1c-7,3%, TSH-2,4mIU/l, Anti-TPO-216,5 IU/ml, Anti-Tg-76,4 IU/ml.

Conclusion: Patient 16 years has DM, AIT, Pernicious anemia, cutaneous candidiasis, hypogonadism, that we give a possibility to diagnose APS. We think, that it is type 1 syndrome, although genetic testing for the AIRE gene was not made because of financial problems. Early identification of this syndrome gives us a chance to for early detection and proper management of associated conditions and its complication with maximal efficacy.

P3-P276

Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy: A Case Report

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Introduction: Autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy (APECED) is a rare hereditary disorder with autoimmun manifestations affecting both endocrine and non-endocrine tissues. It is caused by mutations in the autoimmune regulatory (AIRE) gene which is defined by the presence of two of the three major components: Chronic mucocutaneous candidiasis, autoimmune hypoparathyroidism and Addison's disease. Clinical manifestations may be developed during early years of life and may continuous throughout decades. Moreover, the syndrome also includes many other autoimmune diseases such as type 1 diabetes mellitus, idiopatic trombositopenic purpura, pernicious anemia, chronic active hepatitis, vitiligo, alopesia, Hashimoto thyroiditis and sistemic lupus eritematosus.

Here, we present a case with APECED from a consangineus family, who had mucocutaneous candidiasis, hypoparathyroidism, Addison's disease, Hashimoto thyroiditis, pernisious anemia and trombositopenia.

Case Report: Our case was a six years old boy who was presented to our outpatient endocrinology clinic with nause and vomiting, fatique, hypopigmentation, constipation and diarrhea attackes. He had a convulsion due to hypocalcemia and hypoparathyroidism. On physical examination, he had mucocutaneous candidiasis, alopesia, teeth-nail deformations and normal vital signs. On laboratory examination, anemia, trombositopenia, hypoglycemia and hyponatremia were determined. The results of ACTH stimulating test confirmed primary adrenal insuffiency. Genomic DNA from the periferal blood lymphocytes was extracted with QIA amp DNA Blood Mini Kit (Qiagen GMBH, Hilden, Germany) using standard procedures. AIRE gene mutation analyses has demostrated a homozygous missense mutation p.Arg15 His (c.44G>A) in exon 1. Mutation analyses of the both parents have revealed heterozygous mutation p.Arg15 His (c.44G>A) in exon 1.

Conclusion: Although first clinical manifestation of APECED usually begin in childhood, appearence order of other components might be delayed to make diagnosis more challenging. In case, patients might be undiagnosed or misdiagnosed. Clinicians should be aware of this antity in terms of endocrine and non endocrine problems, because of the broad clinical spectrum. In many cases, the diagnosis should be considered presenting at least one of the major clinical manifestations because of its high morbidity and mortality.

P3-P277

Wolman Disease: Long-term Endocrine and Metabolic Comorbidities

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Introduction: Wolman Disease [WD] is a rare, autosomal recessive disease caused by lysosomal acid lipase deficiency and characterized by accumulation of cholesterol-esters and triglycerides primarily in the liver and spleen. Patients present within the first year of life with a rapidly progressive disease.

Case: A girl born to consanguineous parents was diagnosed with WD due to characteristic manifestations and family history (genetically confirmed). At the age of 2 months (ms) she underwent allogeneic cord blood transplantation (SCT) with conditioning therapy of TBI, antithymocytic globulin & Cytoxan. The girl continued follow-up for 16 years (yrs) at a single center.

Growth: At 5yrs, she underwent growth hormone (GH) stimulation testing due to short stature (height -2.4s.d.), with normal GH secretion. Due to continued growth deceleration (height -3.1s.d.) at the age of 7.5yrs, GH axis was reassessed with normal response. IGF-1 levels were mildly elevated with continuous increase above +2SD over time. All other pituitary hormones were normal. OGTT showed normal GH suppression. IGF-1 receptor gene analysis revealed a novel heterozygous benign variant. By 14yrs, final height was reached (-4.5s.d.) and IGF-1 levels normalized spontaneously.

Puberty: Adrenarche started at the age of 9.6yrs, gonadarche started 8ms later and proceeded spontaneously despite elevated FSH and low AMH levels. She had menarche at the age of 11.4yrs with regular menses since then. At the age of 15.7yrs, AMH levels were sub-normal, with a decrease in FSH levels to normal range.

Thyroid: Immediately after BMT, she developed hypothyroidism and was treated with thyroxin replacement.

Adrenal: Normal response of cortisol post standard-dose ACTH stimulation tests at diagnosis and throughout follow-up.

Metabolic: BMI was constant at the 50th percentile. OGTT at 10.4yrs demonstrated impaired glucose tolerance. After completion of puberty, we observed continued elevation of HbA1c levels up to 6.6% (normal 4.6-5.7%) with impaired fasting glucose, impaired glucose tolerance and hyperinsulinemia. At the age of 12yrs, she developed hypertriglyceridemia. At the age of 13.5yrs she was diagnosed with non-alcoholic fatty liver. Metformin treatment with dietary changes partially improved HbA1c levels (6.2%), hypertriglyceridemia and non-alcoholic fatty liver disease.

Conclusion: WD is a rare disease. We present long term follow-up of a girl with WD treated with SCT at the age of 2ms, formerly presented at the age of 4yrs with only hypothyroidism. Continuous follow-up for more than 16yrs revealed significant endocrine and metabolic consequences. We recommend continued follow-up for development of endocrine and metabolic complications.

P3-P278

Pallister Hall Syndrome: With a Varied Spectrum of Endocrine Disorders

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Introduction: Pallister Hall Syndrome (PHS) is a rare autosomal dominant disorder clinically diagnosed by hypothalamic hamartoma, mesoaxial or postaxial polydactyly, and can have several endocrine abnormalities associated with.

Case: We report a case of a 7year old boy presented with precocious puberty and short stature. He was the youngest of 11 siblings, who used to have laughing spells and global developmental delay till four years of age.

He had an MRI, which showed a hypothalamic hamartoma, and a normal EEG. Following which he developed generalized tonic-clonic seizures lasting a few minutes following which he used to sleep for 2-3 hours; accompanied with the laughing spells, uncontrolled on anti-epileptics. The boy continued to have speech and cognitive delays. The child started pubarche at 6 six years of age and was brought to us at 7 years for evaluation of puberty. He was diagnosed as proband Pallister Hall syndrome with precocious puberty with hypothyroidism with gelastic and generalized tonic clonic seizures.

He was started on a combination on phenytoin and levetriacetam, thyroxine 50ugms, and GnRH analogues. Surgery was deferred in this case and the child is under regular follow up.

Conclusion: It however needs a high index of suspicion and knowledge of the spectrum of neurological and endocrine associations to monitor and treat such children.

P3-P279

Near Electromagnetic Fields – Induced Syndrome: Unsuspected and Newly Recognised

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This present study investigates the impact of a common environmental hazard, the radiofrequency fields (RF), such as those regarding cell phones, cell phone base stations, wi-fi, portable phones (DECT), etc., as close to the body sources of exposure, on endocrine function. This is of importance, particularly for developing children, that have been and are exposed to this potential hazard. We performed analyses on endocrine assessments regarding stress, thyroid hand reproductive hormones, as well as melatonin and several growth factors. Both the acute response and circadian disturbances were also addressed. The studies are presented in accordance to the end-organ responses evoked after the hypothalamus-pituitary (HP)-end-organ response of the five main endocrine axes: adrenal axis (HPA), thyroid HPT and

gonadal (HPG axis) axes, somatotropic axis and other hormones, such as melatonin. According to the reported findings it is evident that endocrine axes are influenced by the exposure to RF even at frequencies lower than the limits set by the International Commission on Non -Ionizing Radiation Protection (ICNIRP) guidelines. Prolonged exposure suppresses thyroid function, melatonin and growth hormone circadian rhythms, suggesting that there is a Near Electromagnetic Field (NEMF)-Induced syndrome (NEMF-IS). Even blue light smartphones used during the night may disrupt circadian rhythms, suggesting prudence in their use. Endocrine effects are age-, frequency- and/or long-term cell phone use - dependent and appear to be modulated by the thyroid axis.

Thus, the thyroid axis emerged as a key player in the body's attempt to maintain homeostasis during/after RF exposure. The nuclear receptor interactome, which involves all endocrine axes, is structurally and functionally conserved in evolution and may provide explanatory mechanisms. Importantly, its major hub is a thyroid hormone signaling modulator, the nuclear receptor coreceptor 1 (NCOR1).

P3-P280

Polycystic Ovary Syndrome Gene/Gene Products Interaction Network

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Aim: This study aims to screen the genes/gene products associated with the polycystic ovary syndrome (PCOS) and to predict any possible interactions among them with high confidence. These interactions networks could contribute to the better understanding of PCOS pathophysiology and help generate new hypotheses

Methods: Systems medicine approach using STRING v10.5 database and confidence level 0.7, interactions networking.

Results: We created a highly interconnected network of 48 nodes, of which insulin (INS) was the major hub. INS upstream and downstream analysis revealed that kisspeptin and glucagon are upstream, while reproduction and other endocrine gene/gene products are downstream.

Conclusion: PCOS's different underlying pathogenetic factors, phenotypes and suggested remedies need to be re-weighed and re-assessed.

P3-P281

Basal Metabolic Rate as Moderator of Inflammation in PCOS

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This prospective population study focuses on metabolic differences between adolescent patients with polycystic ovary syndrome (PCOS) and age/BMI matched non-PCOS controls recruited by the Centre for Adolescent Medicine and UNESCO Chair on Adolescent Health Care of the First Department of Paediatrics, at the "Aghia Sophia" Children's Hospital, in Athens, Greece.

Bioimpendance is an established non-interventional method for the determination of the body composition and several metabolic parameters in health and disease investigations. The markers of metabolism chosen are: abdominal adipose tissue (AAT), basal metabolic rate (BMR), extra cellular water to body cell mass ratio (ECW/BCM). Finally, phase angle (PhA) was chosen as marker of tissue inflammation. No differences in metabolic markers were shown. Yet, a strong correlation between the BMR and PhA in adolescents with PCOS was observed (p=0.0.17); the correlation is suggested to be specific for the syndrome.

P3-P282

Insight Of Differential Diagnosis of DAX-1 from Two Patients with Elevated Testosterone in Early Infancy

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DAX-1 is Dosage-sensitive sex reversal - Adrenal hypoplasia congenita critical region on the X chromosome 1, caused by mutation of NR0B1. It commonly presents X-Linked adrenal hypoplasia congenital, hypogonadotropic hypogonadism and infertility. However, we observed two patients whose testosterone elevated in their early infancy. Both of them are males with uneventful gestation and birth, and have a primary symptom as jaundice. For patient 1, poor feeding and pigment genital area is observed. His maximal ACTH is more than 2000pg/ml, minimal cortisol is 40.05nmol/L, maximal testosterone is 14.33ng/ml, serum sodium is 118.7mmol/L, serum potassium is 8.1mmol/L, and 17-hydroxyprogesterone is normal. Both sides of adrenal gland are undetectable by adrenal ultrasound. Gene analysis shows pathogenic mutation on NR0B1 (NM_000475.4) Exon1: c.433_434insGGAT. For patient 2, there's no other symptom or sign. His maximal ACTH is up to 2000pg/ml, minimal cortisol is 0.71nmol/L, maximal testosterone is 181ng/ml, serum sodium is 121mmol/L, serum potassium is 9.1mmol/L, and 17-hydroxyprogesterone is 3.01nmol/L. Adrenal ultrasound shows hypoechoic nodule in adrenal region which is similar to adrenal gland structure, the size is smaller than normal. Gene test finds NR0B1 (NM_000475.4) Intron1: c.1169-1G>T. After the replacement of hydrocortisone and fludrocorti-

sone, their levels of testosterone come down to normal range in 4 months, 6 months respectively. Bone age of Patient 2 is 2.5 years when his chronological age is 3 years and 4 months. Primary adrenal insufficiency combined with high level of testosterone tends to be misdiagnosed as congenital adrenal hyperplasia. With this report we can summarize DAX-1's distinct features as follows: 1. DAX-1 is absent from elevated 17-Hydroxyprogesterone in general; 2. DAX-1 occurs delayed bone age which is opposite to congenital adrenal hyperplasia; 3. Adrenal ultrasound has certain value for recognizing DAX-1 and congenital adrenal hyperplasia; 4.Genetic testing is an optimal way to distinguish DAX-1 from other diseases. Overall, although DAX-1 commonly occurs hypogonadotropic hypogonadism at puberty or in early adult, gonad and sex hormones could be normal in early time.

P3-P283

Rapid onset and Progression of Chronic Kidney Disease in a Child with Autoimmune Polyglandular Syndrome Type 1

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Introduction: Autoimmune Polyglandular Syndrome Type 1 (APS-1) is a rare autosomal recessive hereditary disorder resulting from a mutation in the AIRE gene. APS-1 is characterized by three classic clinical features: hypoparathyroidism, Addison's disease and chronic mucocutaneous candidiasis. Additionally to the classic triad, the phenotype of APS-1 includes several endocrine and non-endocrine autoimmune manifestations.

Purpose: Topresent a rapid onset and progression of chronic kidney disease(CKD) in a boy with APS-1.

Case Presentation: A 10-year-old Greek boy was diagnosed with APS-1 at the age of $2^{6/12}$years old. At the age of 6 years he was diagnosed with hypothyroidism due to Hashimotos' thyroiditis. Despite the good thyroid function control, he presented with short stature while growth hormone deficiency and coeliac disease were excluded. He was under substitution therapy with hydrocortisone, fludrocortisone, levothyroxine, alfacalcidol as well as calcium, magnesium, dactarin oral gel and nystatin mouthwash. At the age of 10 years old he presented on his annual routine follow up with high levels of creatinine, urea and anemia; however, serum sodium, potassium, calcium and phosphorus levels were within normal range. Clinical examination revealed no pathological findings except from short stature and decreased height velocity. Further nephrological assessment with 24hour urine collection confirmed the renal function impairment. Over the next few weeks and while creatinine levels had up-regulated, a 51Cr- EDTA glomerular filtration rate (GFR) assessment and a renal biopsy were conducted. GFR was measured at 33ml/min/1,73m^{2}and renal biopsy revealed findings of transmembrane nephritis, few tubular calcifications and chronic vascular lesions, leading to the diagnosis of stage 3b CKD. Autoimmune disease evaluation was negative. Pending the whole exome sequencing results, the patient remains under very strict serum creatinine, pH, electrolyte and GFR follow up, while future renal replacement therapy seems unavoidable.

Conclusion: Severe renal disease is a rare clinical manifestation in APS-1 and its prevalence varies from 2-17% in both children and adults; underlying pathogenetic mechanism remains unclear. A very few cases of end-stage renal disease in children with APS-1 have till now been reported, while no adjuvant therapy (high doses of corticosteroids or monoclonal antibodies) managed to delay the progression of the disease. Prognosis remains poor and renal replacement therapy or transplantation seems the only existing therapeutic approaches.

P3-P402

Clinical Characteristics and Outcome of Patients with Beta-Ketothiolase Deficiency in China

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Background: Beta-ketothiolase deficiency is a rare autosomal recessive disease caused by *ACAT1* gene mutation. Only 100 cases have been reported up to now.

Methods: Among the 13 patients, four were diagnosed in our institute, and 9 were from a literature review of all reported Chinese cases. Two patients were diagnosed with newborn screening, and the others were diagnosed after ketoacidotic episodes. Clinical characteristics, laboratory and molecular findings and outcome of the 13 Chinese patients were recorded.

Results: All patients had increased urine 2-methyl-3-hydroxybutyric acid, 2-methylacetoacetic acid, and tiglylglycine, or elevated blood levels of C5:1 and C5-OH carnitines. Eight patients were found with *ACAT1* gene mutations. Except the two patients diagnosed by newborn screening, all patients were symptomatic and experiencing acute ketoacidotic episodes upon admission. Severe metabolic acidosis was found in eight patients or respiratory acidosis in two patients. Common triggers of the episodes included respiratory infections in and/or gastroenteritis. One patient died after the first ketoacidotic episode at eight months of age, and the other 11 patients had favorable outcomes.

Conclusions: Early diagnosis and treatment is very important for the favorable outcome. Patients with beta-ketothiolase deficiency may remain asymptomatic if with early diagnosis and preventive management.

Keywords: beta-ketothiolase deficiency; genetic testing; newborn screening; outcome

P3-P405

Lessons from Wolfram Syndrome: Initiation of DDAVP Therapy Causes Renal Salt Wasting due to Elevated ANP levels, Rescued by Fludrocortisone Treatment

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Background-Hypothesis: Sudden initiation of treatment for diabetes insipidus (DI) with DDAVP causes abrupt volume expansion resulting in particularly high secretion of Atrial Natriuteric Peptide (ANP) (1). ANP blocks all stimulators of zona glomerulosa steroidogenesis, resulting in secondary mineralocorticoid deficiency and acute hyponatremia, causing renal salt wasting (RSW) (2).

Cases: Two sisters, a 19-year-old girl (A) and a 7-year-old girl (B) with Wolfram Syndrome presented to our pediatric endocrinology clinic with severe polyuria-polydipsia and neurogenic bladder due to never treated DI (3). Both hospitalized, initiated therapy with oral melt preparation of DDAVP at the dose of 120-240 mg x 3/day, under close clinical and biochemical surveillance. Plasma levels of ANP were quantitatively detected by a competitive enzyme immunoassay kit (RayBiotech, Norcross, USA, sensitivity 1.02 pg/ml).

Results: Patient A presented RSW at day 2 after DDAVP initiation. Hyponatremia 123 mmol/L, hyperkalemia 5.7 mmol/L with high natriuresis 120-170 mmol/L occurred, with low plasma renin activity (PRA) 0.94 ng/ml/h (0.5-4.7) and aldosterone 2.26 ng/dl (4-31) and extremely elevated ANP 2359.5 pg/ml (normal < 42). Patient B presented RSW at day 11 after DDAVP initiation. ANP was elevated 1911.5 pg/ml with low PRA 0.78 ng/ml/h and aldosterone 3.46 ng/dl. Both had signs of volume depletion: negative water balance, tachycardia and increased cardiac rate with low blood pressure. Fludrocortisone 100-200 x 2 μg/day controlled natriuresis and restored electrolytes to normal within 48hrs in both patients. Fludrocortisone could be stopped at 1 month in patient B, but ANP levels remained too high 1200-1350 pg/ml, probably due to severe hydronephrosis secondary to grade III bilateral vesicoureteral reflux, in addition to the neurogenic bladder already installed. Patient A still requires - a year after - fludrocortisone at 50 x 2 μg/day with elevated but much lower ANP (250-500 pg/ml).

Conclusions: Fludrocortisone treatment rescues otherwise potentially life-threatening hyponatremia due to RSW and the secondary mineralocorticoid deficiency driven by elevated ANP, caused by sudden volume expansion following DDAVP initiation.

References

1. Mineralocorticoid deficiency in post-operative cerebral salt wasting. Papadimitriou DT et al. J Pediatr Endocrinol Metab. 2007 PMID: 18051934
2. Cerebral Salt Wasting Complicated by Central Diabetes Insipidus and Growth Hormone Deficiency. Papadimitriou DT et al. Indian J Pediatr. 2018 PMID: 29455327
3. A novel detrimental homozygous mutation of WFS1 gene in two sisters from non-consanguineous parents with untreated Diabetes Insipidus. Papadimitriou DT et al. ESPE 2018

P3-P410

A Novel Detrimental Homozygous Mutation of WFS1 Gene in Two Sisters from Non-Consanguineous Parents with Untreated Diabetes Insipidus

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Background: Wolfram Syndrome (WS) is a rare autosomal recessive genetic disorder. We present two sisters from non-consanguineous parents, who presented to our pediatric endocrinology clinic due to severe polyuria-polydipsia with inappropriately treated DM (HbA1c 8.2% and 10.1%) and untreated DI.

Methods: DNA was tested with PCR amplification and sequencing analysis (Sanger sequencing) of the entire coding region and all exon-intron splice junctions of the WFS1 gene (chromosome 4): reference sequence: NM_006005.3, with the A of the ATG start codon at position 1.

Results: A novel homozygous point missense c.2069G>A mutation in amino acid position 690 (p.C690Y) replacing Cysteine with Tyrosine in exon 8 was found in both sisters, the parents be-

ing heterozygous. The mutation causes amino acid change and is damaging with a score of 1.000 (Polyphen-2).

Cases: Sister-A, 19yrs old with a BMI<-2SDS, totally blind since 13yrs, had primary amenorrhea and bladder incontinence; normal cranial nerve examination except oculomotion with roving eye movements; normal muscle strength and deep tendon reflexes 2/4; no extrapyramidal or ataxia signs; visual acuity "No Light Perception" in both eyes; pupillary light reflex completely absent with mid-dilated pupils; normal anterior segment; intraocular pressure 12mmHg bilaterally; complete optic nerve atrophy in dilated fundus examination; tympanogram type A, TOAEs "pass" bilateral, as well as aABRs in Otologic and Audiologic testing; appropriate for age mental status with signs of severe depression. Sister-B, prepubertal 7yrs old had normal neurological examination; visual acuity 6/15 (0.40 LogMAR) and 6/19 (0.50 LogMAR) with +1.00 diopters sphere corrective lens in both eyes; symmetrically reduced pupillary light reflex with not relative afferent pupillary reflex; normal anterior segment; intraocular pressure 12mmHg and 11mmHg; moderate optic nerve atrophy; tympanogram type C, right side "pass" and left "fail" of TOAEs, with aABRs "pass" bilateral. Both had normal electrolytes, severe neurogenic bladder and Grade III hydronephrosis. Both presented salt-wasting due to ANP elevation when treatment for DI was started, successfully treated with fludrocortisone along with frequent bladder catheterizations. Within six months, patient's A BMI normalized, and she had menstrual onset. Persistence of hydronephrosis in patient B revealed a grade III bilateral vesicoureteral reflux treated with endoscopic injection of Deflux.

Conclusions: We present a novel detrimental homozygous WFS1 gene mutation in two sisters from non-consanguineous parents of Greek descent, both originated 5-6 generations before from Trapezund, an ancient Greek colony located in the former Greek Pontos, presently in Turkey, indicating a founder mutation effect.

P3-P411

General Public' Attitudes Towards the Use and Storage of NBS Blood Samples for Research in China

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Background: Given the absence of a systematic evaluation of general public' attitudes towards the storage and use of newborn screening (NBS) blood samples for research in China, we firstly conducted this internet-based survey to explore these issues.

Methods: We conducted a national-based internet survey with self-designed questionnaire. We mainly studied three categories: 1) the willingness to have their children's residual NBS samples used for research; 2) respondents' willingness to have their children's blood samples stored by the institutions; 3) the respondents' knowledge on NBS. Spearman correlation test and multi-factor non-conditional logistic stepwise regression analysis was used to examine the variables affecting the respondents' willingness to store and use NBS blood sample for research.

Results: The survey has a completion rate of 73%. And results of 1480 questionnaires were included into final analysis. If permission was obtained, 41.4% and 36.3% of the respondents will be very willing or somewhat willing to have their children's blood samples used for research. However, if permission not obtained, remarkably more respondents were unwilling to have blood samples used for research study (somewhat unwilling, 29.2%; very unwilling, 18.7%). 82.7% of the respondents were willing to allow the institutions to store NBS samples; among them, 56.4% would allow the samples to be stored indefinitely. Multi-factor logistic regression analysis showed that respondents with higher education level and younger age will be more willing to have children's newborn screening blood samples used for future research. Respondents were more likely to allow the samples to be stored if they had a high family income, with more children, and high awareness of knowledge on NBS.

Conclusions: In conclusion, our study is very important for understanding the general public's attitudes toward storage and use of residual NBS samples for research. Asking permission or consent is a very important issue regarding policies and procedures for NBS sample use.

Keywords: newborn screening; dried bloodspots; research; public health.

Pituitary, Neuroendocrinology and Puberty P1

P1-P194

A 7-Year Update Report of a National, Interdisciplinary Endeavour to Improve Outcomes for Children and Young People Under 19 Years of Age with Hypothalamic Pituitary Axis Tumours (HPAT) Using Multi-Site Video Conferencing

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Background: Paediatric HPAT, though generally benign, incurs significant neuro-endocrine morbidity. Their management

is unclear and the paediatric neuro-oncology or adult pituitary forum at which they are discussed lack pituitary or age-specific expertise respectively. The UK National HPAT Interest Group has pioneered a monthly, multi-site, interdisciplinary, video conferencing decision-making forum, to garner necessary experience and evidence of outcomes to assist worldwide referrers in management of childhood neuro-endocrine tumours. It delivers educational lectures, promotes research, and publishes evidence based (AGREE11) national guidance on idiopathic thickened pituitary stalk (TPS), craniopharyngioma, pituitary adenomas, and continuously audits evidence since 2010.

Patients: 182 patients were discussed on 256 occasions (46 repeated reviews) over 7 years from UK, Europe, Hong Kong, Canada and Australia. It receives referrals from 8 London hospitals, 7 UK paediatric oncology centres and occasionally 6 international centres. Paediatric and adult pituitary, surgical, neurooncology and neuroradiological specialists contribute.

Results: Craniopharyngiomas (47), pituitary adenomas (45) and TPS (36) constituted 70% of the cases. In craniopharyngiomas the commonest presenting features were growth failure, visual and intracranial pressure symptoms, while panhypopituitarism occurred in 78% of cases post treatment. Prolactinomas (23) accounted for 51% of the adenomas- often macro/giant/or resistant (56.5%)-presenting with pubertal delay, amenorrhoea, galactorrhoea, and neurological symptoms in one third of the patients. ACTH (3), GH (1), TSH (1), and dual producing adenomas (3.8%) occurred less frequently. Idiopathic TPS was most usually associated with cranial diabetes insipidus (72%). Referring institutions requested investigation and management guidance (44.5%) for surgical (e.g. biopsy in idiopathic TPS) and medical (e.g. radiation or cabergoline) treatment indications (22.5%) and initiation of GH replacement (6.0%). In 19.2% the MDT discussed complex surgical options (e.g. infant hypothalamic craniopharyngioma) and facilitated regional transfer for specialist endoscopic transsphenoidal surgery unavailable at referring centre (1 Cushing disease, 2 craniopharyngioma). Finally, clinical surveillance plans were agreed in 35% and discharge facilitated in 4% cases.

Conclusion: A supra-regional childhood HPAT discussion forum is clearly welcomed and continues to expand. It facilitated centralised clinical decision-making, patient referral and outcome audit, and raised awareness of rare disabling diseases. Our evidence regarding benefit suggests there is a demand for this expert advisory body to be formally recognised as a model of care, which might be adopted in a wider European research network (ERN) thereby sharing knowledge and facilitating research in these rare and often aggressive pituitary tumours.

P1-P195

Long Term Reversibility of Presumed ACTH Deficiency (ACTHd) In Children and Young People (CYP) with Intracranial Germ Cell Tumours (IGCT)

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Introduction: ACTHd is life-threatening and difficult to differentiate from ACTH suppression (ACTHs) especially in CYP receiving perioperative corticosteroids. In our experience, this is always the most robust anterior pituitary hormone to brain injury, whilst GH deficiency (GHd) is the first and LH/FSHd and TSHd intermediate in hierarchy.

We previously showed HPA axis recovery at 3.08(2.38-10.33) years after cortiscosteroid therapy for ACTHd in 13.6% of 44 CYP with craniopharyngioma and ACTHd, and showed that intact TSH and post-pubertal LH/FSH axis and pre-dose ACTH>10ng/L are predictive of recovery.

Aim: To assess the same recovery rates in CYP with IGCT and analyse data by tumour position.

Methods: 46 CYP with IGCT (24M) were identified from local databases and longitudinal records retrospectively reviewed.

Results: At diagnosis, CYP were aged 10.78(5.13-17.87) years and followed for 7.92(0.75-24.18) years. Of these 46 CYP, 13(28.3%) had pineal, 24(52.2%) suprasellar and 9(19.6%) bifocal IGCT. All but 14(30.4%) CYP had ACTHd 32/46(69.6%). Of these 14 with intact ACTH, 8(57.1%) had pineal, 4(28.6%) suprasellar and 2(14.3%) bifocal IGCT. Of these 14, 8/10(80%) with data available had GHd, 3/10(30%) TSHd, 0/10(0%) LH/FSHd and 1/10(10%) ADHd at last review. 6/32(18.8%) with presumed ACTHd discontinued hydrocortisone after 3.79(0.02-6.16) years with adrenal reserve "recovery" and detectable ACTH 23.05ng/L(15.9-26.2). Of these, 2/6(33.3%) had pineal, 3/6(50%) suprasellar and 1/6(16.7%) bifocal IGCT. At latest follow-up, 4/6(66.7%) had GHd, 2/6(33.3%) TSHd, 1/6(16.7%) LH/FSHd and 2/6(33.3%) ADHd. The remaining 26/46(56.5%) ACTHd CYP continue on hydrocortisone with ACTH<0.7ng/L(<0.7-25.0), 7.59(1.33-24.18) years later. Of these, 3/26(11.5%) had pineal, 17/26(65.4%) suprasellar and 6/26(23.1%) bifocal IGCT. Of these 26, 19/21(90.5%) with data available had GHd, 19/21(90.5%) TSHd, 16/21(76.2%) LH/FSHd and 18/21(85.7%) ADHd. A persisting hydrocortisone requirement was significantly associated with co-existing TSH, LH/FSHd and ADHd ($p<0.01$). CYP remaining on hydrocortisone showed greater increment in BMISDS than those with intact ACTH ($p=0.039$).

Conclusion: Interval reassessment of the HPA axis in CYP with suprasellar disease shows recovery in 18.8% of CYP at 4 years follow-up. It is vital to differentiate ACTHs from ACTHd to avoid secondary obesity and overdiagnosis attributable to therapy. A pineal tumour position, a detectable pre-dose ACTH and intact TSH or LH/FSH axis increase the likelihood of intact ACTH.

P1-P196

Endocrine Follow-up of Children with a History of Brain Tumour. Data from Our Large Cohort at Necker University Hospital, Paris, 2010–2015

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Background: Brain tumours are the most frequent solid tumours during childhood. Many of these patients develop endocrine disorders.

Objective: To describe our cohort of patients with primary brain tumours, followed in the Pediatric Endocrinology Unit at *Hôpital Universitaire Necker–Enfants Malades*, Paris, France between 2010-2015, to assess current practice and propose recommendations.

Methods: Retrospective and prospective observational study, data collection from medical records of patients seen at least once between 2010- 2015. Patients with pituitary adenomas, untreated fortuitously diagnosed gliomas (NF1 context) or insufficient data were excluded.

Results: 228 patients were included, 49.5% females, mean age at diagnosis: 7.1±3.9, mean follow-up time: 5.9±3.7 years. Main tumour subtypes: medulloblastoma (36.8%), craniopharyngioma (28.5%), glioma (20.6%), dysgerminoma (4%). Patients were divided into 2 groups: suprasellar (SS: 48.3%), involving the sellar/suprasellar region, hypothalamus or optic pathways, and non-suprasellar tumours (NSS: 51.7%), mainly involving the posterior fossa. Initial height was similar between both groups (SS: -0.3±1.6SDS Vs NSS: -0.1±1.2SDS), but body mass index (BMI) was significantly higher in SS (+0.8±2.0SDS, 20% >+2DS: obese) than in NSS (-0.2±1.3SDS, 5.1% obese, p<0.0001). Treatment was surgery (SS: 83.6%, NSS: 94.1%), and/or radiotherapy (SS: 58.2%, NSS: 95.8%) and/or chemotherapy (SS: 35.5%, NSS: 76.3%). GH deficiency was similar in both groups (SS: 86.8%, NSS: 83.9%), hypothyroidism was more common in SS (69%, all with TSH deficiency), than in NSS (33.9%, 2/3 TSH deficiency), as well as cortisol deficiency (SS: 69%, NSS: 4.2%) and diabetes insipidus (SS: 61.8%, NSS: 0.9%). Precocious and early puberty was noted in 16.4% SS and 11% NSS. Hypogonatropic hypogonadism was predominant in SS (47%, Vs 0.9% of NSS), and gonadal insufficiency in NSS (37.4%, Vs 1.2% of SS). Final height was available for 93 patients, with a significant difference between both groups (SS: -0.3±1.4SDS, NSS: -1.0±1.3SDS, p<0.0001). NSS had a significantly lower final height compared to initial height (p<0.0001) and to target height (-1.1 SDS p<0.0001), attributable to craniospinal radiotherapy (p=0.020). BMI increased at final visit in both groups (p=0.0001), with obesity in 46.4% of SS and 16.9% of NSS. Thyroid nodules were found in 11/45 patients, including 2 cancers.

Conclusions: This large cohort shows a high incidence of early endocrine disorders. An endocrine follow-up should be mandatory for all patients with a history of brain tumour, including nutritional evaluation.

P1-P197

A Single Centre Experience of Managing a Series of Childhood Macro/Giant-prolactinoma

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Introduction: Childhood prolactinomas often occur as aggressive macro (1-4cm) or giant (>4cm) tumours, with little consensus regarding timing of optimal therapies.

Aim: To highlight the phenotype and treatment outcome of childhood macroprolactinomas.

Subjects & Methods: Case-note review of 10 (5 male) children (<18 years) (presenting to our centre between 2009-2017 with hyperprolactinaemia due to macro/giant-prolactinomas.

Results: At diagnosis children were of median (range) 13.9 (11.0-16.3) years and had symptoms for 24 (1-84) months, including headaches (10/10), visual deficit (5/10), short stature (2/10), pubertal arrest (4/10) and galactorrhoea (2/10). A family history of pituitary adenomas was identified in 4/10; one proved heterozygous for an *MEN1* mutation. None harboured an *AIP* mutation. At

diagnosis, all children had 1-4 anterior pituitary hormone deficits. All received first-line cabergoline treatment apart from one misdiagnosed elsewhere as craniopharyngioma. Five required surgery (2 repeatedly) of whom two have also had radiotherapy, due to cabergoline side effects (1), visual compromise (2) or tumour regrowth (2). Two required urgent transsphenoidal surgery for either presenting pituitary apoplexy or CSF leak following cabergoline. Seven continue on dose-escalating cabergoline (1.0-7.5mg/week). Four experienced cabergoline side effects (headaches, aggressive behaviour, impulse control disorder, CSF leak). At diagnosis the median (range) prolactin levels were 61,173mIU/L (9,176-1,238,960). After 24 (16-96) months these are 4,294mIU/L (358-44,944). Prolactin levels decreased by 93% (83-99.6%) in 9/10, in parallel with tumour volume shrinkage by 41.8% (24%-90%), excepting the *MEN1* positive patient whose prolactin increased by 62.7%., in keeping with a tumour volume increase of 70%. In two the prolactin has normalised (<450mu/l). All had suprasellar extension and cavernous sinus infiltration, 8/10 had optic chiasm compression, 5/10 had skull base infiltration and 4/10 had haemorrhage. At diagnosis, four had normal vision which remained unchanged but six had visual deficits (hemianopia, quadrantanopia), of whom, two are now registered blind and four have persisting visual impairment.

Conclusions: Cabergoline should be the first-line treatment in childhood-onset macroprolactinomas; tumour responsiveness correlates with prolactin levels. Fast dose-escalation and prolonged administration may be necessary for disease control, but close monitoring for resistance, complications and side effects is essential. In resistant disease, surgery increases endocrine deficits, may not prevent blindness, and radiotherapy (which has proved effective) may be necessary. *MEN1* and *AIP* analysis is strongly recommended to inform pathogenesis, allow screening for other disease manifestations and identify at-risk relatives.

P1-P198

A National UK Guideline for Managing Pituitary Adenomas in Children and Young People Under 19 Years Developed According to The AGREE II Framework

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Pituitary adenomas are usually benign tumours arising from the hormone-secreting cells of the anterior pituitary gland. These adenomas can result in excess hormone secretion and the development of characteristic syndromes, such as Cushing's disease, acromegaly and hyperprolactinaemia, and/or mass effects on surrounding vital structures causing for example visual disturbances and pituitary hormone deficiencies. In children and young people under 19 years (CYP), the management of pituitary adenomas is particularly challenging given their extreme rarity, more aggressive phenotype and likely genetic predisposition, as well as the lack of age- and pituitary-specific multidisciplinary teams in current decision-making and service provision. Hence, the UK sought to create national, high-quality, multi-professional guidance using AGREE II methodology under the auspices of the UK paediatric endocrine (BSPED), paediatric oncology (CCLG) and paediatric (RCPCH) societies. Twenty geographically diverse experts in adult and paediatric endocrinology, neuroradiology, clinical oncology, neurosurgery, paediatric neuropathology, and neuro-ophthalmology constituted the guideline development group and formulated 155 clinical questions. Following a systematic literature review of 409 identified papers dating from 1990 to 2016, the group made 56 evidence-based recommendations for biochemical, radiological, cytological, genetic, and ophthalmic assessment of suspected pituitary adenomas as well as surgical and oncological treatment, and follow-up. A further 55 recommendations were made based on group expert opinion and were reviewed by two rounds of an international Delphi expert consensus process. This guideline should facilitate improved clinical care and outcomes in CYP with pituitary adenomas.

P1-P199

Growth Hormone Deficiency and Cryptorchidism in a Family with Xq26.3 Duplication and Position Effect on *SOX3*

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SOX3 is located on the X-chromosome (Xq27.1) and encodes a SRY-related protein that acts as a developmental transcription factor. Copy Number Variations (losses and gains), mutations of polyalanine stretches (deletions or expansions) and missense mutations of *SOX3* have been associated with growth hormone deficiency with incomplete penetrance, hypogonadism, differences of sexual development and variable additional endocrine disorders (MIM #312000 and #300123).

We report on a family in which three male members (aged 40 years; 4.3 years and 6.3 years at presentation) with growth hormone deficiency and cryptorchidism/ hypogonadism. Array CGH analyses revealed a novel 3.3 Mb duplication in Xq26.3-q27.1 that was located 86 kb downstream of *SOX3* on the X-chromosome in all three patients. Female carriers of the duplication were detected, but are clinically healthy.

We hypothesize that this duplication exerts a position effect on *SOX3* transcription. Further investigations in familiar growth hormone deficiency, cryptorchidism, and ectopic pituitary gland must be performed to learn more about the role of the copy number variations in the vicinity of *SOX3*.

P1-P200

PROKR2 Mutations in Patients With Growth Hormone Deficiency and Multiple Pituitary Hormone Deficiency

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Background: Prokineticin receptors(*PROKR1*and*PROKR2*) belong to the family of G protein-coupled receptors. Bi-or mono allelic mutations in *PROKR2* gene have been identified in Kallmann syndrome which is characterized by hypogonadotropic hypogonadism and anosmia/hyposmia. Recently, *PROKR2* mutations were reported in patients with multiple pituitary hormone(MPHD) and growth hormone deficiencies(GHD), suggesting a potential role for the PROK2 pathway in pituitary development, in addition to its role in GnRH neuron development.We present here clinical and molecular findings of one patient with MPHD and two patients with GHD.

Patients and methods: Patient-1 and Patient-2 were presented with short stature and Patient-3 was diagnosed with central hypothyroidism at age of 5 months and started on L-T4 replacement therapy and referred for further endocrinological evaluation.Clinical features of the patients are summarized in Table-1. There were no dysmorphic findings in the patients.Six months after presentation,Patient-1 and -2 showed a low height velocity and growth hormone(GH) stimulation tests were performed.GHD was diagnosed and GH replacement therapy was started.Patient-1 has not yet been completed pubertal development; Patient-2 has completed pubertal development and had menarche at age of 15 years.Patient-3 is still prepubertal.This patient was suspected to have hypogonadotropic hypogonadism without anosmia because of low gonadotropin levels, bilateral cryptorchidism and micropenis at presentation.Prolactin level was 1.9 ng/ml. GH treatment was started at age of 2.2 years and orchiopexy was done at age of 2.7 years. Chromosomal abnormalities were excluded before the admission of molecular genetic analysis. Screening of targeted regions for in-house designed short stature panel with 25 genes revealed two different heterozygous clinical variants previously reported with Kalmann syndrome in each patient in *PROKR2* gene.

Conclusion: Heterozygous *PROKR2* mutations should be kept in mind as a very rare cause GHD and MPHD.

Table 1. Some clinical and laboratory findings of the patients (for Abstract no P1-P200)

At presentation	Patient 1	Patient 2	Patient 3
Age (year)	12	11	0.5
Gender	Female	Female	Male
Consanguinity	3rd degree	1st degree	None
Birth weightSDS	-2.0	0.7	-0.6
HeightSDS	-2.8	-2.5	-3.3
Pubertal stage	Ph1B2/2	Ph1B2/2	Ph1T0.5/0.5 ml
Bone age (year)	8 $^{10/12}$-10	7 $^{10/12}$-8$^{10/12}$	-
Target height SDS	-2.4	-0.7	-0.9
At recent evaluation			
Age (year)	13.3	18.4	10
Height SDS	-2.6	-1.7	2.4
Pubertal stage	A3Ph3B4/4	A3Ph5B5/5	A2Ph2Testis 2/2ml
Bone age (year)	11	16	
Hormonal deficiencies	GH	GH	GH-TSH-PRL
MRI (Cranialand pituitary)	Normal	Normal	Normal
PROKR2			
NM_144773.2	c.254G>A	c.254G>A	c.518T>G
NP_658986.1	p.Arg85His	p.Arg85His	p.Leu173Arg

P1-P201

Anastrozole is Safe as Monotherapy in Early Maturing Girls with Compromised Growth, Further Improving Gain in Predicted Adult Height by the Initial Combination Therapy of an LHRH Analogue and an Aromatase Inhibitor. Results from the "GAIL" Study ISRCTN11469487

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Background: Third generation aromatase inhibitors (AI) have never been used as monotherapy, except for Mc Cune-Albright syndrome and autonomous ovarian cysts, to increase predicted adult height (PAH) in girls, mainly due to the theoretical concern of hyperandrogenism. Our previously published GAIL study [J Endocrinol Invest. 2016 Apr;39(4):439-46] has shown that the combination of anastrozole to an LHRH analogue for 24 months is safe and effective in ameliorating PAH in girls with early puberty +1.21 SDS (+7.51 cm) compared to inhibition of puberty alone +0.31 SDS (+1.92 cm, p = 0.001).

Objective and hypotheses: We assessed the efficacy and safety of anastrozole monotherapy after completion of the combined treatment (Leuprorelin + Anastrozole) in further improving PAH in early maturing girls with compromised growth who participated in the GAIL study ISRCTN11469487.

Methods: Group A1 (10 girls), after completion of the combined therapy with anastrozole and leuprorelin for 24 months or until age 11, were randomized to receive anastrozole 1 mg/day as monotherapy until bone age of 14 yrs with a 6-month follow-up. Each visit comprised of physical examination, laboratory tests,

bone age X-ray and pelvic ultrasound. DEXA scans were performed yearly.

Results: There was significant gain in PAH by 30 months (p=0,04). This was mainly achieved due to the reduction in the advancement rate of the bone age, extending the growth period in combination with the increase in girls' height velocity SD (statistically significant at 12,18,24 and 30 months). Testosterone levels rose slightly in 3 girls, but none developed clinical hyperandrogenism. One girl presented ovarian stromal hyperplasia and one hyperlipidemia. Overall, hematocrit, lipid and biochemical profiles did not change significantly during treatment. DEXA scans showed normal BMD z scores for bone age without significant interpatient changes. Anastrozole monotherapy until bone age 14 yrs further improved adult height or near adult height by +3.85 cm (+0,62 SDS) p=0.001, related to the gain in the PAH at the end of the initial phase of the GAIL study.

Conclusion: Aromatase inhibitors in conjuction to an LHRH analogue as well as in monotherapy seem to be safe and effective in ameliorating PAH and adult or near-adult height in girls with accelerated bone age and compromised growth potential. Our results imply the possible role of aromatase inhibitors in the treatment of short stature in girls, even as monotherapy.

P1-P202

Long-acting Octeotride Treatment in Children with Neurofibromatosis Type 1 - Optic Pathway Tumors and Growth Hormone Excess

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Introduction: Growth hormone excess (GHE) in children with neurofibromatosis type 1 (NF-1) has been reported in some sporadic cases. Whether GHE stimulates progressive optic pathway glioma (OPG) growth is of concern. The prevalence of GHE in NF-1 has not been described and the scheme treatment has not been well characterized.

Objective: To describe in children with NF-1/OPG and GH excess the treatment regimen and long term response to long- acting octeotride

Population and methodology: Descriptive study including NF-1-OPG patients with GHE followed in a terciary hospital between 2008-2018. The diagnosis of GHE was established from acceleration of growth, high levels of insulin-like growth factor 1 (IGF-1 >1DS) and the absence of GH suppression (glucose tolerance test). Clinical and laboratory data, secondary side effects and the response to treatment were also described.

Results: From our cohort, 80/ 379 children with NF-1 were diagnosed of OPG (21%). In a prospective follow up 7/80 patients were identified as having GHE; all were prepubertal, 5 boys (71%), mean age of 4.4 ± 1.9 years.

The mean height at the moment of diagnosis of GHE was +0.87±1.38 SD (> 0.86±0.76 SD above the midparental height); growth velocity increased from +0.35±1.19 SD to + 4.07 ± 2.7, mean IGF-1 > 1SD (457.8±151.3 ng/mL). In 4 patients the GHE was observed during progression of OPG (3) or neurocutaneous fibroma (1).

The first three patients were initially treated with short-acting octreotide in a daily subcutaneously dose (1.5 μg/kg/day). After confirming efficacy and tolerability, it was replaced by long-acting preparation of octeotride (Sandostatin-LAR 10 mg/28 days, intramuscular). Four patients were initially treated with (10 mg/28 d), one needed to increase the dose to 20 mg.

After 3 months, 6/7 patients showed a normalization of IGF-1 and growth velocity. Treatment was stopped in 4 patients after 21.85±0.72 months, and they remained stable for 26.6 months (12-49 months). Three patients are still on treatment (15.9±6.9 months). Except for mild diarrhea, no other adverse events were observed.

Conclusions: We should consider the risk of GH excess in patients with NF-1- OPG, and this may be a cause for concern. Treatment with long -acting octeotride was effective and safe. After treatment, auxological and analytical parameters remained within normal range, confirming GH excess reversibility.

P1-P203

Serum Concentrations of the Endocrine Disruptors-organochlorine Pesticides (OCPs) in Greek Children with Neurodevelopmental Disorders

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Background: The exposure to environmental toxicants has been estimated to contribute directly to 3% of human neurodevelopmental disabilities (NDDs). Organochlorine pesticides (OCPs), which are widespread persistent organic pollutants, have been implicated mainly because of their endocrine disruptive nature. Several studies have reported the above relations between maternal serum, the placenta barrier and the breast milk levels of OCPs and NDDs.

Aim: The aim of this cross-sectional study was to evaluate serum concentrations of dichlorodiphenyltrichloroethane (DDT) and its metabolites, hexachlorocyclohexane (HCH) and its isomers, cyclodienes and methoxychlor in serum samples from children diagnosed with High Functioning Autistic Disorder (HFA), Attention-Deficit Hyperactivity disorder (ADHD), and Moderate Learning Difficulties (MLD) compared to Typically Developing children (TD).

Method: The study sample consisted of 114 schoolchildren of normal intelligence, aged between 6 and 13 years old, distributed into four groups: HFA (n=39), ADHD (n=21), MLD (n=32) and TD (n=18). Serum concentrations of OCPs were determined by gas chromatography. Total cholesterol and triglyceride levels were

evaluated by an enzymatic colorimetric method.OCPs concentrations were adjusted for serum total lipids and are presented as nanograms/gram lipid.

Main Results: Each clinical group was compared to the TD group. The levels of β-HCH, ∑HCHs (i.e. the total concentration of HCH isomers) and 2,4'DDD (i.e. a DDT breakdown product) were significantly higher in HFA children:HFA *vs.* TD, mean ± SD: 10.5 ± 7.7 *vs.* 6.1 ± 4.0, p=0.049;12.0 ± 10.3 *vs.* 6.6 ± 4.0, p=0.025;7.4 ± 6.5 *vs.* 2.8 ± 2.3, p=0.0019, respectively. Interestingly, the detection rates (i.e., at least one substance from the group detected) of 4,4′DDT, ∑DDTs and Heptachlor epoxide (group of Cyclodienes), were significantly lower in HFA children: HFA *vs* TD: 12.8% *vs.* 38.9%, p=0.037;69.2% *vs.* 94.4%, p=0.044;10.3% *vs.* 38.9%, p=0.026, respectively. No statistically significant differences regarding both the concentrations and the detection rates of OCPs were found between the ADHD or MLD groups and the TD group.

Conclusion: Our findings demonstrate higher serum concentrations and lower detection rates of selected OCPs in HFA children than TD children. No differences were observed between the ADHD or MLD group and TD children. These findings are in line with previous studies reporting that exposure to environmental toxicants during the fetal period, infancy and early childhood is associated with NDDs in children. Yet comprehensive evidence in children is limited, highlighting the need for in-depth research towards the understanding of possible mechanisms linking OCPs with autism spectrum disorders.

P1-P204

Whole-Exome Sequencing Identifies Novel Pathogenic Variants In Korean families with Central Precocious Puberty

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Objective: Central precocious puberty (CPP) is characterized by the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. Early activation of hypothalamic-gonadal axis is influenced by both environmental and genetic factors. Especially, genetic factors have critical role of pubertal progression, but mutations associated with CPP have only been discovered in three genes: *KISS1, KISS1R*, and *MKRN3*. The aim of this study was to identify novel, potentially pathogenic variants from a whole-exome sequencing study in Korean families with CPP.

Methods: Whole-exome sequencing was performed in 52 members of 14 families with CPP. Familial CPP was defines by the presence of more than one member of a family with a history of precocious puberty. Data analysis selected only very rare variants (MAF<0.1%). Rare stop-gain, stop-loss, splice-site variants, frameshift, in-frame insertions/deletions were considered as the most candidate variants. Additionally, non-synonymous missense variants with three or more deleterious predictions (SIFT, Polyphen, LRT and Mutation Taster) were further considered. Ingenuity Pathway Analysis (IPA; Qiagen; http://www.qiagen.com/ingenuity) was used to detect significant enrichment for biological functions and molecular networks. Exome sequencing results for prioritized variants were validated using Sanger sequencing. We also measured the messenger RNA (mRNA) expression of the candidate genes in the hypothalamus of mice at different ages.

Results: The sequencing achieved good coverage of the target regions (99% average total coverage at 1X and 95% average total coverage at 20X) with enough depth (>200X). After filtering of the exome data, a total of 33 candidate genes were identified. These consist of 2 stop-gain, 7 frameshift, 7 missense, 6 splice-site variant, and 11 in-frame insertions/deletions. Among these genes, *AR, BMP6, EAP1, SLIT2* and *NCOR1* were prioritized. Especially, novel in-frame deletion (p. Gln115del) in *EAP1* was the most interesting variants for CPP and was identified in 12 out of 14 families. Both sexes were affected. The mRNA Levels of *EAP1* declined just before puberty, so levels of *EAP1* in prepubertal mice were significantly higher compared to those in pubertal mice.

Conclusions: We identified new potential genes that could play a role in pubertal progression. Our findings broaden the genetic background of CPP and *EAP1* can be a pathogenic gene for CPP.

P1-P205

A Paternally Inherited Familial Precocious Puberty Caused by a Novel MKRN3 Frameshift Variant

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Background: Precocious puberty is defined as breast development before 8 years in girls and gonad development before 9 years in boys. Central precocious puberty (CPP) results from early activation of the hypothalamic-gonadal axis. One third of idiopathic CPP is reported to be familial. Genetic mutations were initially described in kiss-peptin-1 (KISS1) and its receptor (KISS1R). More recently, Abreu et al identified heterogeneous mutations in the makorin RING finger 3 (MKRN3) gene. We report a sibling pair presenting with signs of precocious puberty within a few months of each other. Next-generation exome sequencing identified a paternally inherited heterozygous MKRN3 mutation in both siblings.

Case: A 5 year old girl presented with breast bud development aged 5.8 years. Peak LH and FSH were 28.3 IU/L and 12.6 IU/L respectively, confirming CPP. No pituitary lesion was seen on MRI; bone age was advanced by 3 years. Treatment with a long acting LHRH analogue was commenced.

Her brother was assessed at 8.3 years with signs of precocious puberty including 8ml testicular volumes, pubic hair, muscular appearance and body odour. Peak LH and FSH were 24.0IU/L and 6.3IU/L respectively; subsequent MRI head scan was normal. He also commenced treatment with a LHRH analogue.

Exploration of family history suggested a paternal 'parent of origin' effect. Their father did not enter puberty early however the paternal grandmother and paternal great-aunt had menarche at 8 years.

KISS1R analysis did not identify a mutation in either child. MKRN3 analysis using exome sequencing identified a heterozygous frameshift variant p.(Met297fs) (c. 890_893del) in exon 1 in both children.

Discussion: The mechanism that reactivates pulsatile GnRH secretion to initiate puberty is poorly understood. MKRN3 defects in sporadic CPP have been identified supporting a fundamental role for this peptide in the initiation of puberty. MKRN3 is a paternally expressed, imprinted gene located in the Prader-Willi critical region (chromosome 15q11-q13) and mutations represent an uncommon mode of transmission in CPP; exclusively paternal transmission is reported in only 1% of familial precocious puberty. Multiple loss of function mutations have been described in patients with CPP suggesting an important inhibitory effect of MKRN3 peptide on GnRH secretion. To our knowledge, the frameshift variant identified in the MKRN3 gene in our cases has not previously been described. Identification of further mutations in MKRN3 causing CPP may help to elucidate the mechanism of action of this important regulator in pubertal initiation.

P1-P206

MKRN3 Levels in Girls with Central Precocious Puberty During GnRHa Treatment: A Longitudinal Study

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Background: Recently, mutations of makorin RING-finger protein 3 (*MKRN3*) have been identified in familial central precocious puberty (CPP). Serum levels of this protein decline before the pubertal onset in healthy girls and boys and are lower in patients with CPP compared to prepubertal matched pairs. The aim of the study is to investigate longitudinal changes in MKRN3 circulating levels in patients with CPP before and during GnRHa treatment.

Methods: We performed a longitudinal prospective study. We enrolled 15 patients with CPP aged 7.2 years (range: 2-8 years) and breast development onset <8 years. Serum values of MKRN3, gonadotropins, (17)estradiol were evaluated before and during treatment with GnRHa (at 6 and 12 months). MKRN3 was genotyped in CPP patients.

Results: No *MKRN3* mutations were found among CPP patients. MKRN3 levels declined significantly form baseline to 6 months of GnRHa treatment (p: 0.0007) such as LH and FSH (p:0.04 and p: 0.009) and for MKRN3 between 6 and 12 months of treatment (p: 0.003).

Conclusions: we showed that girls with CPP had a decline in peripheral levels of MKRN3 during GnRHa treatment. Our data suggest a suppression of MKRN3 by pharmacological continuous administration of GnRHa.

P1-P207

Urinary Gonadotropins As a Useful Non-Invasive Marker of Central Precocious Puberty

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Aims: The current study aimed that first morning voided (FMV) urinary gonadotropin measurements could be used as a noninvasive alternative to the gonadotropin-releasing hormone (GnRH) test in the assessment of the hypothalamic-pituitary-gonadal function in children.

Methods: In a multi-center study, we compared FMV urinary gonadotropin concentrations with GnRH-stimulated serum gonadotropin levels in 140 girls aged 7-9 years who were evaluated for pubertal development, height acceleration, and bone maturation. Urinary and serum LH and FSH were determined by time-resolved sandwich fluoroimmunoassays (Delfia hLH Spec and Delfia hFSH; Wallac Oy, Turku, Finland). The relationship between FMV urinary gonadotropin concentrations and GnRH test results was assessed.

Results: FMV urinary LH (U-LH) and FMV urinary LH to FSH ratio (U-LH to U-FSH ratio) were significantly positively correlated with peak LH in GnRH stimulation test (r=0.49, P=0.030 and r=0.070, P<0.001). In receiver operating characteristic (ROC) curve analyses, the level of 0.89 for FMV U-LH was determined to be a possible cutoff to predicting a pubertal GnRH stimulation test result, with a sensitivity of 90.9%, a specificity of 77.8%, and area under the curve 0.49-1.00 (P=0.006).

Conclusion: FMV U-LH determination may be an alternative assessment for pubertal development and its disorders, reducing the need for invasive GnRH stimulation tests.

P1-P208

Testicular Development and Puberty in Boys with Duchenne Muscular Dystrophy: Results from the ScOT-DMD Study

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Introduction: Delayed or absent puberty is thought to be common in boys with Duchenne Muscular Dystrophy (DMD).

Objective: To evaluate testicular development, function and puberty in DMD in a 12 months prospective longitudinal study.

Methods: 34 boys had assessment of puberty and testes volume by a single endocrinologist. Testes volumes were converted to Z-scores adjusted for bone age. Boys were divided into group A

[Baseline age<11.5 years: median 9.1 years (6.4, 11.4)] and group B [Baseline age ≥1.5 years: median age 14.9 (11.8,16.8)]. Results expressed as median(range).

Results: At baseline, 17/20(85%) and 13/14(93%) of Group A and B were on GC for a duration of 3.3 years(0,8.2) and 8.5 years(3.7,13.4),respectively. In Group A, median testes volume Z-scores at baseline and 12 months were -0.6(-3.6,+1.5) and -2.0(-3.6,+1.7), respectively [p=0.04]. In Group B, median testes volume Z-scores at baseline and 12 months were -1.6(-3.3,+0.8) and -2.3(-3.3,+0.8),respectively [p=0.31]. At baseline and 12 months, 3/14(21%) and 4/14(29%) in Group B were on testosterone. By 12 months follow-up, 9/14(64%) of Group B had testes volume < 4ml, including 5/9(56%) boys who were on testosterone. Testosterone levels were undetectable at baseline and 12 months in the 4 boys who remained pre-pubertal. LH was undetectable at baseline in these 4 boys; whereas 3 had undetectable LH at 12 months, with another boy with LH of 0.6U/L. By 12 months, 5/14(36%) of Group B had signs of puberty (testes volume ≥4ml). 7/9(78%) in Group B who had testes volume <4 ml were on daily Deflazacort whereas 1/5(20%) in Group B had testes volume ≥4 ml whereas 1/5(20%) were on daily Deflazacort. Impalpable testes were reported in 7/34(21%) of the total cohort during 12 months period. Of these, 6/7(86%) were retractile; 1/7(14%) had bilateral inguinal testes throughout the follow-up period, confirmed on testes ultrasound.

Conclusion: This first longitudinal study with clinical examination of testes showed that DMD boys have relatively small testes even after adjusting for bone age. This suggests the possibility of functional hypogonadotrophic hypogonadism given the low LH and testosterine.Spontaneous puberty is uncommon, observed in only 36% of older adolescents.Pubertal disorders may be commoner in boys treated with Deflazacort.Our study documented a relatively high frequency of impalpable or retractile testes in DMD for the first time.

P1-P209

Exposure to BPA and Phthalates and Timing of Puberty in Girls

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Background: Over the past several decades, the age of pubertal onset in girls has shifted downward worldwide. Exposure to endocrine disrupting chemicals (EDCs) during critical windows of development may play a role in this trend. Epidemiological and animal studies showed that exposure to phthalates and BPA could be associated with earlier puberty onset in girls.

Objective: To investigate the association between the exposure to BPA, DEHP's metabolites and alterations of puberty in girls, referred for idiopathic premature thelarche (IPT) and idiopathic central precocious puberty (ICPP).

Methods: A case control study was conducted in 96 girls, subdivided into 3 groups: 29 girls with ICPP (mean age 7.3±0.08), 36 with IPT (mean age 6.56 ± 1.6) and 31 controls (mean age 6.67± 2.3).

Urine BPA and DEHP's metabolites were evaluated by high-performance liquid chromatography coupled with mass spectrometer (LC–MS/MS). Individual exposure was evaluated through an "ad hoc" questionnaires providing data on life styles, diet and other potential determinants of exposure.

Results: The presence of measurable concentrations of the EDCs in all girls, even in the control group, was found.. ICPP and IPT girls showed no significant difference in EDCs levels in comparison with controls (p=0.5). No significant difference in EDCs levels between ICPP and IPT girls was found. In IPT group, a significant correlation between phtalates level and FSH peak was found, suggesting that phthalates could potentially cause self-limited breast development without progression to true precocious puberty (p<0.05).

Conclusions: These data demonstrate the widespread exposure to these compounds in the population. Though no significant difference in EDC concentrations was observed between the study groups and controls, these findings warrant further prospective investigations to clarify the potential role of EDCs on timing of puberty in girls.

P1-P210

Hypothalamic-Pituitary-Testicular Axis Response to Sub-Maximal Aerobic Exercise, in Pre- and Early-Pubertal Normal Weight and Obese Boys

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Objective: To investigate the association of the gonadal axis with pro- and anti- oxidation, in relation to obesity and pubertal status in boys, before and after a stimulatory exercise bout.

Design: Cross-sectional human experimental study.

Methods: 92 healthy normal-weight and obese pre- and early-pubertal boys, participated in this study. All subjects underwent a baseline blood sampling followed by an aerobic exercise bout until exhaustion at 70% VO2max, with a subsequent blood sampling at the end of exercise. LH, FSH, testosterone and markers of pro-

(TBARS and PCs) and anti- (GSH, GSSG, GPX, catalase, TAC) oxidation were measured.

Results: Baseline and post-exercise LH and FSH concentrations did not differ between obese and normal weight both in pre- and in early- pubertal boys. Baseline and post-exercise testosterone concentrations were lower in obese than in normal-weight early pubertal boys. Baseline LH, FSH and testosterone concentrations were greater in early pubertal than in pre-pubertal boys independently of the weight status. Following an acute bout of aerobic exercise, LH concentrations decreased in early pubertal subjects. Baseline and post-exercise FSH concentrations were similar in pre- and early puberty in normal-weight and obese boys. Testosterone concentrations increased following exercise only in early pubertal obese subjects in contrast of the LH decrease. In pre-pubertal boys, baseline LH, FSH and testosterone correlated with baseline anti-oxidation markers concentrations. In pre-pubertal normal-weight and obese boys, baseline LH correlated positively with the increase of TAC, while in early pubertal normal-weight boys baseline testosterone positively correlated with the increase of TAC. In all studied subjects baseline LH concentrations were the best positive predictors for the exercise-associated increase of the anti-oxidation marker TAC. Baseline BMI z-score was the best positive predictor for the post-exercise PCs concentrations. Baseline waist to height ratio was the best negative predictor for the post-exercise GPX concentrations.

Conclusions: Antioxidation is positively associated with gonadotropin and testosterone concentrations, while this association is stronger regarding the LH testosterone components of the HPG axis.

P1-P211

Effect of Pubertal Blockade and Cross-sex Hormone Treatment on the Growth Spurt in Young Transgender Adolescents: A First Report

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Intro: Gender variance is becoming more common in young people. International guidelines recommend GnRH analogues (GnRHa) for gender variant young people from Tanner stage 2 onwards and cross-sex hormones (CSH) from age 16yr onwards. However, no good evidence exists how these affect growth. This first report aims to determine the impact of GnRHa and CSH on growth in young transgender adolescents to help inform prescribing in this patient cohort.

Methods: This is a prospective study of 44 young transgender people, attending the national Gender Identity Development Service early intervention clinic, on GnRHa for 1.3-3.8 years, transitioned to CSH treatment aged 16yr. 14 attained adult height (7 transgirls and 7 transboys) thus far. Changes in height and height velocity were calculated at each transition point.

Results: 7 transgirls, with a mean age at presentation of 12.5yr (range: 12-14 ; SD +/- 0.8), started GnRHa at mean Tanner stage 3 (2-5 +/- 1.2), mean age 13yr (12.2 – 14.6 +/- 0.9) and CSH at mean age 16yr (15.9 – 16.6 +/- 0.2); and 7 transboys all at Tanner stage 5, mean age at menarche 12yr (9-13 +/- 1.5), mean age at presentation of 14.2yr (13.4 – 14.7 +/- 0.46), started GnRHa at mean age 15.1yr (14.2 – 16.7 +/- 0.7) and CSH at mean age 16.5yr (15.8 – 17.7 +/- 0.3).

Mean adult height was 180cm (range: 167 – 190.1+/- 7.2) in transgirls and 162.5cm (range: 157.7 – 165.3 +/-3) in transboys. Mean height velocity on GnRHa was 3.6cm/yr (range: 0.03 - 5.5 +/- 1.8) in transgirls and 0.9cm/yr (range: 0 - 2.2 +/- 0.7) in transboys. Mean height velocity on CSH for transgirls 3.5cm/yr (range: 0.7 - 8.5 +/- 3) and 0.3cm/yr (range: 0 - 0.8 +/- 0.3) for transboys. Mean total pubertal growth for transgirls was 16.8cm (range: 1.2 - 24.2 +/- 7.7) and 2.3cm (range: 0 - 4.2cm +/- 1.6) for transboys.

Conclusion: Transboys did not show significant growth on GnRHa or CSH, but they were were older at presentationand all post-pubertal at start. Transgirls grew extensively on GnRHa and then unexpectedly only had modest growth when female puberty was induced with oestradiol. This may have arisen from the extension of the pre-pubertal growth phase leaving little growth potential. In some cases, this might challenge gender preferences as a taller final adult height could interfere more with "passing" in their preferred female gender. These are preliminary conclusions and further study is required.

P1-P212

Real-World Safety Data in a Cohort of Children with Noonan Syndrome Treated with Growth Hormone: Final Results from Nordinet® International Outcome Study (IOS) and Answer Program

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Objectives: Current safety data do not indicate an association of GH therapy with increased risk for development/progression of tumours, or worsening of congenital cardiac conditions in individuals with Noonan syndrome (NS); however, data are limited. This report describes real-world safety data on GH therapy in paediatric patients with NS.

Methods: Two complementary non-interventional, multicentre studies, NordiNet® IOS (NCT00960128) and ANSWER Program (NCT01009905), evaluated long-term effectiveness and safety of Norditropin® (somatropin; Novo Nordisk A/S) as prescribed by treating physicians in a real-world clinical setting. Safety events (serious adverse events not related to therapy [SAEs], non-serious and serious adverse reactions [NSARs/SARs]) were

evaluated in GH-treated patients with NS (n=412) enrolled in these studies.

Results: Baseline characteristics [% or mean (SD)]: female, 29.1%; age at treatment start, 9.48 (3.92) years; height standard deviation score (SDS), −2.65 (0.95); weight SDS, −2.03 (1.31); IGF-I SDS, −1.13 (1.62); IGF-binding protein-3 SDS, −0.91 (1.72); GH dose (μg/kg/day), 43.9 (13.7); GH naïve (68.5%). Mean (SD) follow-up time on GH treatment, 3.1 (2.6) years and mean GH dose (μg/kg/day) during treatment, 46.6 (13.6). A total of 35 (8.5%) patients were diagnosed with cardiovascular (CV) comorbidities prior to GH start, with pulmonary valve stenosis (n=19) and atrial septal defect (n=5) being most frequent. After start of GH treatment, five patients were diagnosed with (potentially pre-existing) CV comorbidities: unspecified CV disease (n=3), ruptured abdominal aortic aneurysm (n=1), pulmonary valve stenosis (n=1). Overall, 31 safety events were reported in 21 patients (#events/#patients): NSARs, 21/15; SARs, 2/1; SAEs, 8/5. Most patients with a safety event reported one occurrence (16/21). For patients with safety events, mean (SD) age at treatment start was 9.90 (4.13) years and baseline height SDS was −3.14 (0.82). The most common NSARs were headache (six events/six patients) and arthralgia (five events/three patients). Two SARs (brain neoplasm; metastases to spine) were reported in one patient. The SAEs reported: giant cell epulis (one patient), scoliosis and spinal fusion surgery (both in one patient), moyamoya disease (one patient), glioneuronal tumour (one patient), and aggravated glioneuronal tumour and epilepsy (one patient). Glioneuronal tumours have previously been associated with Noonan syndrome and RASopathies. No cardiac safety events were reported in these patients.

Conclusions: These data suggest a favourable safety profile of GH therapy in patients with NS, including those with pre-existing cardiovascular comorbidities.

Pituitary, Neuroendocrinology and Puberty P2

P2-P301

Efficacy and Safety of Triptorelin 3-Month Formulationin Patients with Central Precocious Puberty and BMI Evaluation

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Background: Different formulations of gonadotropin-releasing hormone agonist (GnRHa) are available for the treatment of central precocious puberty (CPP). Currently there are few data on quarterly formulation depot (11,25 mg) during treatment.

Aim: The purpose of this study is to analyse the effect of Triptorelin 11,25 mg 3-months depot in comparison with the monthly 3,75 mg formulation at the beginning and during the treatment of CPP.

Methods: A retrospective/observational study of 127 patients (11 adopted) with CPP treated with GnRHa from 2014 to 2017 was conducted in the Pediatric Endocrinology Centre of Verona, Italy. 110 of them, treated with monthly Triptorelin 3,75 mg depot, were compared with 16 patients treated with quarterly Triptorelin 11,25 mg depot. Suppression of hypotalamus-pituitary-gonad axis, as determined from serum LH, FSH, estradiol or testosterone, was analysed in patients treated with Triptorelin 11,25 mg. Pubertal signs, auxological data, bone age and uterine length were evaluated at the beginning, after the first and second year, and at the end of both therapies.

Results: No significative differences during treatment were found in the comparison between patients treated with monthly formulation and patients treated with quarterly formulation. Only at the end of the therapy, the standard deviation score (SDS) of weight and BMI resulted lower in patients treated with quarterly formulation (weight SDS: quarterly= 0,05 ± 0,67 vs. monthly=1,08 ± 0,58, p<0,01; BMI SDS: quarterly= 0,24 ±0,88 vs. monthly=0,75 ±0,55, p<0,01). Moreover, in patients treated with monthly formulation, a significative increasing from the beginning to the end of therapy was found in weight SDS (beginning: 0,68 ± 0,94 vs. end: 0,99 ± 0,66: p<0,01) and in BMI SDS (beginning: 0,35 ± 0,91 vs. end: 0,63 ± 0,71, p<0,01). This trend was not present in patients treated with quarterly formulation.

Conclusions: Quarterly Triptorelin 11,25 mg depot has the same efficacy as the monthly formulation during the treatment. It does not cause any significant increase of weight and BMI, contrary to the monthly formulation.

P2-P302

Triptorelin Test in Idagnosing Central Precocious Puberty

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Introduction: GnRH test is standard in confirming the diagnosis of central precocious puberty (CPP). However, GnRH (Relefact) is not always readily available in Serbia and several other countries. Two studies so far have assessed use of triptorelin in diagnosing CPP, with different sampling protocols, and in only one of these studies were triptorelin test findings compared to GnRH test findings.

Objective: to evaluate the diagnostic accuracy of triptorelin test compared to the GnRH test in girls with suspected CPP. Secondary objective was finding the optimal timing for blood sampling during triptorelin test. Study was officially approved by the Hospital Ethics Committee.

Method: both triptorelin and GnRH tests were performed in all enrolled girls with premature breast development, within two weeks, in randomized order. After collection of baseline samples and administration of 100 μg of GnRH i.v. or 100 μg of triptorelin s.c, sampling times for FSH and LH were 30, 45 and 60 min for GnRH test; and 30, 60, 90, 120 and 180 min for triptorelin test, with additional 24h sample for FSH, LH and

estradiol. The diagnosis of CPP was made based on GnRH test LH peak ≥3.3 IU/l.

Results: out of 14 girls with premature breast development which have enrolled and completed the study so far, 5 girls were diagnosed with premature thelarche (PT), and 9 with CPP. Girls with CPP differed significantly from girls with PT regarding bone age advancement (+1.7±1.2 vs -0.1±1.1 years, p=0.012), had higher LH peaks during triptorelin test (16.3±20.1 vs 2.1±0.7 IU/l, p=0.002) and higher estradiol levels 24h after administration of triptorelin (782±457 vs 109±75 pmol/l, p=0.002). LH peak cutoff of ≥3.0 IU/l during triptorelin test showed 100% specificity and 89% sensitivity in detecting CPP. Using this cutoff resulted in missing one girl with CPP (LH peak during GnRH test 6.1 IU/l), which had non-progressive form of CPP with mild bone age advancement (+0.75 years). Lowering triptorelin LH peak cutoff to 2.6 IU/l would increase the sensitivity to 100%, reducing specificity to 60%.

Conclusion: triptorelin test with LH peak cutoff ≥3.0 IU/l can be used as alternative test for diagnosing CPP. GnRH test should be performed in girls with triptorelin test LH peak <3.0 IU/l if they show advancement of bone age or other signs of pubertal progression during follow-up.

P2-P303

Foot Length Growth Is a Novel Marker of Early Puberty

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Introduction: Pubertal growth is hormone dependent. The anthropometric (height, weight) and sexual (Tanner stage (TS)) changes are accompanied by growth in foot length. However, the relationship between changes in foot length and other anthropometry remains unclear. Our aim was to determine how changes in foot length relate to growth parameters (height and weight), self-rated TS and serum sex steroids.

Methods: We used data from the Adolescent Rural Cohort study of Hormones, health, Education, environments and Relationships (ARCHER); a community sample of adolescents (aged 9-14y at baseline) who were followed for three years. Annual data collection included: anthropometry (height, weight, foot length), self-rated TS, date of menarche and blood samples. Blood was analysed using LC-MS/MS for oestradiol (E_2), testosterone (T) and dehydroepiandrostenedione (DHEA). Insulin-like growth factor 1 (IGF-1) was measured via radioimmunoassay. Pre-puberty was defined by baseline T <0.5 nmol/L for males or E_2 <40 pmol/L for females.

Results: Data were available for 293 subjects. 13% (17/128) of females and 43% (71/165) of males were pre-pubertal at baseline. In the three years from baseline to final follow-up, both sexes showed expected increases in anthropometry, TS and most serum hormones. Average annual % increase in foot length was greater for adolescents classified as pre-pubertal compared to pubertal (F:2.7% vs 1.5% p<0.001; M:4.2% vs 2.9%, p<0.001). Increased foot length was associated with increases in height, weight and TS (all p<0.05; β (95% CI) Height: F:5.78cm (5.32-6.23), M:6.71cm (6.50-6.93), Weight: F:6.64kg (5.93-7.35), M:6.20kg (5.87-6.53), TS: F:0.50 (0.42-0.59), M:0.54 (0.50-0.59)). In males, increases in T, E_2, and IGF-1, respectively, were associated with increases in foot length (all p<0.05; T 0.18cm (0.16-0.20), E_2 0.017 cm (0.012-0.022), IGF-1 0.03cm (0.02-0.04). In females, increases in T, E_2 and IGF-1 in pre-menarcheal girls were associated with increased foot length (all p<0.05; T:0.74cm (0.09-1.4), E_2:0.004cm (0.001-0.006), IGF-1:0.03cm (0.01-0.05)) but not post-menarcheal girls.

Discussion: We provide the first longitudinal evidence that foot length is related to conventional pubertal changes in physical characteristics and serum sex steroids using highly accurate LC-MS/MS methodologies, with more foot growth in pre-pubertal adolescents. Change in foot length is a novel, cost-effective and easily demonstrable marker of early pubertal changes, something of utility to adolescents, parents and clinicians alike. We postulate that early foot growth provides a physical base to support the future pubertal growth spurt.

P2-P304

Ultrasound-Based Measurements of Testicular Volume in 6-16 Year Old Boys: Intra- and Inter-Observer Agreement and Comparison with Prader Orchidometry

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Background: Prader orchidometry has been the standard method for evaluating testicular size. As this technique is subjective and tends to overestimate the testicular volume, ultrasound has been proposed as a more reliable method.

Objective: To evaluate the intra- and inter-observer agreement of ultrasound measurements of testicular volume and comparison with Prader orchidometry.

Materials and methods: Length, width and depth of the right testicle were measured using ultrasound in 57 boys between 6.5 to 16.4 (mean 12.0) years of age. Volume calculated by Lamberts formula: L×W×D×0.71. The measurements were performed twice by a main observer and once by a second observer. Testicular volume was also estimated using a Prader orchidometer by a third

observer. Agreement was investigated with Bland-Altman plots, and summarized as the mean and standard deviation (SD) of differences, 95% limits of agreement (LOA), and technical error of measurement (TEM).

Results: The mean intra-observer difference of testicular volume was 2.2% with an SD of 9.2% (LOA -20.3 to 15.9%) and TEM of 6.5%. The mean inter-observer difference was 4.8% with an SD of 20.7% (LOA -35.7 to 45.3%) and TEM of 14.6%. Comparing ultrasound and orchidometer volumes required a power transformation to remove bias, estimated as $Vol_{OM} = 1.96*Vol_{US}^{0.71}$. The mean difference after transformation was 0.7% with an SD of 18.0% (LOA from -34.5 to 35.9%).

Conclusion: Our results showed a relatively small mean intra- and inter-observer difference that indicates the potential of ultrasound for measurement of testicular volume on a group level. The intra-observer error was limited which justifies its use in longitudinal follow up of testicular development in an individual child, but the larger inter-observer variability indicates the need for good standardization of methods. Agreement between the two methods required a power transformation to remove bias.

Key words: Agreement, Intra-observer, Inter-observer, Testicular volume, Ultrasound, Orchidometer

P2-P306

Longitudinal Follow-up to Near Final Height of Auxological Changes in Girls with Idiopathic Central Precocious Puberty Treated with Gonadotropin-releasing Hormone Analog and Grouped by Pretreatment Body Mass Index Level

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Purpose: Reported changes in body mass index (BMI) in central precocious puberty (CPP) during and after gonadotropin-releasing hormone analog (GnRHa) treatment are inconsistent. We, therefore, investigated auxological parameters in GnRHa-treated girls with idiopathic CPP (ICPP) until attainment of near final height (NFH).

Methods: From the medical records of 59 ICPP girls who attained NFH after GnRHa therapy, auxological changes were compared between overweight (BMI ≥ 85 percentile) and normal-weight (BMI < 85 percentile) groups. BMIs were changed into standard deviation scores (BMISDSs) for subject's chronologic age (BMISDS-CA) and bone age (BMISDS-BA).

Results: The incidence of overweight including obesity was high at the start of therapy (35.6%). The predicted adult height (PAH) at start of therapy was significantly shorter than the mid-parental height (MPH), whereas PAH at end of therapy approached MPH, and NFH was greater than MPH. The height velocity (HV) in overweight group was higher during GnRHa therapy than that in normal-weight group, but those in the two groups were not different after therapy until NFH. Both BMISDS-CA and BMISDS-BA increased significantly during therapy, but, after therapy both BMISDSs decreased significantly until NFH. At NFH both BMISDSs were not different from those at baseline. In the normal-weight group, both BMISDSs increased during therapy and maintained that level until NFH. In overweight group, neither BMISDS changed during therapy, but there was a decrease after therapy until NFH.

Conclusion: The different patterns of BMISDS change during and after GnRHa therapy until NFH between the two groups were related to the different HV during GnRHa therapy.

P2-P307

The Effect of GnRH-Analogue Therapy on the Quality of Life of Patients with Central Precocious Puberty and their Families

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Introduction: Quality of life (QoL) is a multidimensional indicator including several functions and represents an important evaluator of patient's health, especially in chronic diseases. Treatment with aGnRH in Central Precocious Puberty (CPP) is source of stress for patients and families. The aim of our study is to evaluate QoL and levels of therapy-related stress in patients with CPP and in their families during and after treatment.

Material and Methods: 56 patients (2 males) with CPP attending a tertiary Endocrinological Outpatient Clinic in 2015 and 2016 were enrolled. The population was divided, according to their age, in 4 categories: G1: 3 patients, 4-7 years; G2: 15 patients, 8-12 years, G3: 13 patients, 13-18 years, G4: 25 patients beyond 18 years. Groups G1 and G2 were on therapy with aGnRH, G3 were off therapy, still on clinical follow up, G4 were off therapy. We also evaluated 30 controls paired for age and level of instruction. Each patient underwent 2 questionnaires: the "Pediatric Quality of Life Inventory" (PedsQL) and a tailored "ad-hoc" questionnaire to investigate self perception in CPP. Parents also underwent the latter questionnaire.

Results and Discussion: No significant differences were detected comparing PedsQL scores among G1, G2 and G3 groups each others nor comparing patients and controls. A difference statistically significant was detected in the evaluation of physical functions between G2 and controls (p: 0.02). In G2 and G3 no significant association was found between the duration of treatment and the 4 functions of PedsQL. For the self perception questionnaire scores, although no significant differences among G1, G2 and G3 themselves nor between patients and their parents were detected, the scores trend showed in patients an amount of stress therapy-related increasing proportionally with age. For G4 a direct

correlation was identified between duration of treatment and emotional stress, and lower scores about self-esteem were identified, referring both to the period of therapy and the period of questionnaire's compilation.

Conclusion: In CPP, from the PedsQL, it appears that therapy with aGnRH only affects QoL on physical functions. Levels of emotional stress therapy-related, detected through ad-hoc questionnaire, increase in treated patients, independently from the treatment interruption. In off-therapy patients a decreased self-esteem and an indirect correlation between emotional stress and duration of treatment were found, underlining the effect of therapy in self perception.

P2-P308

A Novel Inactivating Compound Heterozygous Mutation in KISS1R/GPR54: Cases of Three Siblings

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Introduction: Kisspeptin is a neuropeptide, encoded by the KISS1 gene, which acts upstream of gonadotropin-releasing hormone (GnRH) neurons and also has a critical role for maturation and function of the reproductive axis. Inactivating mutations of its receptor (*KISS1R*) cause normosmic isolated hypogonadotropic hypogonadism (IHH). In this report, we aim to present three siblings who have IHH due to novel compound heterozygous KISS1R mutation.

Case Report: Index case applied to our outpatient clinic with delayed puberty when he was 14 years old. On newborn period, he had bilateral cryptorchidism and micropenis and bilateral orchiopexy was done. His parents were nonconsanguineous. On physical examination, his height was 165.3 cm (0.14 SDS), weight was 62 kg (0.94 SDS). Pubertal stage was Tanner stage 1, stretched penis size was 4 cm, bilateral testises were in skrotum and testis sizes were 3 ml. On laboratory; FSH: 0.9 mIU/ml, LH: 0.13 mIU/ml, total testosterone: 15 ng/dl, ACTH: 34 pg/ml, cortisole: 15 µg/dl, 17OH progesterone: 0.11 ng/ml, AMH: 51.2 ng/ml (normal range 2-30.7). Karyotype analysis revealed 46 XY. The results of GnRH test confirmed IHH. In molecular analysis of index case, c.969C>A (p.Y323X) and novel c.170T>C (p.L57P) compound heterozygous mutations were obtained in KISS1R gene. In molecular analysis of family, while mother had novel p.L57P mutation, father had p.Y323X heterozygous mutation which was known as an inactivating mutation caused IHH. The rest three siblings who were 5, 12 and 14 years old were evaluated. All of the three sisters had normal female genitalia and their karyotypes were 46 XX. Also the same mutation was obtained in two siblings who were 12 and 14 years old.

Conclusion: Recent studies demonstrated inactivating mutations in *KISS1R* gene cause normosmic isolated hypogonadotropic hypogonadism (IHH) in animal models and human. We identified a novel inactivating compound heterozygous mutation in KISS1R gene in three members of a Turkish nonconsanguineous family. We recommend that if IHH is obtained in a member of a family, we might investigate the whole family members although the family is nonconsanguineous.

P2-P309

MKRN3 Gene Mutations in a Cohort of Patients with Central Precocious Puberty

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Background: *MKRN3* gene, encoding Makorin RING-finger protein 3, is a maternally imprinted gene located at a Prader-Willi syndrome region on chromosome 15q11.13. Deleterious mutations of *MKRN3* gene are a common cause of paternally inherited central precocious puberty (CPP), being identified in 33-46% of familial cases and in about 5% and 40% of apparently sporadic female and male cases, respectively.

Objectives: To evaluate the presence of mutations, deletions and methylation abnormalities in *MKRN3* gene in a cohort of patients with CPP.

Population and methods: Patients with familial CPP demonstrating paternal (n=12) or recessive (n=10) inheritance from 11 pedigrees, their unaffected relatives (n=8), and 22 patients (3 males) with sporadic idiopathic CPP were included. CPP was diagnosed by clinical signs of central puberty, increased basal and/or peak luteinizing hormone, growth spurt and/or advanced bone age. Coding regions of the *MKRN3* gene and exon-intron boundaries were analyzed using Sanger sequencing in all probands. In the 6 probands with familial CPP without identified mutations in the reading frame and in sporadic males, *MKRN3* deletion and methylation analysis by commercially available methylation- specific MLPA (SALSA®MS"MLPA® - A probemix ME028-C1 Prader-Willi/Angelman) was performed.

Results: A previously reported heterozygous *MKRN3* mutation (c.482dupC) was identified and segregated with disease in 10 patients from 5 pedigrees with familial CPP, two pedigrees were distantly related. No mutations in the *MKRN3* gene were identified in sporadic patients nor in 12 patients from other 6 pedigrees with familial CPP. No abnormal methylation pattern or gene deletion was identified in any of the tested patients by methylation-specific MLPA. Estimated average age at the beginning of puberty in 8 female carriers of an *MKRN3* mutation was 6,3 years (range 5,3-8 years), two girls untreated with GnRH analog had menarche at 7 and 9 years. Two male carriers reported growth spurt at 9 years. Estimated average age at the beginning of puberty in patients without

identified *MKRN3* mutation was 6,5 years in 6 boys (range 4,5-8,5 years) and 5,8 years in 23 girls (range 1-8 years), two girls untreated with GnRH analog had menarche at 7,9 and 8,5 years.

Conclusions: We demonstrated a high frequency (45%) of *MKRN3* mutations in patients with familial CPP, but not in sporadic cases. Although MKRN3 is one of the gatekeepers of the postnatal activation of the gonadotropic axis, other inhibiting factors, are yet to be discovered.

P2-P310

Can Basal Levels of Luteinizing Hormone (LH) replace the GnRH Test in the Diagnosis of Precocious Puberty in Girls?

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Aim: To determine the sensitivity, specificity of basal LH measurement compared to the GnRH test in patients with Central precocious puberty (CPP) and determine the cut off point for basal LH to diagnose CPP.

Methods: 680 female patients were referred for presumptive diagnosis of central precocious puberty in the city of Bogota. All patients went through a GnRH test, using a Roche immunoassay for Luteinizing hormone (LH) and follicle stimulating hormone (FSH). The stimulus used was triptorelin pamoate measured at 0,30,60,90,180 minutes.

Results: 680 tests of GnRH were performed. The result was positive for CPP (peak LH greater than 5 uUI/ml) in 401 patients (59%). In 114 patients (16.8%) the basal HL result was positive (>0.1 uIU/ml) with a response peak < 5 uUI/ml. In 95 (14%) patients, the basal LH was negative with a time later than 5 uIU / ml, which explains why the test was considered reactive for CPP. 306 patients (45%) had basal LH > 0.1 uIU/ml and the peak was > 5 uUI / L once, confirming the test as reactive. The sensitivity of the basal LH is 76%, specificity 59%, positive predictive value 72% and negative predictive value 65%. The sensitivity increases with a cut-off point higher than 0.7 uIU / ml of basal LH, which is 92% in patients at puberty stages Tanner 4-5.

Analysis: The diagnosis of precocious puberty requires a judicious evaluation of clinical parameters, diagnostic images such as bone age and pelvic ultrasound, and the determination of activity of the hypothalamic-pituitary-gonadal axis. With the arrival of more sensitive of gonadotropin measurements, the replacement of dynamic tests for basal measurement of gonadotropins to determine the presence of ovarian activity was proposed. This study shows how the sole measurement of gonadotropins has a low sensitivity and specificity, with high sensitivity values at puberty stages greater than Tanner 3. he measurement of basal gonadotropins has an important role in monitoring the treatment for precocious puberty but it is not considered to be a good marker for the patient with suspected precocious puberty.

Conclusion: In girls with suspition of CPP, the determination of basal LH is not a good indicator of pubertal onset in patients with suspected precocious puberty, mainly in the early pubertal stages.

P2-P311

Incidence of Delayed Puberty in Adolescents. A Population-Based Study in a County in Central Sweden

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Introduction: Delayed puberty is defined as the absence of physical signs of puberty by the age of 14 years in boys and 13 years in girls. According to this definition, the prevalence of delayed puberty would be 2%, if the ages of pubertal onset were normally distributed in the population. However, the prevalence or incidence of delayed puberty has not been described before, as far as we know. Our aim was to study the incidence of delayed puberty in central Sweden.

Methods: In this population-based retrospective study all adolescents given the ICD-10 diagnosis "delayed puberty" in Örebro county during the period 2013-2015 were identified. Adolescents with other diagnoses potentially related to delayed puberty (e.g. short stature) were also identified to ensure that there were no additional cases. The medical records of these patients, except those not willing to participate, were systematically reviewed to ensure that the diagnosis was correct. The cases were then categorized into four groups depending on how accurate we found the diagnosis (certain, possible, wrong diagnosis, or unclear cases). Data on the total numbers of adolescents in Örebro county were obtained from the authority of statistics in Sweden.

Results: One hundred and twenty-eight of 180 eligible medical records were reviewed (response rate: 71 %). Nine boys and one girl were diagnosed with delayed puberty during the study time period and fulfilled our strict criteria for a certain diagnosis and 4 boys were classified as possible new cases. The total population in Örebro county for boys aged 14-18 years was on average 6,546 each year during the time period. The minimal annual incidence for boys was 46 per 100,000 (95% confidence interval (CI) 15-142 per 100,000). When possible cases were included, the annual incidence for boys increased to 66 (CI 26-170) per 100,000. Due to the low number of girls with delayed puberty no incidence for girls was calculated.

Discussion: This is, to our knowledge, the first study describing the incidence of delayed puberty in boys. We evaluated the accuracy of the diagnosis using strict criteria. The presented incidence should be regarded as the minimum incidence since some adolescents with delayed puberty may not seek medical advice or may be unrecognized by the health services in schools. Because of our small study population, larger studies are needed to confirm our findings and for calculation of the incidence in girls, where our data implies a much lower incidence.

P2-P312

Ultrasound Assessment of Pubertal Breast Development: Intra- and Inter-observer Agreement

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Background: Clinical assessment of pubertal breast development using Tanner staging is subjective. This has led to the introduction of ultrasound, aiming for a more objective analysis. However, information regarding its reliability is lacking.

Objective: To examine intra- and inter-observer agreement of breast maturity staging using ultrasound, and to examine the precision of direct measurements of the gland.

Materials and methods: Fifty-seven healthy girls (mean age 10.9 years, range 6.1 to 15.9 years) were examined independently by two observers using ultrasound to score the glandular maturity stage at a 0-5 scale, and to measure the depth and diameter of the left breast. One of the observers repeated the examination after 20 to 35 minutes to assess intra-observer agreement. Cohen's kappa with linear weights was used to examine intra- and inter-observer agreement of the ultrasound staging, while the measurement precision was analyzed using Bland-Altman plots and 95% limits of agreement.

Results: The agreement of ultrasound staging at a 0-5 scale was very good (kappa 0.84; 95% confidence interval (CI): 0.78, 0.91) for intra- and good (kappa 0.71; 95 % CI: 0.62, 0.80) for inter-observer. Measurements of glandular depth and diameter were unbiased for one observer, but the variances were large both within and between observers.

Conclusion: Ultrasound, using a 0-5 scale, is a reliable method to stage glandular breast tissue development during puberty in healthy girls and adolescents. Direct measurements of glandular tissue is however imprecise, which limits its use in clinical practice or research.

Keywords: Pubertal staging, breast development, ultrasonography, observer agreement, measurement error

P2-P313

Neuroendocrine Consequences of Hypothalamic Hamartoma and their Imaging (MRI) and Surgery Correlates

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Background: Hypothalamic hamartomas(HH) are rare heterotopic congenital malformations causing central precocious puberty (CPP) and/or resistant epilepsy whose natural history is unknown.

Aim: To describe clinical and imaging features, and the risk of developing endocrine deficits, particularly after surgery.

Method: Retrospective case note and imaging review of all HH diagnosed by MRI between 30.08.1991 and 24.11.17, analysed by initial presentation, imaging (Delalande grading), and surgery.

Results: 59(36male) children of median age 2.72 (antenatal-15.59) years at diagnosis presented with A) gelastic/dacrystic epilepsy (n32) at 5.62(0.16-15.59) years, B)CPP(n17) at 1.35(0.64-8.49) years or C)incidentally (n10) at 0.9(antenatal-9.78) years of whom one was diagnosed with CPP 0.41 years later. 14(9=GpA,5=GpB) respectively developed additional CPP after 1.83(0.19-5.83) or epilepsy after 0.55(0.17-1.0) years.

Despite 60% experiencing seizures in their first year, 37 with epilepsy, had a 2.96 years delay in HH diagnosis compared with 27 with CPP (Mann-Whitney $p<0.05$). Grade 1 tumours (below 3rd ventricle) were more often associated with CPP than Grade 2 or 3 tumours (above 3rd ventricle), more likely to cause epilepsy ($x^2p<0.05$).

66%(n=39/59) were followed endocrinologically for 5.32(0.29-14.34) years. At last assessment, BMI and height SDS were 0.54(-3.68_3.63) and 0.19(-1_1.80) respectively; in 66%(n=26/39) BMI increased by 1.05(0.1-4.18) SDS. GH deficiency (GHD) occurred in just 2 (unoperated).

20(18=GpA,2=GpB) underwent surgery (4=endoscopic, 10=open, 4=radiosurgery, 2=laser) for intractable epilepsy at 8.10(0.17-16.88) years, 3 of whom required multiple attempts [(endoscopic + laser) (4 endoscopic + open + radiosurgery), (open+ radiosurgery + open)]. In 14/20 followed after surgery, 4(29%) developed TSHD after 0.61(0.18-1.51) years, 3(21%) GHD at 1.89(1.40-3.45) years of whom 2 also had ACTHD and CDI [one after 3 endoscopic surgeries and another with additional TSHD**,** LH/FSHD after laser surgery and earlier CPP, and GHD from earlier endoscopic resection]. One patient developed isolated CDI and two hypodipsia after open surgery. GHD and ACTHD were associated with endoscopic surgery,$p<0.05$.

Conclusion: Grade 1 HH more often cause CPP, and grade 2/3 tumours epilepsy, but the features overlap and all should be endocrinologically screened for CPP, GHD and obesity over time. Surgery causes additional deficits in 50% of those operated, with life-threatening CDI and ACTHD in 15%, including one who received modern laser surgery. These data help inform therapeutic choices and hypothalamic morbidity in this disease and require close monitoring.

P2-P314

The Start Predictors of Puberty in Boys with Constitutional Delay of Puberty

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Objective: To examine the clinical and hormonal predictors of start pubertal in boys with constitutional delay of puberty (CDP).

Materials and methods: The study included 42 boys with CDP (Tanner1, max LH>10 IU/l of GnRH stimulation test). At the first

visit in 14.5±0.7 years we evaluated anthropometric indicators, bone age, testicular volume and hormonal status (TSH, freeT4, prolactin, IGF-1, insulin, DHEAS, cortisol, LH, FSH, estradiol, testosterone, SHBG, free testosterone index, inhibin b, antimullerian hormone). At the second visit after 1 years, we evaluated stage of sexual development on the Tanner scale. The patients were divided into two groups: Tanner 1 (n=9), Tanner 2 (n=33).

Results: At the first visit all patients had the same age (14,6±0,9 vs 14,5±0,7 years old, p=0,8), height (Me Ht-SDS -2,2 vs -1,7, p=0,1), weight (Me SDS-BMI-0,03 vs 0,07, p=0,3), bone age (Me SDS -3 vs -2,5, p=0,3), TSH (Me 2,2 vs 2 mU/l, p=0,9), freeT4 (Me 12,7 vs 13,1 pmol/l, p=0,5), prolactin (Me 201 vs 139,5 mU/l, p=0,1), IGF-1 (Me 187,6 vs 202,4 ng/ml, p=0,8), insulin (Me 4 vs 5,3 mcU/ml, p=0,4), DHEAS (Me 3,2 vs 3,7 nmol/l, p=0,3), cortisol (Me 379 vs 376,5 nmol/l, p=0,8), LH (Me 1,1 vs 1,3 mU/ml, p=0,3), FSH (Me 2,02 vs 2,6 U/l, p=0,7), estradiol (Me 73 vs 67 pmol/l, p=0,4), SHBG (Me 96,6vs 81,2 nmol/l, p=0,7), free testosterone index (Me 1,0 vs 1,8 %, p=0,1).

However, in boys with Tanner2 at the first visit testicular volumes was much more (Me 2,3 vs 1,4 cm^3, p=0,001), testosterone (Me 1,4 vs 0,8 nmol/l, p=0,03) inhibinB (Me 144,3 vs 120,9, p=0,03 pg/ml) were significantly higher and antimullerian hormone (Me 22,8 vs 57,3 ng/ml, p=0,03) was significantly lower than in boys with CDP and Tanner1.

The most informative predictors of start pubertal in boys with CDP during the first year were: testicular volume>1,7 cm^3 (sensitivity 70,4%, specificity 100%), inhibinB>143 pg/ml (sensitivity 57%, specificity 100%), testosterone>0,9 nmol/l (sensitivity 81%, specificity 71,4%). But the combination of inhibinB>143 pg/ ml with testicular volume>1,7 cm^3 increased diagnostic value (sensitivity 85%, specificity 100%).

Conclusion: The combination of inhibinB>143 pg/ml with testicular volume>1,7 cm^3 had the best sensitivity of 85% and specificity of 100% in predicting the start puberty during the first year in boys with constitutional delay of puberty.

P2-P315

Research on the Relationship Between Secular Trends of Pubertal Development and Obesity in Child and Adolescent

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Objective: To research the the relationship between secular trends of puberty development and obesity in child and adolescent in area of southwest China.

Methods: Selected respectively 4010 childs and adolescents aged between 6 and 17 years in April 2003 to May 2005, and 1387 childs and adolescents aged between 6 and 18 years in December 2013 to November 2015 in China Chongqing area.Height, weight and the breast, pubic hair development of girls, and the testicles, pubic hair development of boys were measured.Questionaire surveied the menarche age in girls and spermatorrhea age in boys.

We used mean and standard deviation, percentile to describe children physical development while chi-square test and Spearman rank correlation analysis were to test the correlation between puberty development and obesity.

Results:

1. In girls, during 2013-2015, the median age of breast and pubic hair developed to stage II was respectively 0.12 years (P > 0.05) and 0.71 years (P <0.05) later than the period 2003-2005,while the medianage of menarche was 0.28 years earlier than that in 2003-2005.

2. In boys, during 2013-2015,the median age of testis development(volume of testes≥4ml)and pubic hair developed to stage II was respectively 0.45 years (P > 0.05) and 1.28 years (P <0.05) earlier than the period 2003-2005,while median age of spermatorrhea was 0.31 years later than that in 2003-2005.

3. In girls, during the period 2003 to 2005 and 2013 to 2015, the overweight/obesity rates of early sexual maturation was significantly higher than normal sexual maturation group, Spearman correlation analysis suggested there was a positive correlation between early sexual maturation and obesity(r=0.178/0.281,P<0.05). BMI level from 2013 to 2015 in Tanner stage II or III was higher than the same period in 2003-2005 BMI level (P < 0.05).

4. In boys, during the period 2003 to 2005 and 2013 to 2015, the overweight/obesity rates was no difference between early sexual maturation group and normal sexual maturation group(r=0.009/0.058,P>0.05). However, BMI level from 2013 to 2015 in Tanner stage II was higher than the same period in 2003-2005 BMI level (P < 0.05).

Conclusion: The process of puberty in girls and the testis and pubic development in boys was accelerated during the decade in southwest China area. There were a positive correlation between early sexual maturation and increased obesity in both girls and boys.

P2-P316

Gonadotropin Levels and Frequency of Testosterone Supplementation in Adolescents with Klinefelter Syndrome

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Background: Klinefelter syndrome (XXY) is characterised by sex hormone aneuploidy. It is one the most common causes of primary hypogonadism, impaired spermatogenesis and testosterone deficiency. It affects around 1 in 500 phenotypic males. Approximately 25% of the patients are diagnosed in childhood. The hallmark of the condition is the small volume of the testicles and azoospermia. Most adolescent progress through puberty at the expense of elevated gonadotrophins.

Aim: To review the investigations, management and treatment all adolescents with XXY who were seen within a tertiary UK paediatric endocrine service.

Methods: We retrospectively reviewed the data for all adolescents with XXY born after 2000. All boys over 11 years of age were included. The pubertal stage was documented and whether gynaecomastia was present. The levels of LH, FSH and testosterone were recorded and finally whether additional treatment with testosterone was provided.

Results: Seventeen adolescents of pubertal age were identified with an age range of 11.7 to 17.1 years. The majority of the boys (13) were Tanner stage 3 to 5. Two patients did not have pubertal stage recorded and 2 were Tanner stage 1 or 2. Seven had gynaecomastia; this was the presenting symptom in 4.

The range of testosterone levels was 4 to 20.1nmol/L (normal range 8 - 30). Only one had a testosterone level in the upper half of the normal adult range (>19nmol/L).

In the group of adolescents with Tanner stage 3+, median LH was 18.2, FSH 54.6 and testosterone 10.65 nmol/L. This was at a median age of 15.2 years. The gonadotrophins were not elevated in one boy with Tanner stage 2, one other prepubertal boy did not have blood tests checked as yet.

Three out of the seventeen adolescents required testosterone treatment with a median start age of 15.9 years. Blood results showed a median LH 15.9, FSH of 68.2 nmol/L and testosterone of 9.8nmol/L. Four of the adolescents have not had blood tests.

Conclusions: Hypogonadism in XXY is common. Three out of thirteen boys who had blood tests done required testosterone treatment. Our group rarely had a testosterone level above the mid-adult range. These teenagers should continue to have on going surveillance to ensure adequate testosterone referrals. A referral to adult endocrinology and fertility teams should also be considered so that they are well versed in future management options.

P2-P317

The Effect of Letrozole on the Reproductive Function and Linear Growth in the Early and Mid Puberty Boys

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Objectives: To investigate the effect of Letrozole on the reproductive function and linear growth in adolescent boys.

Methods: 43 early and middle pubertal boy with seriously damaged predicted adult height(PAH), treated with letrozole 1.5mg/m2/d Po(>2.5mg/d) with a duration of 3-18 months were enrolled as Short-, medium- and long- treatment group with letrozole of 3-6, 6-12, 12-18 months, respectively. 48 healthy pubertal boys were enrolled as control. Genital stages were evaluated and serum concentrations of FSH, LH, T, E2, IGF-1, AMH and Inhibin B(INHB) were measured at the beginning, mid time and the end of letrozole treatment. Height velocity(HV), HtSDSba, PAH and the serum indexes mentioned above were compared at the beginning and after letrozole treatment.

Results: After letrozole treatment, compared with the control group, mid- and long- treatment group had obviously delayed bone age(BA) and increased PAH. The testicular volume of short- and medium- treatment group were significantly increased compared with the control group, while the long- treatment group had the same increment of testicular volume with the control group. The T levels in the three treatment group were significantly higher than their control group, as well as serum FSH, LH level and LH/FSH. Serum E2 level of long- treament group was significantly reduced than the control group.

17 cases of control group and 13 cases of treatment group had serum AMH, INHB level tested before and after letrozole treatment. Serum AMH level in the control group appeared with a decreasing trend with the progress of puberty, while the treatment group showed the opposite tendency. During the pubertal progress, serum AMH in the control group decreased as blood T elevated, but appeared falling delay in the treatment group.

Serum INHB increased after letrozole treament with non-statistically significant less increment in the treatment group compared with the control group.

For the linear growth, there was no significant height improvement in short- treatment group, while BA inhibition was evident in long- treatment group. PAH was significantly increased after letrozole treatment in medium- and long- treatment group.

IGF1SDS and HOMASDS had no statistical difference before and after treatment.

Conclusion: Letrozole can obviously promote the sex development in adolescent boys, with elevated serum T levels, reduced E2, delayed BA and improved PAH. As to the reproductive function, letrozole may have inhibitory effect on testis maturity and one cannot ignore sertoli cells function affected with letrozole exposure.

P2-P318

SOX3 Gene Duplication Associated with Midline CNS Malformations, Hypopituitarism and Neurodevelopmental Abnormalities: 5 Unrelated Cases

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Introduction: Duplications of *SOX3* at Xq27.1 are known to be associated with a spectrum of midline defects, isolated/multiple pituitary hormone deficiencies and learning difficulties. We report 5 cases of *SOX3* duplication with hypopituitarism and differing presentations.

1) Male neonate presented with poor feeding and prolonged jaundice. Investigations revealed central hypothyroidism and inadequate cortisol response to Synacthen. Appropriate hormone replacement was commenced. MRI showed pituitary hypoplasia and ectopic posterior pituitary. Array CGH revealed maternally inherited duplication of *SOX3*. He has a maternal cousin with hypopituitarism and another with spina bifida. At 10.7 years, he is of normal stature with severe expressive language delay.

2) 15yr old boy was referred with short stature (Ht -1.78SDS) and pubertal delay. He had brachycephaly, learning difficulties and hyposmia. Investigations revealed GH deficiency (low serum IGF1, peak GH 6.1mcg/l on glucagon stimulation test). MRI

showed partial agenesis of corpus callosum and absent septum pellucidum. Array CGH identified maternally inherited duplication of *SOX3*. Testicular volumes failed to progress to mature volume. Aged 20 yrs he is on full testosterone replacement.

3) Male infant noted on antenatal scans to have lumbar meningomyelocoele. Post-natal imaging showed hydrocephalus and agenesis of corpus callosum. He had micropenis, small testes; normal thyroid function and cortisol response to Synacthen at week 1 of life. Array CGH revealed *de novo* duplication of *SOX3* and part of chromosome 6. At 2 years of age, serum IGF1 measured 4.89nmol/L (RR: 3.67-14.8) & GH was 4.4mcg/L with cortisol of 452nmol/L on glucagon stimulation. He has bilateral optic atrophy and left temporal lobe epilepsy with severe developmental delay.

4) 4.9 yr old boy presented with short stature (Ht -3.52SDS) and mild developmental delay. Examination revealed clinodactyly, hypoplastic right thumb and hyperextensible fingers. CGH array revealed maternally derived Xq27.1 duplication including *SOX3*. Endocrine assessment is normal (fT4: 16pmol/l, peak GH: 26.2 mcg/l and cortisol: 612 nmol/l). MRI brain is pending.

5) 5yr old boy was referred with developmental delay and obesity. CGH array showed duplication of Xq27 to Xq28 including *SOX3*. Investigations revealed borderline fT4 (12.6pmol/l), normal TSH and undetectable GH on glucagon stimulation with normal cortisol levels. MRI brain showed anterior pituitary hypoplasia and ectopic posterior pituitary. Thyroxine and GH replacement have been initiated.

Conclusion: These cases expand our knowledge of the clinical phenotype associated with *SOX3* duplication in boys. Array CGH is recommended in boys with hypopituitarism and intellectual disability.

P2-P319

An 18 Month Old Boy with Hypoglycemic Convulsion and Obesity Due to POMC Deficiency

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Objectives: Proopiomelanocortin (POMC) is the polypeptide precursor of several peptides including adrenocorticotropic hormone (ACTH), melanocyte stimulating hormone (MSH) and β-endorphin. POMC deficiency is a very rare disease characterized by adrenal insufficiency, early-onset obesity, and pigmentation abnormalities.

Here we describe an 18 month old boy with central adrenal insufficiency, hypothyroidism, obesity and fair skin. Genetic analysis revealed a homozygous p.G99Afs*59 (c.296delG) mutation in the *POMC* gene.

Case: An 18 month old boy was referred for hypoglycemia. He was born to parents from close villages at 37 weeks gestation with a birth weight of 2,500 kg. Medical history revealed neonatal intensive care hospitalization for 28 days due to respiratory distress.

He was admitted to emergency department with seizure. The laboratory tests revealed hypoglycemia (venous glucose:30 mg/dl), hyponatremia, hypocortisolism as well as hypothyroidism. Morning ACTH was < 5 pg/mL, and cortisol was 0,488 µg/dl. Magnetic resonance imaging (MRI) of the brain and pituitary gland was normal. On his initial examination height SDS was 2,28 (90,5cm), weight SDS was 3,34 (17,2kg) and BMI SDS was 2,46 (21 kg/m^2). He was noted to have mild developmental delay, obesity, fair skin and hepatosplenomegaly. A homozygous p.G99Afs*59 (c.296delG) mutation in the *POMC* gene was detected. Thyroxine and hydrocortisone replacement was initiated.

Conclusions: Central adrenal insufficiency is rare in children. In our patient, p.G99Afs*59 mutation of the *POMC* gene results in ACTH deficicency subsequently leading to impaired adrenal steroidogenesis, dysregulation of food intake and early-onset obesity, increased linear growth, and melanocyte dysfunction. Early identification of these patients may enable early management of adrenal failure and its associated morbidities as well as severe obesity by novel therapeutic approaches.

P2-P320

Pituitary Stalk Interruption Syndrome (PSIS) is not a Rare Cause of the Congenital Hypopituitarism

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Aim: Pituitary hypoplasia, empty sella syndrome, and ectopic neurohypophysis are common causes of pituitary MRI of the patient with congenital hypopituitarism. We aimed to search clinical and radiological examination of the patient with congenital hypopituitarism.

Method: We evaluated age, diagnosis, laboratory evaluation, hormone deficiencies, accompanying diseases, and MR images of the patients with multiple pituitary hormone deficiency.

Results: Of the 50 cases, 54 % (n = 27) were female with mean age of 6.43 ± 5.15 years, and 7.09 ± 5.21 years for admission and diagnosis, respectively ($p<0.05$). The reasons for referral were as follows; short stature (n = 36), jaundice and/or cholestasis (n = 5), hypoglycemia (n = 4), thyroid test abnormalities (n = 4), menstrual problems (n = 3), polyuria/enuresis (n = 2), cyanosis (n = 2), micropenis (n = 1), constipation (n = 1) and weight gain (n = 1). The height, weight and BMI SDS were -3.18, -1.93 and -0.03, respectively. Hormonal evaluation revealed growth hormone deficiency (peak growth hormone response 0.84 ng / ml) in 48 cases, hypothyroidism (fT4 0.59 ng / dl, TSH 2.78 mIU / ml) in 40 cases, adrenal insufficiency (cortisol 2.8 mcg / dl, 14.2 pg / ml), sex hormone deficiency (LH 0.98 mIU / ml, E2 16.5 pg / ml, t. testosterone 0.86 ng / ml) in 25 cases. More than half of the cases with growth hormone deficiencies had very low IGF levels (<25 ng / ml). The third or fourth hormone deficiency appeared later in the 17 cases (34 %). MR imaging showed pituitary stalk interruption syndrome (PSIS) (54 %) in 27 cases, anterior pituitary hypoplasia in 9 cases (18 %), partial empty sella in 6 cases (6 %), and normal pituitary

defect in 11 cases (22 %). When the patients were divided into two groups as having PSIS and not, the prolactin level was significantly higher (44.97 vs 11.9 ng / ml, p <0.005) and the st4 level was significantly lower (0.58 versus 0.60 ng / dl, p = 0.019) in the PSIS group.

Conclusion: The striking feature of the study was diagnosing PSIS more than expected with a significantly higher prolactin level. Increased prolactin may help to diagnose for PSIS. The PSIS that genetic cause is still unclear must be kept in mind in the patient with hypopituitarism. Therefore, presence of stalk should be evaluated carefully in cranial imaging especially if there is an apparent ectopic neurohypophysis.

P2-P321

Pallister Hall Syndrome: An Unusual Case of Central Precocious Puberty, Prolonged Vaginal Bleeding, Gelastic Seizures and Polysyndactyly in a 3 Month Old Infant

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Introduction: Central precocious puberty (CPP) at a very early age is usually caused by an organic lesion. The most common organic cause of CCP is the hypothalamic hamartoma (HH), which, associated with polysyndactyly, cleft palate and gelastic crises, clinically suggests the diagnosis of Pallister Hall Syndrome.

Case: Infant 3-month-old woman with no family history. Polydactyly in hands and feet is evident from the second trimester of pregnancy. Born at 41 weeks. Weight 3330 g, length 52 cm, cephalic perimeter 33 cm. Posterior cleft palate, and polysyndactyly in hands and feet.

Echocardiography evidences ostium secundum -type interauricular communication. From the first months of life, she reports stereotyped episodes of facial expression change, such as sudden laughing or crying of about 4-5 seconds suggestive of gelastic seizures. At 6 months of age, consultation for vaginal bleeding present from birth, with frequencies 1-2 times a month.

Bilateral breast tissue was observed with hyperpigmented areolas, visible urinary meatus and vaginal introitus where the vaginal wall protrudes, so that, in view of this finding, she is transferred for assessment and follow-up by urology. We performed a peak GnRH stimulation test of LH and 79 U / L and FSH of 16.26 U / L, Estradiol 116.47 pg / mL, findings compatible with central precocious puberty.

MRI showed an oval, solid, suprasellar lesion measuring 20 x 18 x 13 mm in diameter, compatible with pedunculated hypothalamic hamartoma. In pelvic MRI of uterus increased in size, with a cervix / fundus ratio greater than 1 with marked endometrial thickening.

We successfully treated her with GnRh analogues (aGnRH), initial dose of 1875 mg: 0, 14, 28 days and then with 1,875 mg every 28 days. A genetic study was performed with the result GLI3 GEN: pathogenesis mutation not described: exon 15 c.3439G> T confirming the diagnosis of Pallister Hall syndrome. Gelastic seizures were treated with oxacarbamazepine, and the surgical resolution of the cleft palate and polysyndactyly was performed.

Conclusion: Precocious puberty at an early age with prolonged vaginal bleeding may be caused by an organic cause. Phenotypic anomalies with gelastic seizures lead us to a Pallister Hall syndrome.

Our patient is one of the youngest infants presenting with CPP and HH in Spain and the treatment was successful after the first doses of aGnRH.

P2-P322

Primary Empty Sella Syndrome and Clinical Endocrine Polymorphisms in Children: A Report of 15 Cases

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Introduction: Primary empty sella syndrome (ES) is rare in children. Reports relating it with various endocrine manifestations have been published. Asymptomatic cases have also been reported, this questions the existence of causal relationship.

Objective: To analyze causal relationship between primary ES and endocrine manifestations in 15 pediatric cases seen in our clinics, and suggest patients follow-up.

Population & Methods: retrospective review of 15 children diagnosed with primary ES. Anthropometric measures, mode of presentation, clinical manifestations and associated endocrine manifestations were extracted from medical records. Results of endocrine work-up and cranial MRI were analyzed.

Results: 15 cases of primary ES were gathered (11 boys and 4 girls, mean age 11 years [range 3 yrs 5/12 to 17 yrs 8/12]), 4 patients were obese. Cranial MRI was performed to investigate endocrine abnormalities in 10 cases, 1 patient had Noonan syndrome. MRI was performed for other reasons in 3 cases, ES discovery was fortuitous in 2 cases. Endocrine manifestations were present in 11 patients (7 GHD, 2 HH, 3 pubertal delay (2 in association with GHD, isolated in 1), 1 boy had CPP. Primary ES was total in 9 cases and partial in 6 (pituitary height 3mm: 5 cases; 2-2.5mm:7 cases; < 2mm: 1 case). There seemed to be no relationship between pituitary height and the type of endocrine manifestations. After over 10 years follow-up the arachnoidocele persisted in all cases without additional symptoms or endocrine abnormalities. GHD occured secondarily in 1 patient at age 11 years (ES diagnosed at 3 yrs 3/12), endocrine testing remained unremarkable in another case diagnosed at 6 yrs 5/12.

Discussion: In primary ES, pituitary gland is pushed to bottom or one side of the sella by herniation of subarachnoid space into sella turcica (different from pituitary hypoplasia). Physiopathological mechanisms to explain association of ES with various pituitary pathologies remain unclear. ES is also found in asymptomatic patients. GHD is commonest endocrine manifestations associated with ES, it may occur over time. Lack of correlation between pituitary height and reported pathologies, and variability of associated manifestations raises the question of causality relationship which remains debatable. We suggest annual follow-up (growth, oph-

talmological, neurological and pubertal screenings) with baseline endocrine testing in asymptomatic children. Control MRI, every two years has been our practice despite not being evidence-based.

Conclusion: inspite of being rare in children, ES is associated with endocrine manifestations in some patients. Close follow-up is mandatory in affected children.

P2-P323

Growth Hormone Deficiency (GHD) in a Patient with Persistence of the Craniopharyngeal Canal with Cephalocele

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The patient was referred to our Centre for short stature. Weight and length at birth were within normal limits. In the neonatal period he showed jaundice and hypoglycemia. A reduced growth velocity was reported from the age of six months. At 15 months his length was 70 cm (-3,75SDS), his weight 8,1 kg (-2,26SDS). Parental target height was 167,6 cm (-1,38 SDS). He had normal psychomotor development. The examination showed macrocrania and nasal voice. Blood count, liver and renal function, screening for coeliac disease, thyroid function tests, ACTH, cortisol were within normal limits. IGF1 was undetectable. Growth hormone stimulation test with arginine (0,5 g/kg ev.) showed a growth hormone (GH) peak of 1,2 ng/ml. The brain MRI displayed the persistence of the craniopharyngeal canal with cephalocele and dysmorphic hypophyseal peduncle which reaches the nasopharynx mucosa with stenosis of the air column behind the choanae. Moreover, it showed a malformation of the hypothalamus-chiasmatic region, with apparent absence of the crossing of the fibers of the optic nerves. The patient was diagnosed with GHD associated to cerebral malformation. The patient underwent surgical reconstruction of the sellar floor and correction of the trans-sphenoidal cephalocele. The histological examination of the rhinopharyngeal tissue showed „nasopharyngeal mucosa, and dense fibrous tissue due to meninges, infiltrated by adenohypophysal tissue". After surgery, the blood test were diagnostic of panhypopituitarism (TSH 0,26 mcU/ml, FT4 0,73 ng/dl, FT3 1,43 pg/ml, ACTH 2,2 pg/ml, cortisol 20 ng/ml). The patient was replaced with hydrocortisone, GH, and levothyroxine. He also developed diabetes insipidus and required desmopressin. Currently, the patient is on neuroradiological, ophthalmological, neurosurgical, and endocrinological follow up. Genetic analysis with next generation sequence (NGS) technique for genes associated with short stature was performed (pending result). The craniopharyngeal canal is a rare defect. According to the classification of T.A. Abele et al. (AJNR Am J Neuroradiol 35:772–77 Apr 2014), our patient had a type 3A canal, which consists in a canal containing cephalocele. The persistence of the craniopharyngeal canal has been described in association to SOX3 deletion (J Clin Endocrinol Metab, December 2014, 99(12):E2702–E2708). This case underlines the importance of performing brain MRI in children diagnosed with GHD to identify structural abnormalities of the hypothalamic-pituitary region. Accurate diagnosis and surgical treatment of craniopharyngeal canals are important in order to prevent infective complications such as meningitis, and to provide a multidisciplinary follow-up.

P2-P324

Endocrine-Metabolic Characterization of Pediatric Patients with Craniopharyngioma. A Single-Centre Cohort Study

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Craniopharyngioma is a rare, embryonic malformation of the sellar/parasellar region with low histological grade. In childhood-onset craniopharyngioma (CoCR), endocrine dysfunctions, severe obesity and metabolic syndrome (MetS), neurological impairment and reduced quality of life have been described as consequences of both localization and treatment.

To characterize a population with CoCR and to correlate endocrine/metabolic sequelae with different surgery approach we performed a retrospective longitudinal study on a single-centre cohort of 66 children (36 males) with CoCR, followed from 1990 to 2017. Clinical evaluations were performed yearly.

Age at diagnosis (7.24±4.92 yrs), established in 34/66 patients, was not statistical different between sex. Clinical presentation was heterogeneous: neurological symptoms (55.2%), growth retardation (13.8%), diabetes insipidus (DI) (13.8%), pubertal disorders (6.9%) and other symptoms (10.3%); in 1 case severe obesity was the unique presentation symptom. Only patients with pubertal disorders were older than others. Surgery technique was defined for 32 patients: in 90.6% tumour was removed (by craniotomy in 82.8% and by transsphenoidal/transventricular approach in 17.2%); partial resection was found in 85.7%. Patients who underwent craniotomy were significant younger (p=0.009), probably reflecting the easier feasibility of this technique. Pituitary deficiencies developed in majority of cases after diagnosis: hypothyroidism in 92.9%, central adrenal insufficiency (cAI) in 91%, DI in 78.6%, growth hormone deficiency in 74.5% and hypogonadism in 73.1%. The first disorders that appeared were hypothyroidism, cAI and DI. Only DI was correlated with surgery approach, with a significant prevalence in craniotomy technique (p=0.001), even in case of partial resection. Obesity at the end of follow-up showed no correlation with surgery approach/extension. For 8 patients (4 males) we had data about body mass index (BMI) both at diagnosis and at the end of follow-up: all patients had normal BMI at diagnosis, but 2 patients (1 male) were obese at the last visit. BMI SDS at last control was significant correlated with BMI SDS at diagnosis; no significant differences were found in age at diagnosis, duration of follow-up, surgical approach/extension.

In our cohort of patients with a long follow-up, cAI was present in >90%, indicating the need of frequent assessment of adrenal axis function to avoid adrenal crisis. We also found that BMI during follow-up was related to BMI at diagnosis. We suggest that in every patient, especially in those with initial overweight/obesity, criteria of MetS (waist circumference, blood pressure, glucose and lipid profile) should be strictly evaluated.

P2-P325

Growth Hormone (GH) Secreting Pituitary Adenomas in Paediatric Practice: 5 Cases Over 20 Years in a Single Tertiary NeuroEndocrine Centre

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Background: Pituitary adenomas secreting GH rarely present in childhood. We report the clinical features, management and outcome of the 5 cases referred to a tertiary Paediatric Endocrine/Neurosurgical service over a 20-year period.

Patients: 4 Male:1 Female - all aged 15 years at referral. Tanner puberty stages G3-5; B3. Clinical follow-up data range 2 months – 8 years.

Clinical features at presentation: Headache, n=4, Acromegalic features (skeletal/soft tissue) 4, Visual field (VF) defects 3, Gigantism (Males tall for parental Target limits; 196.5, 203, 189.4 cm) 3, arrested puberty 1, secondary amenorrhoea 1, café-au-lait macules 2, Acanthosis nigricans 1, galactorrhoea – none.

Endocrine baselines: Serum IGF1 mild to markedly elevated(66 – 148 nmol/L RR<66nmol/L); nadir GH to oral glucose load 3-11 mcg/L (n=3); random GH 9.7 and 115 mcg/L in other patients. Elevated Prolactin n=2: 1570 mIU/L (with secondary amenorrhoea) and ~45,000 mIU/L (with arrested puberty). Anterior pituitary hormone deficiencies: ACTH 2, TSH 1, Gonadotrophins 2.

MRI imaging: sellar/suprasellar macroadenomas range 17 to 58mm maximum dimension. Three tumours showed cavernous sinus invasion at presentation.

Treatment modalities: Transsphenoidal tumour debulking n=5, Somatostatin anologue 4, Cabergoline 2, Cranial irradiation 4 (likely to become 5), Pegvisomant 1. Pituitary hormone replacement at last review (T4, hydrocortisone, sex steroids or DDAVP) n= 3. Patient adherence with somatostatin analogue and Pegvisomant prevented full benefit in 2 cases.

Tumour Histology: Somatomammotrophoma 3, somatotrophoma 2; Ki67 range 1 – 8%.

Family Histories: No pituitary or other endocrine tumours known.

Genetics: One patient positive for heterozygous *AIP* mutation c.910C>Tp.Arg304Ter. No tests 3 patients; outstanding 1 patient (*AIP* / *MEN1* / *GNAS*). The 2 patients with café-au-lait macules had no other features of McCune-Albright syndrome, in particular there was no evidence of fibrous dysplasia or precocious puberty.

Conclusions: These rare patients present significant management issues, given their age at presentation, psychological and educational challenges in addition to the complex and long-term treatment strategies. Their care requires close collaboration between Paediatric and Adult Endocrine, Neurosurgical and Clinical Oncology Teams.

P2-P326

Pituitary Adenomas in Children and Adolescents: A Retrospective Single-Centre Analysis

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Background: Paediatric pituitary adenomas are rare and mostly benign disorders which may secrete pituitary hormones. Prolactinomas account for half of all pituitary adenomas (PROLA), followed by non-secreting adenomas (20-40%; incidentalomas), adrenocorticotropic-hormone secreting adenomas (10-30%; ACTHA) and growth-hormone-secreting adenomas (5-15%; GHA).

Methods: In this single-centre retrospective analysis clinical, biochemical and radiological features of paediatric patients with pituitary adenomas diagnosed between 2000 and 2016 were extracted from the electronic patient´s chart and analysed.

Results: 22 patients with pituitary adenomas were identified: 12 PROLA (54%, aged 11-16.6 years; 8 females, 4 males), 4 incidentalomas (18%, aged 10.9-16 years; 3 females, 1 male), 3 ACTHA (14%, aged 8-12 years; 1 female, 2 males) and 3 GHA (14%, aged 9.3-17.9 years; 3 males). Incidentalomas and ACTHA were all microadenomas in contrast to GHA which were giant adenomas with infiltrative growth (diameter 1.9-6.2 cm). PROLA consisted of 7 macro- (diameter 1.4-3.6 cm) and 5 microadenomas (diameter 0.3-0.9 cm).

PROLA presented with headaches (67%) and pubertal delay (67%). All macro-PROLA with prolactin concentrations >10.000 mU/l had at least one pituitary hormone deficiency. ACTHA presented with cushingoid features and headaches. GHA displayed tall stature, headaches and hypopituitarism (2/3). Nausea, headaches, precocious puberty, mental retardation and epilepsy occurred in incidentalomas.

Cabergoline induced normoprolactinemia (8/11), reduced mean tumour volume by 80% and ameliorated clinical signs in PROLA. Operative tumour resection was performed in ACTHA. Symptoms improved, but all of them experienced secondary adrenal insufficiency and hypopituitarism (n=1). GHA were partially resected followed by treatment with lanreotide or pasireotide, with clinical improvement in all and reduction of GH secretion by 56%. However, somatostatin analogous failed to reduce tumour volume. Incidentalomas were observed, but lost to follow-up.

Conclusion: Prolactinomas are most common pituitary adenomas even in children. In contrast to ACTHA and GHA clinical signs are unspecific in PROLA and incidentalomas. Adolescents with headaches and pubertal delay should be investigated for PROLA and incidentalomas. Cabergoline is effective and well tolerated in PROLA by reducing clinical symptoms, prolactin concentrations and inducing tumour shrinkage. Complete tumour resection in ACTH-secreting adenomas ameliorates clinical signs, but may be complicated by secondary adrenal insufficiency. Somatostatin analogues improve clinical symptoms in GHA, but do not reduce tumour size. Incidentalomas may only require symptomatic treatment or observation.

P2-P327

Changes of Body Composition of Male Adolescents with GH Deficiency Are Diagnostic During Transition

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Background: Restarting rhGH treatment in adolescents with childhood-onset GH deficiency (CO-GHD) is usually based on the GH re-test, IGF-1, additional pituitary hormone deficiencies and pituitary gland morphology, but not on body composition. Short-term changes of body composition in adolescents with CO-GHD when off rhGH may contribute to the identification of those in need of continuation of treatment.

Study design: In this prospective single-centre study the body composition of 58 adolescents (12 females) with CO-GHD and low-likelihood GHD of adolescence was measured by DXA 6 months before and at rhGH stop as well as 6 and 12 months thereafter. At diagnosis mean age had been 5.4 y, height -2.85 SDS and stimulated GH peak 5.0 ng/ml. Treatment with rhGH was stopped at 16.4 y at near-final height of -0.48 SDS (target height -0.45 SDS). The adolescents were re-examined after 3 months off rhGH using serum IGF-1 and GHRH-arginine test. GHD of adolescence was defined by stimulated GH < 16 ng/ml and IGF-1 < -1.9 SDS.

Results: In males, those with GHD of adolescence (n=5) gained significantly more relative and absolute fat mass and lost significantly more relative lean body mass during the first six months off rhGH than the healthy individuals (n=41) (P<0.005). These changes were non-significant in females with GHD of adolescence (n=4) (P>0.4). During the first six months off rhGH the sum of absolute fat mass gain und lean body mass loss (kg) correlated highly with the GH peak of the re-test in males (R=0.54; P<0.001), but not in females (R=0.004; P=0.88).

Conclusions: Short term changes of body composition when off rhGH are good clinical markers of GHD in male adolescents, but not in females. Physiological differences in muscle mass, fat mass and testosterone levels may cause these sex differences.

P2-P328

AMH and Inhibin B Level in Girls with Central Precocious Puberty

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Background/Aim: Anti - Müllerian hormone (AMH) and Inhibin B (INHB) are considered as possible biomarker of central precocious puberty(CPP). This study investigated serum AMH and INHB level in central precocious puberty andanalyzed clinical factors associated with these two hormone levels.

Methods: In total, 48 girls with CPP and35age – matched prepubertal girls were enrolled in the study. The subjects were divided into two groups as CPP and control. AMH and INHB levels were determined in the two groups. In CPP group, AMH and INHB level were evaluated in pretreatment, six - months and twelve – months after GnRH agonist(GnRHa) treatment.

Results: The mean INHB levels of the CPP group were significantly higher than control(54.82 ± 48.65 and 16.17 ± 7.01pg/L, respectively, $p < 0.001$). AMH levels were not different between two groups. After GnRHa treatment, AMH and INHB levels were decreased significantly. Age was negatively correlated with AMH and positively correlated with INHB.

Conclusions: Inhibin B level is possible marker to differentiated CPP to control and reversed with GnRHatreatment in CPP. It remains unclear whether a decrease in AMH is due to the effect of GnRHa or a natural decrease in age.

P2-P329

Gender-Related Differences in Etiological Distribution of Organic Causes of Central Precocious Puberty

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Introduction: Organic lesion underlying central precocious puberty (CPP) is common in boys, and rare in girls. We aimed to compare the etiological distribution of organic causes according to gender, and define the clinical-laboratory characteristics that predict an organic cause to CPP.

Subject and Methods: Medical records of 260 girls and 120 boys with CPP were reviewed retrospectively to analyze the clinical, laboratory characteristics, radiological findings, and gender related differences in organic etiology.

Results: Organic pathologies were more common in boys (26/120; 21.7%) than girls (16/260; 6.2%) (p<0.001). Among girls

3.5% (9/260), and 5% of boys (6/120) had epilepsy and mental motor retardation with developmental anomalies of CNS on admission. None of the remaining 251 girls and 114 boys had any sign or symptom suggesting a CNS lesion, however pituitary MRI revealed a space-occupying lesion in 7.4% (27/365) of this population. A newly identified space occupying lesion was more common in boys (20/114, 17.5%) than in girls (7/251, 2.8%). Suprasellar arachnoid cysts (8/20) and hypothalamic hamartomas (6/20) were more common in boys, whereas less common lesions were hemorrhagic macroadenoma (1/20), optic gliomas (2/20), craniopharyngioma (1/20), pineal germinoma (1/20) and pinealoblastoma (1/20). In girls, suprasellar arachnoid cysts (2/7), hypothalamic hamartomas (2/7) and hemorrhagic macroadenomas (2/7) were equally common; one girl had chiasmatic optic glioma (1/7). Pituitary MRI also revealed incidental findings (microadenoma and pars intermedia cyst) in 22 girls and 11 boys. Overall, developmental anomalies of CNS (56.2%) is more frequent in girls, whereas space-occupying lesions (76.9%) are more frequent in boys ($p<0.05$). Arachnoid cysts were nine times (8/114 vs 2/251), and hamartomas were seven times (6/114 vs 2/251) more common in boys in comparison to girls, whereas incidental findings were similar (8.8% vs 9.6%). Age of onset was younger, bone age more advanced, height SDS corrected for bone age lower, and sex steroid levels were higher in organic vs idiopathic PP. Onset of pubertal findings was before 6 years in all girls, and 7 years in all boys with newly identified CNS pathology.

Conclusion: Organic cause underlying CPP is quite rare in girls older than 6 years, and boys older than 7 years. The frequency and distribution of organic etiology differ between girls and boys. It is more likely to identify a new asymptomatic space-occupying CNS lesion, mainly arachnoid cysts and hamartoma underlying CPP in boys, whereas previously known symptomatic developmental anomalies are more common underlying organic cause in girls.

P2-P330

Final Adult Height in Girls with Idiopathic Central Precocious Puberty Treated with Monthly Leuprorelin Acetate vs Triptorelin Acetate

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Background: Gonadotropin-releasing hormone analogs (GnRHa) are the standard treatment of central precocious puberty (CPP). Many studies demonstrate the effects of GnRHa on preserved final adult height. However, data compares the efficacy of different GnRHa on growth outcome and gonadotropin suppression in girl with CPP was limit

Objective: Evaluate the effect of 2 different GnRHa on final adult height (FAH) and gonadotropin suppression in girl with CPP

Design: Retrospective study

Method: Reviewed the medical record of girls with idiopathic CPP and had been treated with leuprorelin acetate or triptorelin acetate intramuscular injection every 4 weeks at Phramongkutklao Hospital who are now reach FAH determine by growth velocity during the preceding year was less than1 cm and/or a bone age of 16 years

Results: Thirty-five girls, 20 treated with leuprorelin acetate (LA group) and 15 with triptorelin acetate (TA group) were enrolled. Mean age at time of treatment was 8.38 + 0.75 and bone age was 11.09 + 1.37 years in LA group while mean chronological age at time of treatment was 8.18 + 0.41 and bone age was 10.72 + 0.98 years in TA group. There were no different in height SDS, weight SDS, BMI SDS, predicted adult height (PAH), dose of GnRHa at the time of diagnosis and target adult height (TAH) between the groups. However, the duration of treatment in TA group was significantly longer than LA group (3.36 + 0.57 vs 2.38 + 0.89 years, $p = 0.001$) and they were discontinued treatment at older age (11.55 + 0.5 vs 10.76 + 0.76 years, $p = 0.002$). At 6 month after GnRHa treatment, 16.7% in LA group reveals inadequate gonadotropin suppression and peak LH was significantly higher in LA compare to TA group (2.59 + 2.44 vs 0.78 + 0.15 mU/L, $p = 0.03$). In both groups, FAH were comparable with to TAH. The height gain from PAH (FAH-AcPAH) was significantly higher in TA group compare with LA group (5.67 + 4.20 vs 1.88 + 4.92 cm, $p = 0.02$) but after using a one-way ANCOVA controlling for duration of treatment and age of discontinue treatment, no significant different in FAH-AcPAH between 2 groups were found ($p = 0.394$)

Conclusion: Girls with idiopathic CPP treated with GnRHa reach their FAH comparable with PAH and TAH. No different in FAH and FH increase over PAH between LA and TA. LH suppression was more pronounced in TA group

P2-P331

The Impact of Central Precious Puberty on Health-Related Quality of Life and Social, Emotive and Behavioral Competences Among Children Treated with GnRHa

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Background: Central precocious puberty (CPP) may affect quality of life (QOL) due to premature body and psychological changes that characterize this pathology. Few data are available on health-related quality of life (HRQOL) and social, emotive and behavioral competences in CPP children treated with gonadotropin-releasing hormone agonists (GnRHa). This study aimed to investigate these aspects in a group of CPP girls during therapy.

Methods: 54 CPP girls were evaluated during GnRHa treatment. HRQOL was analysed through the administration of questionnaires both to parents and patients: Pediatric Quality of Life Inventory™ 4.0 Generic Core Scale (PedsQL) and 36-item Short-Form Health Survey (SF-36). Social, emotive and behavioral competences were evaluated with Child Behavior Checklist (CBCL 6-18), administered to parents. Pubertal signs, auxological data, bone age and uterine length were collected to estimate the treatment's efficacy at the beginning, after first and second year, and at the end of the therapy.

Results: The results of both patients' questionnaires and parents' questionnaires were no significative different from the scores of general population. In CBCL, the lowest scores appeared in somatic complaints (pathologic in 34,6% of patients) and internalizing problems (pathologic in 21,2% of patients). Moreover, PedsQL showed low scores in emotive functioning of CPP patients.

Conclusions: HRQOL and social, emotive and behavioral competences of CPP patients treated with GnRHa are not lower than general population. This may be caused by the improvement in the management of CPP patients from the appearance of pubertal signs.

P2-P332

Basal and GnRH Analog-stimulated Peak LH Levels for Diagnosing Girls with Early Phase of Central Precocious Puberty

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Background: Subcutaneous gonadotropin-releasing hormone (GnRH) analog test is an alternative to standard intravenous GnRH test for diagnosing central precocious puberty (CPP). Previous studies showed different cutoffs of basal and peak serum LH levels following intravenous GnRH and subcutaneous GnRH analog for diagnosing CPP girls. However, no study that defined the discriminating basal and peak LH levels among CPP and premature thelarche (PT) girls with different breast Tanner stages, is available.

Objective: To determine basal and GnRH analog-stimulated peak LH levels for differentiating girls with PT and CPP at breast stages II and III.

Methods: Medical records of 515 girls with breast onset before 8 years of age who underwent subcutaneous GnRH analog test between the years 2007 and 2017 were reviewed. Girls who had progressive breast development and accelerated growth during a 3-6 month period of follow-up, advanced bone age and pubertal-sized uterus and ovaries were diagnosed with CPP. The girls who had no above-mentioned findings were classified as having PT. In each group, patients were divided into 2 groups according to their breast stages at the time of GnRH analog testing, Tanner II (CPPII and PTII) and Tanner III (CPPIII and PTIII). The GnRH analog test results were analyzed.

Results: Of 515 girls, there were 121, 126, 211 and 57 girls with CPPII, PTII, CPPIII and PTIII, respectively. Their median (IQR) ages at the breast onset were 7.6 (7.2, 7.9), 7.4 (6.8, 7.8), 7.6 (7.0, 7.9) and 7.1 (6.3, 7.6), respectively. Basal and peak LH levels of 0.11 and 5.02 IU/L, respectively provided the sensitivity and specificity of 72% and 82%, and 79% and 91%, respectively in diagnosing CPP. Among the 4 groups, basal and peak LH levels were highest in CPPIII girls [median (IQR) basal LH: 0.24 (0.11, 0.63) IU/L, $p<0.001$; peak LH: 9.53 (5.92, 8.35) IU/L, $p<0.001$]. Subgroup analysis revealed that basal LH cutoff of 0.21 IU/L had 38% sensitivity and 94% specificity in discriminating CPPII from PTII while it provided a sensitivity of 56% and a specificity of 97% in differentiating CPPIII from PTIII.

Conclusion: A single basal serum LH level of greater than 0.21 IU/L can be used for diagnosing girls with CPP. With this basal LH level, CPP can be diagnosed without GnRH analog test in approximately 38% and 56% of girls with Tanner II and III, respectively.

P2-P333

Determination of Urinary Metabolic Profiles of Children with Central and Peripheral Precocious Puberty

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Puberty is a physical, hormonal and psychosocial transition from childhood to adolescence. Precocious puberty (PP) is the beginning of secondary sexual characteristics before eight years of age in girls. The most common type is known as „central precocious puberty (CPP)". CPP occurs due to early activation of the hypothalamus-pituitary-gonad (HPG) axis. Although the real trigger for idiopathic CPP is unknown, it has been proposed that it may be caused by the interactions between genetics, neurotransmitters in central nervous system and hormonal factors. „Peripheral precocious puberty (PPP)" is a rarer and different condition. In PPP patients, there is a deactivation of the HPG axis depending on the peripheral causes. Today, innovative technologies enable detailed screening analyzes of genomes, transcriptomes, proteomes and metabolomes. The most recent "omics technology" is "metabolomics". In metabolomics, metabolites (<1000 Da) in a multitude of different physical properties in a tissue or body fluid can be both qualified and quantified, usually by gas chromatography-mass spectrometry (GC-MS). After the complex chromatograms were separated, the retention times of the peaks are corrected and metabolites can be identified using indexed libraries and evaluated statistically. The aim of this study was to determine urinary metabolic biomarkers that could be used for CPP and PPP diagnosis or perhaps for treatment. Control girls (n=50) with no history of any endocrine disorder, girls with CPP (n=50) and girls with PPP (n=50) with age ranges of 8-10 years were recruited to the study. After extraction, derivatization and GC-MS analysis, urinary metabolic profiles of the study groups were compared by using principle component analysis (PCA) and principle component analysis (PLS-DA). We found that glycolic acid, porphine, leucine, P-cresol and fructose levels were different among the study groups. Moreover, in PPP group; glucose, mannitol glycolic acid and tyrosine levels were markedly increased vs. control. In CPP group, leucine and mannitol levels were higher than control girls. When we compared PPP and CPP groups, porphine, P-cresol, leucine, creatinine, inosine, mimosine and glycolic acid were higher in CPP group vs. PPP group. These findings show that both protein and carbohydrate metabolisms are different among the study groups. However, our results indicate that urine may not be a good biological fluid to determine the metabolic differences in girls with CPP and PPP and plasma may be better choice to investigate the differences between the metabolomics profiles of girls with CPP or PP.

P2-P334

Hypertension During GNRH Analogues Therapy in a 10-Year-Old Girl

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We report a case of a 10-year-old girl born at 41st week and spontaneous birth, in therapy with analogous GnRH for idiopathic central puberty. At 4 years bilateral thelarche, performed first and second level investigations and recives diagnosis of early idiopathic central puberty. Since then, therapy with triptorelin 3.75 mg i.m every 21 days was administrated. Regular checks, good compliance, and response to therapy. At 10 years old recurring episodes of headache and vertigo. Clinical examination was negative. Height 1.5 SDS, weight -0.3 SDS, Tanner stage was P2 B1. Blood pressure (BP) was 124/90 mmHg (95-99th centile for systolic and >99th centile for diastolic). Pressure values were confirmed in several ambulatory and home assessment and were suggestive of stage I hypertension. Ambulatory BP monitoring revealed: mean 24 h systolic/diastolic BP 116/79 mmHg, mean day time and night time systolic/diastolic BP 118/80 and 110/73 respectively, nocturnal dipping 8,7%, and diastolic BP load 39,9%, confirming a stage I hypertension. Electrocardiography and echocardiography were normal. Renovascular and renal parenchymal diseases and endocrine causes of hypertension were excluded. Considering the girl symptomatology, anti-hypertensive therapy was started (Enalapril 0,15 mg/kg/die). No improvement of BP values were observed and GnRH-analog therapy was discontinued. Later the girl showed normalisation of BP values, and Enalapril was stopped. To date BP values persists on normal range for sex, age and height.

Triptorelin is a GnRH agonist used for treatment of central precocious puberty because it suppresses pituitary gonadotropin secretion when administered continuously. Tolerance to GnRH agonist is usually good, although adverse effects such as headaches, rash, gastrointestinal compliants were observed.

In the last years few case reports were published, suggesting a link between GnRH agonist treatment and hypertension. If we consider that: I) the patient had a normotensive condition at the beginning of therapy, II) blood pressure returned to normal values after discontinuation of triptorelin and, III) normal BP values were maintained even after antihypertensive drugs withdrawal, we suggest that hypoestrogenism induced by GnRH agonist treatment might have played a role in the development of high BP.

P2-P335

The Effect of Polychlorinobiphenyls on Premature Puberty in Girls

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Introduction: Studies show that onset of puberty in girls is occurring at increasingly younger ages. Environmental endocrine disruptors are implicated in the etiology of early puberty. Polychlorobiphenyls (PCBs) are one of the endocrine disruptor with proven estrogenic effects.

Aim: To investigate the effect of PCBs on premature puberty in girls.

Materials-Methods: The study group was selected from girls aged 2-8 years with a diagnosis of idiopathic premature puberty or isolated premature thelarche at the Pediatric Endocrinology Clinic (Group 1). The healthy control group consisted of girls aged 2-8 years with no chronic disease or pubertal findings (Group 2). In Group 1, stages of puberty according to Tanner, anthropometric measurements, bone age, ovary and uterus dimensions with pelvic ultrasonography, basal serum LH, FSH, and E2 serum levels, and the luteinizing hormone-releasing hormone test if necessary, were investigated. In Group 2, pubertal findings were evaluated via physical examination, and anthropometric measurements were performed. Twenty PCBs in first morning urine and serum specimens were analyzed in the study groups using gas chromatography-mass spectrophotometry method.

Results: Mean age was 6.7 ± 1.2 years in group 1 and 5.2 ± 1.2 in group 2. Mean weight SDS in groups 1 and 2 were 0.72 ± 0.35, and - 0.20 ± 0.26 (p=0.008), respectively. Mean body mass index (BMI) SDS were 0.49 ± 1.09, and -0.12 ± 1.28 (p= 0.083). Although no statistically significant difference was found between the groups in terms of BMI SDS, values were higher in subjects with premature puberty. No measurable PCBs were detected in any blood or serum specimens in the early puberty and control groups.

Conclusion: No association between PCBs and premature puberty was found in this study. In order for the endocrine disruptors to show their effects time, length and amount of exposure are important. We can conclude the exposure to PCBs in our region is not enough to show their effects on puberty.

P2-P336

A Novel Mutation in 5′ Untranslation Region of Makorin Ring Finger 3 Gene Associated with the Familial Precocious Puberty

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Central precocious puberty (CPP) is the endocrine disorder triggering by many factors those can activate the hypothalamic-pituitary-gonadal axis early which controlled GnRH secretion. However, the mechanism of CPP has not been elucidated. The study of patients with familial CPP helped understanding the complex physiological processes. Recently, loss-of-function mutations in human Makorin ring finger protein 3 (MKRN3) were found to contribute to over 30% of cases of familial CPP. Here we reported a novel mutation of MKRN3 in 5' untranslation region of a boy with familial CPP, and we identified that this mutation cause the reduction of serum MKRN3 which consistent with clinical manifestation. Our study not only further expand the mutational spectrum of MKRN3 but also confirm imprinted inheritance in male patients with familial CPP.

P2-P337

A Case of Testotoxicosis Due to a Constitutive Mutation of the LH Receptor Initially Presented as a Central Precocious Puberty at 3 Years Old

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Background: A thirty-four months old boy was referred for precocious puberty. He was the first child of healthy non-consanguineous parents. His family history was unremarkable. He had no exposure to oestrogenic endocrine-disrupting chemicals. He had presented secondary sexual characteristics for five months: pubic hair, enlarged testicular volume to 6 ml (Tanner stage P2A1G2) and enlarged penile size. He had a deepening voice and aggressive behavior. He had a significant growth acceleration with an advanced bone age (six years according to the Grulich and Pyle atlas). His height was 103 cm (2 SDS).

Laboratory investigations: Testosterone level was high: 190 ng/dl. The gonadotrophin hormone-releasing hormone stimulation test revealed baseline LH and FSH levels at 0.1 UI/l and LH and FSH peaks at 2.6 UI/l and at 1.2 UI/l respectively. AMH level was 26.6 ng/ml. Inhibin B level was 189 ng/ml. IGF-1 level was high at 306 ng/ml (3 DS). The adrenal function was normal. Tumor markers were normal. Ultrasound analysis of testes and adrenal did not reveal any tumor. Brain MRI excluded a hypothalamic tumor.

Evolution and management: The diagnosis of central precocious puberty was made and a treatment with monthly intramuscular injections of gonadotrophin releasing hormone analog (GnRHa) was started. Three months later, no clinical improvement was noticed: testicular volume progressed to 8ml, and height was 109 cm (4 DS). LH and FSH Baseline levels were 0.7 UI/l, and 0.1 UI/l respectively. The testosterone level increased to 310 ng/dl with a lowering AMH level at 12.3 ng/ml. GnRHa treatment was switched to long action every three months associated to cyproterone acetate.

Genetic analysis found a mutation of the LH-receptor gene (Met398Thr) already reported to constitutively activate the LH receptor. The diagnosis of peripheral precocious puberty was made.

Conclusion: This case of testotoxicosis is unusual as it initially presented as a central precocious activation of the gonadotropic axis at a very young age. Due to resistance to GnRH agonist treatment, the diagnosis of constitutive activation of the LH receptor was then suspected and confirmed by molecular genetics. It questions about the cellular mechanism of the central activation of the gonadotropic axis.

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P3-P284

Infant with Osteogenesis Imperfecta and Panhypopituitarism: A Case Report

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Background: Osteogenesis imperfecta (OI) is a genetic disorder mostly associated with mutation in one of the two genes encoding a chains of collagen type 1 (*COL1A1 and COL1A2*). Severity of the symptoms varies widely, caused by increase bone fragility and low bone mass. However, there is no direct relation reported in osteogenesis imperfecta and panhypopituitarism.

Clinical case: 19 months old boy was clinically diagnosed with osteogenesis imperfecta type III. He had a stormy neonatal period presented with multiple fractures since birth, complicated with neonatal hepatitis which has since resolved. He was referred for bisphosphonate treatment. Despite adequate caloric supplementation, he continues to have poor growth (height and weight below 3SD for age). On examination he has large anterior fontanelle, pectus carinatum, blue sclera, high arch palate, generalized hypotonia, shortening of the limbs, micropenis and bilateral undescended testis. No cardiorespiratory abnormality, liver palpable 2cm. Further investigations for failure to thrive revealed central hypothyroidism (TSH: 2.5mIU/LfT4: 7.5pmol/L), low cortisol level (127nmol/L) and low IGF-1 (<25ng/ml) ACTH: 8 pg/ml suggesting panhypopituitarism. LH: <0.1 IU/mL FSH:0.7 IU/mL Testosterone: 0.8. MRI brain and pituitary (contrasted) showed small pituitary gland and hypoplastic pituitary stalk. The child was started on L-thyroxine,

physiological dose of hydrocortisone and planned for growth hormone therapy soon.

Conclusion: There is no doubt that this child has osteogenesis imperfecta with panhypopituitarism. Further genetic analysis is needed to find a novel mutation that links to both condition

P3-P285

Panhypopituitarism With Tall Stature Diagnosed in a 20 Years Old Boy

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Background: Growth hormone plays a primary role in stimulating postnatal growth by way of insulin-like growth factor 1 (IGF1) which is produced in the liver in response to GH. A deficiency of GH arrests maturation during childhood, and the stature of such subjects is generally much shorter than the average stature. However, some cases of GH deficiency attain normal stature as adults.

Case presentation: A 20 years old man was referred for a further evaluation of hypogonadism. The patient's medical history revealed that he was the child of healthy and unrelated parents. His father is 185 cm and his mother is 168 cm which results in a target height of 182,5 cm. He was born 36 weeks of gestational age, birth weight of 4 kg, regular school performance. During infancy, although he had a normal stature for age, his stature was short for his target height. But he subsequently continued growing and attained the stature of 186,5 cm by age 21.

On admission to our hospital, his height was 183,5 cm (mean+ 1,57 SDS) with his upper trunk being 86 cm, arm span 190 cm, and body weight 101 kg (mean + 3,39 SDS). Body mass index 29,9 kg/m2. He had central obesity, prognathism, small mouth, voice high pitched. He had no goiter. He was devoid of secondary sexual characteristics, with Tanner stage P1G1. Blood pressure was normal. His bone age corresponded to that of 14-year-old boy. Magnetic resonance scanning of the brain showed a small anterior pituitary and an ectopic neurohypophisis. He has a normal karyotype and a normal chromosomal microarray analysis. Laboratory investigations, including dynamic tests showed hormone levels consistent with severe multiple pituitary deficiency, including severe growth hormone deficiency, gonadotropin deficiency, adrenal insufficiency and central hypothyroidism.He started treatment with levothyroxine, hydrocortisone and sex steroids.

Conclusion: This is the natural history of a patient with panhypopituitarism, with tall stature. It is likely that potent growth-promoting factors, other than GH and IGF1 may have played a role in stimulating the growth.

P3-P286

Post-Traumatic Hypopituitarism Caused by Pituitary Stalk Transection

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Common cause of hypopituitarism is congenital, genetically determined abnormality called pituitary stalk interruption syndrome (PSIS). It is characterised by hypoplastic anterior pituitary gland with thin or absent infundibulum and ectopic posterior pituitary location in MRI examination. Post-traumatic hypopituitarism may mimic this image.

We present 7 years and 10 months old girl who was admitted to Pediatrics Institute due to hypoglycemia during an acute gastroenteritis. Hypoglycemia was not responsive to the infusion of glucose. She had no medical history of any serious diseases or health problems until the age of 3 years and 10 months when she was admitted to Intensive Care Unit because of severe head trauma after being hit by a swing. Computer tomography of the head revealed basilar skull fracture, cerebral edema, subarachnoid hemorrhage. For few days she has been kept in medically induced coma and treated with desmopressin because of transient diabetes insipidus. After the accident the patient did not undergo any routine medical check-ups.

On admission to our hospital physical examination revealed skin pallor, orthstatic hypotension and short stature with body weight appropriate for the height and no signs of pubertal maturation. Based on laboratory studies and auxological data secondary hypothyroidism(ft4:6.6 pmol/l N:10-25, TSH:2.89uIU/ml N:0.3-4.0, ft3:1.8pmol/l N: 3.0-8.1), growth hormone deficiency(0.13 ng/ml during hypoglycemia and max. 0.49 ng/ml in twa stimulation tests, IGF1:27.1 ng/ml N:59-297, growth on the 90thpercentile on the growth chart respectively to mid-parental high with growth retardation since the age of 4 years, bone age delayed 5 years), secondary adrenal insufficiency(morning cortisol 44.8ng/ml N:50-230, ACTH 5.3pg/ml N:10-60, max. cortisol in glucagon stimulation test 55.5ng/ml, low serum sodium level 135mmol/l N:135-145) were found. Magnetic resonanse imagining of the pituitary gland showed disruption of the pituitary stalk with hiperintense signal of distal axon of the hypothalamus, hypoplastic anterior and ectopic posterior pituitary gland. The introduction of multiple hormonal replacement therapy (hydrocortisone,L-tyroxine, human recombinant GH)caused resolution of hypotonia, hypoglycemia and normalization of the general condition and growth of the child (GV=16cm/year).

Head trauma followed by biochemical or somatic symptoms of pituitary insufficiency together with hyperintense signal of distal axon of the hypothalamus suggest traumatic stalk transection with secondary hypoplasia of anterior pituitary gland.In every case of severe traumatic head injury hormonal evaluation and MRI of hypothalamic-pituitary axis should be performed.

P3-P287

Invasive Macroprolactinoma with Cabergoline Induced Cerebrospinal Fluid Rhinorrhoea in Childhood

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Background: Nonsurgical development of nasal cerebrospinal fluid (CSF) leaks may occur in the setting of pituitary adenomas, especially following a favorable response of invasive prolactinomas to initiation of Dopamine Agonist (DA) therapy, but this has not previously described in children.

Case description: A girl of Srilankan origin, aged 13.8 years, whose parents spoke no English, presented with headaches and secondary amenorrhea. Pituitary MRI revealed a large pituitary macroadenoma, invading the sphenoid sinus and elevating the optic chiasm. Thyroid and adrenal reserve was normal while she had growth hormone deficiency. There was no family history of pituitary-related disease and *MEN1* and *AIP* genetic testing was normal. She was commenced on cabergoline at 0.5mg twice a week with prolactin drop to less than 3% of original value and significant tumour size drop. However, she developed a CSF leak, which was managed surgically. Tumour biopsy confirmed a prolactinoma and was low Ki-67 staining. Postoperatively her prolactin levels normalized.

Conclusion: Childhood prolactinomas are often large invasive macroadenomas, and significant tumour response to cabergoline can lead to a CSF leak, if the tumour invaded the sphenoid sinus. This case emphasizes the importance to monitor these patients closely and warn them of sign and symptoms of CSF leak.

P3-P288

Bilateral Optic Nerve Hypoplasia Revealing Septo Optic Dysplasia or De Morsier Syndrome: A Case Report

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Background: Septo-optic dysplasia(SOD) is a congenital affection characterized by classic triade: optic nerve hypoplasia, hypothalamic-pituitary endocrine deficits and mdline abnormalities of the brain. It is typically diagnosed in infancy and has a variable presentation.

Case presentation: The patient is an 5 year old Algerian girl. At birth, bilateral congenital nystagmus and strabism was noted? Right blindness was suspected by parents at age of 2 years but confirmed only at 4 years old. Ophtalmological evaluation and brain magnetic resonance imaging demonstrate hypoplasia of the optic nerves, chiasma and optic tracts mainly on the right with small pituitary gland. At 5 years 10 months she was referred to our hospital because of short stature. Endocrinological evaluation showed somatotroph, corticotroph and thyrotroph deficiencies. She was treated with hydrocortisone, L-thyroxine and GH.

Conclusion: SOD remains a rare, heterogeneous and phenotypically variable disorder. He still represents a diagnostic challenge. Ophtalmologist and neurologists should be aware to the identification of any of the features of the syndrome.

P3-P289

Investigating Malnutrition Among Children Diagnosed with Neuroendocrine Tumors Receiving Chemotherapy in a Tertiary Care Hospital of Pakistan

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Background: Children under 25 diagnosed with neuroendocrine tumors often suffer from Malnutrition which raises the risk of infections. Being immunocompromised, there is a marked reduction on quality of life (QoL) and health outcome. Malnutrition also enhances the incidence of postoperative complications such as delayed wound healing, wound dehiscence, morbidities and mortalities.

Aims: To investigate malnutrition among children diagnose with neuroendocrine tumors and to assess the nutritional status of children receiving chemotherapy.

Methods: The study was conducted in Sir Ganga Ram Hospital, Lahore. Simple screening tool (Short screening sheet) for malnutrition was used. Nutritional assessment of 80 patients receiving chemotherapy was done by assessing BMI, mid upper arm circumference MUAC, triceps skin-fold thickness TST, serum albumin, Total lymphocytes count. Nitrogen Balance and intake of macronutrients were also analysed.

Results: According to full nutritional assessment, 42 patients (52.5%) out of 80 were found malnourished. Short screening sheet identified 51 patients as malnourished who were receiving chemotherapy. The SSM had a specificity of 0.88 and sensitivity of 0.72. 62% of the patients exhibited negative nitrogen balance.

Conclusions: Nutrition is the most neglected area of clinical care. Early nutritional support and counselling is essential in order to improve patients Quality of Life (QoL)

P3-P290

An Interesting Etiology in Childhood Central Diabetes Insipidus HIBERNOMA

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Introduction: Central Diabetes Insipitus (CDI) results from the inability to secrete ADH secreted by the neurohypophysis system to control water-electrolyte metabolism. In the etiology of CDI many congenital and acquired CNS tumors, infiltrative diseases, infections, autoimmune events, head trauma and idiopathic can be responsible. In this article, a child case with CDI due to intracranial occurence which is very rare in etiology is presented and the approach and follow up are discussed.

Case: Twenty-month-old girl presented with excessive thirst and water intake and frequent urination for about three or four months. The general condition of the patient was good, there were normal physical examination findings. and the somatic development was compatible with age. It was learnt that there were no traits in the medical history.

Results: The urine excretion of case was found to be polyuric (11.68 ml/kg/h) and the ratio of urine osmolarity to serum osmolarity was found to be 0.27. Serum ADH level of <0,5 pmol / l, and observed >50% increase in urine osmolarity was observed after desmopressin administration in case. In the contrast-enhanced pituitary MRI, protein and lipid-containing semisolid structures in the size of 2.5x2 mm were noted in the nasopharyngeal localization, suggesting that this formation led to narrowing of the neurohypophysis volume. This appearance was evaluated as likely to be choristoma-hibernoma.CDI was diagnosed in the light of these data.Desmopressin treatment was begun.

Discussion:Hibernoma is a benign soft-tissue well-limited tumor that develops from brownish fatty tissue that is extremely rare in childhood and is observed mostly in adults. Up to now, approximately 100 cases have been reported in the literature and 10% are located in the head and neck region. Although they are benign total excision is suggested when the tumor reaches a certain size due to the possibility of reaching very large dimensions and pressurizing the surrounding tissues. This lesion, which is detected in a very small size in the nasopharynx region of our case, by narrowing the neurohypophysis and causing central diabetes insiput is very important in terms of it being the first in literature. On the other hand, our case is valuable in that it shows the value of imaging in the approach of diagnosis and treatment of SDI We also think that the follow-up of this patient in terms of mass size is a necessity because it may have cautionary value in terms of other hormone defects that can develop.

P3-P291

Neonatal Panhypopituitarism with Hypoglycemia, Edema, Inspiratory Stridor and Cholestasis

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We report the case of a female newborn, first child of healthy, non-consanguineous parents, born at 42+0 weeks of gestation, who was admitted 21 hours after birth with severe hypoglycemia, hypothermia, decreased muscle tone, inspiratory stridor and edema. The course included poor feeding and failure to thrive, hyperbilirubinemia and cholestasis. Infectious or metabolic diseases were ruled out by clinical and laboratory investigations. Hormonal evaluation confirmed the diagnosis of congenital hypopituitarism with central hypothyroidism, cortisol deficiency and growth hormone deficiency. MRI of the brain demonstrated an empty sella and ectopic neurohypophysis. There was no evidence for other causes of the stridor like cardiovascular anomalies or a mass of the head and neck region. Genetic testing showed no mutations in genes associated with combined pituitary hormone deficiency (LHX4, HESX1, LHX3, PROP1, POU1F1).

Hormone replacement therapy was started with hydrocortisone and levothyroxine and improved muscle tone, stridor and feeding, but failure to thrive eventually resolved after initiation of growth hormone replacement at three weeks of age. An association of cholestasis with hypopituitarism is described in the literature. Our patient showed highly elevated GGT-levels, which normalized under hormone replacement therapy. Stridor and respiratory distress are not typically described in neonatal panhypopituitarism. The complete resolvement of these symptoms can be explained by improvement in muscle tone, a consequence of hormonal replacement therapy.

Conclusion: Clinical presentation of neonatal hypopituitarism is variable and non specific. Hypoglycemia in combination with cholestasis, edema and respiratory distress should lead to a hormonal evaluation to assure an early diagnosis and management.

P3-P292

MRI Changes in Time After Cranial Irradiation, and their Relation with Pituitary Function in Survivors of Childhood Medulloblastoma

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Background: Hypothalamic-pituitary (HP) deficiencies are frequent in childhood brain tumor survivors (CBTS) after cranial radiation. There is currently no consensus on the most optimal way to screen for HP dysfunction regarding diagnostic tests or time interval. It is not known whether MRI changes in time in the HP-region or in brain volume are predictive of HP dysfunction.

Aim: To quantify changes in the HP-region and in brain volume on MRI in CBTS after exposure to craniospinal radiotherapy (CRT) and to study its relationship with changes in HP-function.

Methods: Eighty childhood medulloblastoma survivors selected from a previous reported nationwide cohort[1] and treated with CRT between January 2002 and December 2012, were included.

All MRI scans were retrospectively systematically evaluated regarding the HP-region, at time of diagnosis, post-neurosurgical intervention, post-radiation and during follow up at 6 time points until 5 years of FU. The observers were blinded for outcome of HP function. Additional data on endocrine function and growth were collected.

The pituitary gland (PG) and pituitary stalk (PS) were measured on mid-sagittal and coronal images. The coronal height and width of PG were evaluated on coronal images. PS abnormalities were assessed by measuring the ratio of the PS to basilar artery. The presence or absence of the neurohypophysis and brightness of the bright spot were reported. The mamillary bodies were measured on mid-sagittal images. Volume measurements of the total brain, hypothalamus and mamillary bodies were performed. Observations were compared with reference values for brain volume, hypothalamus and mamillary bodies and measurements of PG and PS in childhood and adolescence.

Results: Analyses are currently being performed.

Conclusion: During the ESPE meeting 2018 the results and conclusions of our study will be presented

Reference

1. Prevalence and Risk Factors of Early Endocrine Disorders in Childhood Brain Tumor Survivors: A Nationwide, Multicenter Study. Sarah C. Clement et all. JOURNAL OF CLINICAL ONCOLOGY. 2016. Vol. 34 (36); 4362-4370.

P3-P293

Two Identical Twins... But Not in Everything. A Difficult Diagnosis

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GR and GT are diamniotic monochorial preterm twins (32 GA), both AGA (GR: W -1 SDS, L -1.5 SDS; GT: W and L 0 SDS), with normal karyotype and array-CGH on amniotic fluid, with no major complications associated to prematurity. At birth GT presented bilaterally cryptorchidism associated with micropenis, GR presented normal male genitalia. In the first year of life a severe growth deceleration in length (from -3SDS to -5 SDS) was observed, mainly after six months of life in both brothers. At 9 months GT was sent for endocrinological evaluation, he presented: baby doll facies, weight and length around -3 SDS, penis 20 * 11mm, left testicle in scrotum, right testicle in inguinal canal, which could be brought in scrotum. He underwent: LHRH test LH <0.1… 3.8 mUI /ml, FSH 0.8 …4.9 mUI /ml; Inibine B and AMH were normal. HCG test was adequate (testosterone <0.025...4.74ng/ml, di-hydrotestosterone 5.6. .. 479pg / ml) (*). A hypogonadotropic hypogonadism (HH) could not be excluded.

At 1 year 3 months a wider hormonal evaluation for hypopituitarism was performed in both brothers:

At 1 year and 7 months also GT started L-thyroxine treatment, for low FT4 values. Currently both brothers are waiting for low-dose ACTH test to evaluate ACTH deficiency, for persistent asthenia and suspected occasional hypoglycemias.

NGS revealed in both brothers unexpected results: heterozygous variants for ACAN and RAF1.

We concluded for multiple pituitary deficiencies in both brothers with different expression: despite a common genotype a certain variability is observed, possibly related to epigenetic involvement.

Currently a genetic cause of hypopituitarism has not been found. In these patients a careful hormonal monitoring is required, in order to early diagnose the possible onset of new pituitary defects in time.

P3-P294

Growth Hormone Deficit Associated to Complex Arteriovenous Malformation – Case Report

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Background: Arteriovenous malformations (AVMs) are rare in kids, estimated to represent 3% of all AVMs. They tend to rupture more frequently than in adults and, usually, are brought to attention after rupture, as the most common non-traumatic intracerebral hemorrhage. AVMs could also present with recur-

Table 1. (for Abstract no P3-P293)

	GR	GT
Height (SDS)	-4.8	-5.2
IGF1 ng/ml (15-200)	<15	<15
Glucose mg/dl (70-100)	27	29
ACTH pg/ml (7.2-52)	19.1	21.2
Cortisol ng/ml (48-195)	207	208
TSH mcUI/ml (0.25-5)	1.15	2.83
FT4 ng/dl (0.93-1.7)	0.84…0.8	1.1
LH mUI/ml	<0.3	*
FSH mUI/ml	0.8	*
Testosterone ng/ml	<0.025	*
Urine analysis	Normal	Normal
Brain MRI	Small hypophysis - ectopic neurohypophysis - cerebellar vermis anomaly	Small hypophysis - ectopic neurohypophysis
Diagnosis	GHD Central hypothyroidism	GHD HH suspected
Treatment	GH 0.2 mg/kg/sett L-thyroxine 2 mcg/kg/day	GH 0.2 mg/kg/sett Testosterone: 25 mg i.m.monthly for 3 months
Delta H SDS after 12 months of GH treatment	+2.92 SDS	+3.73 SDS

rent seizures or headaches. Their optimal management remains controversial. **Case report:** We present the case of a 4,5 y old boy, presented in our department because of growth deficit. The history of the child revealed he was a healthy newborn, with normal parameters at birth, has grown up normally, until the age of 18 months, when he has experienced an episode of seizure. He was hospitalized in a pediatric department and the complete evaluation revealed mild hypoglycemia as the cause of seizure. The evaluation included serum IGF1, GH, cortisol, insulinemia, oral glucose test (OGTT), revealing normal levels. Thus, hypoglycemia was thought to have occurred in the absence of a proper meal schedule. He was recommended an appropriate for age meal plan and followed – up for the next 6 months, as later, the parents did not show-up for the scheduled check-ups. At the age of 4,5 y the parents addressed the child to our department because of a slow growth, poor weight gain. Evaluation showed height deficit SDS_{height}= -3, weight deficit (Weight<3rd percentile), no particular clinical features. Investigations revealed retarded bone age, growth hormone deficit (hypoglycemia, low IGF1, low stimulated GH) confirming GHD. MRI exam of the head revealed complex arteriovenous malformation involving the left carotid artery and the Willis polygon. The optic chiasma was dislocated anteriorly and the pituitary gland and stalk difficult to identify, possibly also dislocated by the AVM located in and above the sella turcica. The child was scheduled for surgical intervention, results are to be communicated subsequently. **Discussions:** GHD is frequently encountered in any process that compresses the sella and pituitary gland. The particular evolution of this case lies in the lack of clinical signs suggestive either for compression by the AVM (headache, vomiting) or for GHD/other pituitary deficits, except for an isolated hypoglycemia associated with seizures. Therefore, the diagnosis was delayed and confirmed just when the growth deficit was evident.

Conclusion: Hypoglycemia requires complete evaluation for pituitary deficits, including GH stimulation tests and imaging of the pituitary and sella, in order to exclude hypopituitarism that may be due to a process exerting compression in this area.

P3-P295

Does Acquired Hypothyroidism Lead to Precocious Puberty?

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Introduction: Hypothyroidism without treatment usually leads to delayed puberty in pediatric patients, sometimes it may rarely lead Van Wyk Grumbach syndrome (VWGS) which is characterized by isosexual precocious puberty. Exact mechanism of VWSG is unknown. High thyroid stimulating hormone (TSH) levels may directly effect on follicular stimulating hormone (FSH) receptors and lead precocious puberty. Interestingly simple thyroid hormone replacement therapy resolves symptoms in this syndrome.

Case report: Here we reported 9-year-6-month-old female patient with Down syndrome presented with recurrent vaginal bleeding and 7-year-6-month-old female patient with cerebral palsy presented with breast development. Although both patients were presented with precocious puberty symptoms, their height and bone age were behind their chronological age. Their free T4 levels were extremely low and TSH levels were high. Thyroid heterogeneity in the ultrasound and thyroid antibody positivit confirmed autoimmune thyroiditis. Further history evaluation re-

vealed somnolence, fatigue, constipation, dry skin, low intellectual capacity. Until this time all these symptoms have been attributed to their primary status and have not been further evaluated. Their estradiol levels were in pubertal range while FSH and Luteinizing Hormone (LH) levels were low. These laboratory results confirmed peripheral precocious puberty diagnosis. Their prolactin levels were twice of the normal range. Pelvic ultrasound revealed pubertal size uterus and multicystic large ovaries. VWGS diagnosis was made by primary hypothyroidism, precocious puberty and multicystic ovaries. Thyroid hormone replacement therapy was started, symptoms resolved over time and bleeding stopped.

In conclusion, bone age delay, growth retardation with precocious puberty should be warning signs for VWGS. In these cases like Down Syndrome and cerebral palsy, symptoms like growth retardation, pubertal problems, intellectual disability, malnutrition may mask long term effects of hypothyroidism and may cause treatment delay. We aim to emphasize that disabled patients should be assessed according to their special circumstances in terms of growth and neurocognitive development.

P3-P296

Analysis of Influencing Factors on Bone Maturation in Girls with Central Precocious Puberty (CPP)

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Background & objective: The occurrence of CPP seems to be increasing in our clinical practice thesedays. It is known that CPP causes socio-psychological disturbances relating to early pubertal changes and finally leads to a significant decrease in the final adult height because of premature closure of the growth plate. This study was conducted to see major factors affecting to the bone maturation, which is closely related to the final adult height in girls with CPP.

Materials & Methods: The study patients consisted of 164 girls who was diagnosed with CPP for previous 5 yrs in the department of Pediatric Endocrinology, Kyungpook National University Children's Hospital, Daegu, Republic of Korea. The diagnosis of CPP was made when the patient showed the first pubertal sign of breast enlargement before the age of 8 years, and peak LH> 5 mIU / mL in GnRH stimulation test. We compared and analyzed relations between the severity of bone-age advancement and various clinical and laboratory chracteristics retrospectively.

Results: The chronological age(CA) of study patients was 7.18±0.82 yrs, and their bone age(BA) was 8.66±1.33 yrs. We compared various clinical & laboratory data with Δ BA-CA(yr) to find out (a) factor(s) affecting the bone maturation. The only statistically significant correlation was observed between Δ BA-CA(yr) and peak LH/FSH ratio(r=0.344 p=0.000). No other significant correlation was observed with the age, height, weight, body mass index, pubertal stage (SMR), basal & peak FSH and basal & peak LH in our patients.

Conclusions: It appears that the bone-age advancement was significantly correlated with the peak LH/FSH ratio in girls with CPP. This suggests that the peak LH/FSH ratio is one of key indicators ralated to bone maturation. Large-scaled studies are neccessary.

P3-P297

Is Prematüre Adrenarch Associated With Precocıous Puberty Vıa Kisspeptin?

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Aim: Premature pubarche is defined as the start of axillary and pubic hair before age 9 in boys and 8 in girls. 10 times more common in girls than boys. Central precocious puberty is a condition due to early activation of hypothalamic-pituitary- gonadal axis associated with breast development before age 8 in girls and testicular volume growth before age 9 in boys. Despite this axle is not known exactly which hormones are respnsible for the activation, the role of kisspeptin's role as a trigger factor has been demonstrated in many studies. The aim of this study is to evaluate activation of kisspeptin which is the first hormon level known tor ise.

Method: Girls with <8 yeras of age were enrolled in our study. 17 patients diagnosed with prematüre pubarche, 20 patients diagnosed with central precocious puberty and admitted to the general pediatrics clinic reasons nonendocrine, 20 healty age- matched girls were divided into groups as the control group. Each group of basal LH,FSH, E2 and were adrenal androgens. LHRH test was administered to patients. Kisspeptin levels were studied from all patients in the study.

Results: Plasma kisspeptin level central puberty precocious puberty group (122.1±51 pg/ml) in premature pubarch to (209.4±56 pg/ml) by statistically significant difference was observed (p<0.001). Premature pubarche group with in the control group (143±51 pg/ml) showed a significant difference (p<0.001). estrogen levels were negatively correlated with kisspeptin. In the group of central precocious puberty peak LH/FSH ratio and kisspeptin was a positive correlation between levels.

Discussion: The mean value of estrogen in central puberty precocious group was significantly higher than the other groups, and the high estrogen levels may be responsible for the decreased level of kisspeptin. The possitive correlation between peak LH/FSH ratio and kisspeptin levels shows the importance of Kisspeptin/GPR54 signaling system for onset of puberty.

Keywords: central precocious puberty, premature adrenarch, kisspeptin

P3-P298

Distinct Presentations of McCune Albright Syndrome, Report of Two Cases

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McCune-Albright Syndrome is a rare genetic disorder characterized by triad of polyostotic fibrous dysplasia of bone, precocious puberty and café au lait skin pigmentation. It is resulted from an activating mutation in the *GNAS* gene encoding the alpha subunitof stimulatory G protein. Here we present two cases with McCune Albright syndrome presenting with different clinical findings.

Case 1: A 7-year and 6 month-old girl presented with breast development beginning 7 months ago. Her height was 129 cm(93p),on physical examination her breasts were consistent with Tanner stage 4, without axillary and pubic hair. She didn't have any caffe au lait spot. Her bone age was 10 years, basal LH<0.1 mIU/ml, estradiol<5 pg/ml, pelvic USG showed enlarged ovaries (right 29 ml, left over 22 ml) and numerous follicles. It was learnt that a large number of cysts were seen in both ovaries on the prenatal ultrasound, and ovary cysts were aspired on postnatal day 5 as she had an ovarian hyperstimulation syndrome. Numerous variants in the *GNAS* gene were detected by whole exome sequencing performed in the ovarian biopsy material, however no mutation was detected in the *GNAS* gene in peripheral blood cells. Her other hormone tests were normal. Fulvestrane treatment was started in order to control pubertal progression.Case 2: A 9-year and 11 month- old girl presented with vaginal bleeding. Her height was 149 cm (96p), development of breast was consistent with Tanner stage 4-5 and pubic hair was consistent with stage 4. There were a lot of nevus on her face and body but no caffe au lait spot.

The bone age was 13 years, serum estradiol: 92 pg/ml, LH:0.18 mIU/ml, pelvic USG revealed enlarged ovaries (right:11.8 cc, left:37 cc) with many cysts. X-Ray revealed subcortical frosted glass densities in the left radius and right tibia, scintigraphy showed that these lesions were consistent with fibrous dysplasia. GNAS gene analysis of the case is pending. Tamoxifen treatment was started.

Conclusion: The absence of mutation in the *GNAS* gene in peripheral blood does not exclude the diagnosis of McCune Albright syndrome because of the mosaic / heterogeneous nature of this syndrome. The diagnosis is mainly based on clinical findings.The presence of multiple ovarian cysts and asymmetric enlargement of one ovary should suggest McCune Albright syndrome, even if there is no other feature such as caffe au lait spots and fibrous dysplasia.

P3-P299

A Case of Atypical McCune-Albright Syndrome with Vaginal Bleeding

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Background: McCune-Albright syndrome (MAS) is a rare, heterogenous, clinical condition caused by a rare genetic mutation. The disorder is more common in females and is characterized by a triad of cutaneous, bone and endocrine abnormalities.

Case Presentation: We report a girl with MAS, presenting initially with vaginal bleeding at the age of 12 months. Ultrasonography revealed bilateral ovarian cysts and ureteral and ovarian enlargement. Bone age rapidly advance, growth spurt.Considering the clinical and paraclinical findings, the patient diagnosed as a case of gonadotropin-independent precocious puberty was treated with Tamoxifen. During the follow up, recurrent episodes of bleeding, ovarian activation and cyst formation, as well as breast size development were reported. At the age of 2 years, fibrous dysplasia was detected, which in coexistence with precocious puberty confirmed the diagnosis of MAS. The patient had cafe-au-lait skin stomach during follow up.

Conclusion: Considering that clinical manifestations of MAS appear later in the course of recurrent periods of ovarian activation and cyst formation, a careful clinical observation and follow up of patients is necessary and the diagnosis of MAS must be kept in mind in cases with gonadotropin-independent precocious puberty.

Keywords: McCune-Albright Syndrome, Bleeding, Fibrous Dysplasia of Bone, Precocious Puberty

P3-P300

Evaluation of Cases with Pubertal Gynecomastia

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Introduction and Aim: Pubertal gynecomastia is the transient proliferation of glandular tissue in breasts of men without any endocrin pathology. Relatively higher levels of estrogen than plasma testosteron levels and imbalance between tissue estrogen and testosteron levels are considered to be important in pathogenesis. In this study it is aimed to determine the clinical and laboratory properties of our patients who were diagnosed as pubertal gynecomastia and compare with healthy population.

Material and method: 39 healthy adolescent boys and 39 adolescent boys diagnosed as pubertal gynecomastia in our clinic between July 2015 and January 2018 were evaluated retrospectively. Age, puberty, weight, height, body mass index and standard deviations, LH, FSH, estradiol (E_2), total testosteron, TSH, fT_4, prolactin, alpha fetoprotein (AFP), β-HCG, AST, ALT, BUN, creatinin

levels of both groups were detected, E2/T rate calculated, and differences between two groups were determined. Breast glanduler tissue diameters measured ultrasonographically in gynecomastia group was noted, family history, drug usage and comorbidities were evaluated.

Results: Mean age was 13.7±1.6 (10.2-16.8) in pubertal gynecomastia group and 13.6±1.9 (10.0-17.5) in control group, no differences determined between two groups (p=0.748). Weight, height and BMI SDS were similar in two groups (p=0.696, p=0.541, p=0.461,respectively). Mean puberty phase was 4 (2-5) with no difference between groups (p=0.361). Similarly, there was no difference in LH, FSH, TSH, fT_4, AST, ALT, BUN, creatinin, AFP and β-HCG levels (p>0.05), but T and E_2 levels and E_2/T rate was higher in gynecomastia group with no statistical difference (p=0.389, p=0.07, p=0.116, respectively). Prolactin levels were normal but higher in gynecomastia group (p=0.015). In gynecomastia group, right breast glanduler tissue diameter was 1.88±0.88 (0.6-4.1) cm and 1.95±1.02(0.6-3.6) cm in left breast, there was statistically difference between two breasts (p<0.01). 71.7% of gynecomastia patients (n=28) were bilateral. Plasma T levels was lower and E_2/T rate was higher in patients with bilateral gynecomastia than with unilateral gynecomastia (p=0.02, p=0.01, respectively). Mean complaint duration was 18.6±25.2 (1-104) weeks, 10.3% (n=4) had family history, 7.7%(n=3) had drug usage and 12.8% (n=5) had comorbidities.

Conclusion: We determined that there is no difference in E_2 levels ve E_2/T rate between gynecomastia patients and control group. Therefore, it is considered that increased estrogen sensitivity of breast tissue takes role rather than increased estrogen levels or imbalance between estrogen and testosteron.

P3-P301

A cAse of Central Diabetes Insipidus Developed 4 Years After the Non-CNS-Risk Unifocal Bone Lesion of Langerhans Cell Histiocytosis

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Background: Langerhans cell histiocytosis (LCH) is a rare disease with an incidence of less than 10 per million, and characterized by the clonal proliferation of pathogenic Langerhans cells. The clinical courses are diverse, ranging from spontaneously remitting single organ disease to life-threatening multisystem involvement. One of the serious complications of LCH is diabetes insipidus (DI), and patients with CNS-risk lesions had higher cumulative incidence of DI. On the other hand, the risk of DI has been reported to be extremely low in LCH with non-CNS-risk single-system single site lesion.

Case presentation: A six-year-old boy was referred with one and a half months history of polyuria and polydispia. At the age of two years, he had a single lytic lesion in his femoral head, which was curettage surgically and diagnosed as LCH at the other hospital. As any other affected organs were not detected, he was not followed up thereafter. He was diagnosed as DI by confirming hypernatraemia (Na: 148 mEq/l) with hyperosmolar serum (s-Osm 298 mOSM/kg) and inappropriately diluted urine (u-Osm 205 mOSM/kg). His polyuria and polydispia improved dramatically by perioral diuretic hormone. Anterior pituitary functions were not impaired. MRI imaging study revealed enlarged pituitary stalk and placental alkaline phosphatase and b-hCG in the spinal fluid were not detected, suggesting relapse of LCH.

Discussion: At the onset, the type of LCH in the patient was compatible with non-CNS single organ affected, and systematic follow in collaborating with pediatrician was not carried out, that would have led to delayed diagnosis of DI. Several literatures suggested that DI is not commonly present at initial diagnosis of LCH, and DI develops with various time lags, even more than five years in some cases. We recommend to systematically follow up the patients with a history of LCH, even non CNS-risk single-system single site affected type.

P3-P302

Effect of Triptoreline in Patients with Central Precocious Puberty at Children's Hospital 1, Ho Chi Minh City, Vietnam

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Precocious puberty is defined by the development of secondary sexual characteristics before the age of 8 in girls and before the age of 9 in boys. If not diagnosed and treated at an early stage, precocious puberty can compromise final adult height and trigger psychological disturbances. Gonadotropin- releasing hormone analogs (GnRHa) contributes to achievement of target final height by reducing the acceleration of bone maturation.

Objectives: To analyze clinical and para clinical features in patients with precocious puberty, effect of triptoreline in improvement of secondary sexual characteristics and predicted adult height (PAH) after 12 months of treatment.

Subjects and Method: Case-series study included 79 patients with precocious puberty at Children's Hospital 1 up to July 2016.

Results: After 12 months of Triptoreline treatment, secondary sexual characteristics reduced or ceased, acceleration of bone age decreased, sexual hormonal levels (FSH, LH, Estrogen/testosterone) fell below puberty range. We analyzed PAH of twenty-three female with initiation of treatment before the age of 8, PAH improve significantly before and after 12 months of treatment in this group 163.4 ± 7.7cm and 164.7 ± 7.6cm, respectively ($p < 0.05$).

Conclusions: Triptoreline decreases secondary sexual characteristics such as menarche, breast development, pubic hair, penis enlargement, acne, body odor and reduces the concentration of hormons (FSH, LH, Estradiol, Testosterone). In addition, Triptoreline increased PAH resulting in improving final adult height.

P3-P303

Morning Basal Luteinizing Hormone, a Good Screening Tool for Diagnosing Central Precocious Puberty

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Background: The current standard method to diagnose central precocious puberty(CPP) is gonadotropin releasing hormone stimulation test (GnRHST). But, it is inconvenient for children because of time-consuming and multiple samples. This study aimed to present utility of morning basal luteinizing hormone (LH) for the screening of central precocious puberty with emphasis on the influence of diurnal variation.

Methods: This study is a retrospective review of 160 female children who were suspected onset of pubertal signs such as breast budding before 8 years of age, and were evaluated using a GnRH stimulation test (GnRHST). And we compared the level of LH, FSH and bone age between CPP and prepubertal group. The prognostic value of single basal gonadotropin levels for screening of central precocious puberty was examined.

Results: In the 160 patients, central precocious puberty(CPP) group was 121(75.6%) and prepubertal group was 39(24.3%). The mean concentration of LH at CPP and prepubertal group were 1.01 ± 1.80 IU/L and 0.21±0.28 IU/L respectively ($p < 0.007$). Bone age at CPP group and prepubertal group were 9.3 ±1.09 yr and 9.0 ±1.18 yr ($p < 0.163$). Receiver operating curves (ROC) was used to evaluate the sensitivity and specificity with morning LH levels and 78.5 % and 71.8% respectively. And cut off point of single basal LH levels for screening of central precocious puberty was 1.2IU/L in this study.

Conclusion: Our findings suggest that single morning basal LH presents clinical efficacy for screening of central precocious puberty. And bone age advanced over chronological age is not significant in screening of central precocious puberty.

P3-P304

A 2-year-Old Boy with Epiphysis Tumor and Precocious Puberty

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Epiphysis inhibits formation and secretion of the most pituitary hormones and at the first turn gonadotropins. Frequency of epiphysis tumors, pinealomas in children is 2.5% of all verified tumors of brain. 75% of epiphysis tumors are malignant. Endocrinological disturbances can be the first signs of pinealoma. In 10% cases there is precocious puberty syndrome.

A 2.5 year-old boy presented to the endocrinology department with an 16-month history of accelerated physical development, fast growth of external genitalia, pubis pilosis, frequent erections, masculinization, low voice, forced laughter attacks. The growth velocity before treatment was 18 cm per year.

Physical examination: height 1.04 m, weight 20 kg (97% higher). Masculine habitus with elongated torso and O-shape distorted legs. Head circumference 51 sm, frontal tubers was increased. Blood pressure 90/ 60 mm Hg. External genitalia development corresponded to 14 yrs. Pubic-hair stage was P3 on the Tanner scale. Penis length is 8 sm, diameter 2.5 sm in calm state. Testicular volume was 11 ml. Scrotum is plicate, pigmented. Boy had frequent spontaneous erections and aggressive behavior. Voice was low, rough.

Laboratory tests: The content in plasma of LH was 10.0 U/L; FSH 7.5 U/L, testosterone 12.3 nmol/ L. Bone age corresponded to 7 years. Craniogram showed increased intracranial pressure. Magnetic resonance imaging of the brain revealed a pinealoma. Ophthalmologist: signs of increased intracranial pressure. In neurological status - organic symtoms.

Treatment: radiotherapy, cyproterone acetate 75 mg daily.

P3-P305

Central Precocious Puberty as a Result of Hypotalamus Hamartoma

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Presentation of case: A 3-year-old boy with central precocious puberty as a result of the organic lesion of brain (hamartoma of hypotalamus).

Complains. Increased height velocity, masculinization, fast growth of external genitalia, frequent erections, acne, low voice.

Medical history. The baby was born with weight 3400g. The age of the mother at birth of the child was 23 years. The breast feeding 6 months. In the age of 24 months boy started to grow very fastly. In the age of 2.5 years was marked pubic hair, acnae, increased external genitalia, voice turned low, frequent erections. The growth velocity was 16 cm per year.

On physical examination, height 1.12 m, weight 27 kg. Masculine habitus with elongated torso and O-shape distorted legs. A heart rate of 82 beats per minute, blood pressure - 90/60 mm Hg, and a respiratory rate of 22 breaths per minute. External genitalia development corresponds to the age of 14 yrs. Pubichair stage is P3 on the Tanner scale. Penis length was 6.5 cm, diameter 2.5 cm in calm state. Testiclar volume was 15 ml. Scrotum is plicate, pigmented. Boy had frequent spontaneous erections and aggressive behavior. Voice was low, rough. Delay in speech development.

Biochemical evaluation revealed pubertal levels of testosterone - 5.4 nmol/L, LH - 1.6 U/l; FSH - 0.86 U/l. Normal levels of alpha-fetoprotein – 3.0 ng/ml (normal 0-13). A thyrotropin level of 1.8 mIU per liter (normal range, 0.4 to 4.2), a free thyroxine level of 1.7 ng per deciliter (normal range, 0.8 to 2.2 ng per deciliter); hydrocortisone – 280.5 nmol per liter.

Bone age corresponds to the age 7 - 7.5 years. Ophtslmologist: fundus of the eyes without pathology, visual nerve disks pale-pink, borders are clear, vessels are not changed.

Brain MRI revealed hamartoma of hypothalamus, hypotrophy of vermis and cyst of right temporal lobe.

Neurosurgeon: numerous congenital anomalies of brain (retro-cerebellar cyst, cerebellum worm hypoplasia, hamartroma of hypotalamus, right temporal lobe cyst). Surgical treatment was not recommended.

Therapy: Cyproterone acetate 50 mg daily. The examination after 1 month revealed the positive dynamics: erections disappeared, penis size decreased, appetite got lower, and the child calmer.

Conclusion: Central precocious puberty in this patient was a result of numerous congenital anomalies of brain: retro-cerebellar cyst, cerebellum worm hypoplasia, hamartroma of hypotalamus, right temporal lobe cyst.

P3-P306

Precocious Puberty as a Result of Ectopic Hormone-Producing Tumor

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Ectopic hormone products are typical for cancerous cells. Cancerous cells can produce ACTH, lipotropin, alfa-melanocytostimulating hormone, beta-endorfin, vasopressin, oxytocin, insuline, glucagon, gastrin, secretin, VIP, calcitonin, hypothalamic releasing-hormones, prolactin, parathyroid hormone, growth hormone, chorionic gonadotropin, growth factors. In the majority of ectopic hormone-producing tumor cases clinical symptoms are absent. This is explained by the fact that tumors secretion either pro-hormones, or hormones, different from corresponding "normal" hormones, that is why their hormone activity is decreased or absent.

Presentation of case: A 2-year-old boy with precocious puberty and gonadotropin-producing hepatoblastoma.

Complains. The early sexual developmen, increased height velocity, fast growth of external genitalia, frequent erections; pubis, axillary, legs and arms pilosis, mustaches, acne, low voice, sharp abdomen aches.

Medical history. In the age of 18 months the boy started to grow rapidly. He grew 25 cm during 12 months and put on 10 kg. First pilosis appeared on pubis and axillary, there was hair growth on legs and arms, external genitalia grew much, appeared frequent erections, acnea vulgaris, voice turned into very low, sharp abdomen aches appeared.

Physical examination. Height 103 cm, weight 22.5 kg. Masculine habitus, low voice. Mild acnea on faces, hypertrichosis on torso and legs. Heart sounds are 102 per minute. Blood pressure 80/50 mm Hg. Abdomen circumference was the 65 cm. Liver is increased, especially its right lobe (10 cm from the costal arch edge), which is dense and tuberous. Pubertal stage was P3 A2 Fa2 on the Tanner scale. Penis length was 6 cm, diameter 2.2 sm in calm state. Testiclar volume was 13 ml. Scrotum is plicate, pigmented. Boy had frequent spontaneous erections and aggressive behavior.

Biochemical evaluation revealed high levels of testosterone - 23.7 nmol per liter, LH - 95,0 U per liter; FSH - 4.2 U per liter.

Bone age corresponded to 6 years.

Liver ultrasonography: the right lobe tumor 10 x 8 cm.

MRI: tumor right lobe of liver, 11x 8 x 10 cm.

Treatment. Resection of the right lobe of liver with tumor. Morphological study showed tumor nodular 14 x 10 x 14 cm. Microscopy identified it as hepatoblastoma. In 2 weeks after operation the content of testosteron in plasma decreased up to 0.2 nmol per liter, LH - up to 2.2 U per liter, FSH - up to 0.05 U per liter.

This case showed that precocious puberty may be a result of ectopic tumor product chorionic gonadotropin.

P3-P307

Premature adrenarche and Pseudohypoparathyroidism – Mechanistically Linked or Coincidence?

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Aims: To describe a case of premature adrenarche with pseudohypoparathyroidism, an as yet unreported combination.

Case: An otherwise well 8 year old girl presented to a Paediatric Endocrine Clinic with early pubic hair development suggestive of Premature Adrenarche. Blood tests revealed hypocalcaemia, elevated phosphate and highly elevated parathyroid hormone (PTH) level, giving a biochemical diagnosis of pseudohypoparathyroidism. She had normal stature (height 50^{th} – 75^{th} centile) No phenotypic features of Albright Hereditary Osteodystrophy (AHO) were identified: obesity, learning difficulties, brachydactyly, short stature, shortened $4^{th}/5^{th}$ metacarpals, dental hypoplasia or a rounded face.

Investigations: Blood tests revealed low corrected calcium 1.49mmol/L (reference range 2.2-5.7), elevated phosphate 2.78mmol/L (reference range 0.9-1.8) and serum PTH level almost 10 times the upper limit of normal at 66.4micromol/L (reference range 1.6-6.9), with normal Vitamin D 94nmol/L, normal thyroid function: Free T4 5.4pmol/L (reference range 12-22), TSH 4.8miu/L (reference range 0.27-4.2).

Hand and wrist Xray for bone age assessment revealed mildly shortened $4^{th}/5^{th}$ metacarpals, a phenotypic feature of AHO. MRI head was normal with no evidence of white matter calcification. Genetic studies revealed significant loss of maternal methylation pattern at four differently methylated regions (DMRs) within the GNAS cluster, a finding supportive of a pseudohypoparathyroidism type 1b diagnosis.

Treatment: She commenced oral calcium carbonate and alfacalcidol to correct the severe calcium deficiency and to normalise PTH levels. Progressively increasing doses have been required.

Discussion: Pseudohypoparathyroidism is a rare endocrine disorder characterized by resistance to the action of PTH. It has been classified within the AHO group. Recognition of a broader range of phenotypic features and underlying mutations has led to a novel classification system of iPPSD (inactivating PTH/PTHrP signalling disorders) developed by the EuroPHP network. GNAS1 mutations have been identified underlying various pseudohypoparathyroidism subtypes, resulting in reduced function of the G-protein coupled to the PTH receptor. G-proteins are also coupled to other hormone receptors; patients with AHO or iPPSD often present with other endocrine disorders, for example hypothyroid-

ism. There are cases of individuals with GNAS1 mutations presenting concurrently with precocious puberty and pseudohypoparathyroidism but no reported case of premature adrenarche and pseudohypoparathyroidism.

P3-P308

Efficacy of Ziyin Xiehuo Granules and Zishen Qinggan Granules in Girls with Partial Precocious Puberty: A Multicenter, Randomized, Single-Blinded, Controlled Trial

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Objective: To evaluate the effect of Ziyin Xiehuo granules (ZYXH) and Zishen Qinggan granules (ZSQG) on partial precocious puberty (PPP).

Methods: The present study was a multicenter, randomized, single-blinded, positive-controlled trial. A total of 143 patients were assigned to either the ZYXH group or the ZSQG group using a random number table. The ZYXH group received ZYXH three times daily for 6 months, while the ZSQG group received ZSQG three times daily for 6 months. The diameter of the mammary nucleus, the results of uterus, ovarian, and maximum follicle, and Chinese medicine syndrome scores were collected at baseline, 3-month and 6-month of treatment.

Results: After 3-month treatment, there were no significant differences between the two groups in terms of the mammary nucleus index changes (left 3.44±3.09 vs. 3.51±3.07, P=0.790; right 3.05±2.87 vs. 3.60±2.97, P=0.719). The uterine volume in the ZYXH group was smaller than that in the ZSQG group (2.06±1.57 vs. 2.58±2.23, P=0.006). Between the two groups, the differences of ovarian volume and maximum follicular diameter were not significant on either side (ovarian volume: left 1.23±0.68 vs. 1.30±0.64, P=0.809; right 1.25±0.66 vs. 1.37±1.12, P=0.984; maximum follicular diameter: left 3.87±1.72 vs. 3.52±2.17, P=0.158; right 3.55±1.69 vs. 3.90±2.10, P=0.314).

Conclusion: ZYXH granules and ZSQG granules both affect the size of the mammary nucleus in girls with PPP, as well as Chinese medicine syndromes, with ZYXH granules displaying slight advantages over ZSQG granules in terms of the decrease in the size of the uterus, ovaries, and ovarian follicles.

P3-P309

GLP-1 Receptor Agonist in a Patient with Craniopharyngioma-related Obesity

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Introduction: Glucagon-like peptide 1 (GLP-1) receptor agonists have been successfully used in adults with hypothalamic obesity, showing a BMI decrease and metabolic profile improvement. Data on GLP-1 receptor agonist treatment for children and adolescents is limited. Herein, we present a clinical case of a male adolescent treated with GLP-1 receptor agonist for hypothalamic obesity, secondary to craniopharyngioma.

Case report: A 15.8 year-old boy (Height-SDS: -2.59; BMI-SDS: +0.82), who had undergone a clift-lip operation in the 1st year of life, was seen for short stature with diminished growth speed and pubertal delay. His medical history was otherwise uneventful. A cerebral MRI revealed a cystic and solid supra-sellar tumor, extending to the hypothalamus and compressing the optic chiasma, as well as intratumoral calcification. Tumor histology revealed adamantinomatous craniopharyngioma, OMS grade 1. Gamma knife radiotherapy was performed 9 months after the initial operation due to a residual tumor.

Results: After tumor resection, the patient presented hemianopsia and panhypopituitarism, requiring L-thyroxine, vasopressine and hydrocortisone substitution therapy. He showed a rapid onset obesity suggesting hypothalmic damage. Exponential weight gain persisted despite rigorous hygieno-dietetic measures, with BMI-SDS rising from +0.82 to +4.99 in 11 months. Exenatide 5mcg 2x/day was introduced, which allowed BMI stabilization. The treatment was well tolerated without hypoglycemic events as controlled by flash glucose monitoring (FreestyleLibre®). He reported a better quality of life and regained satiation. Testosterone and growth hormone substitution were introduced 17 months after tumor resection, with further improvement of quality of life.

Discussion: GLP-1 receptor agonist treatment appears to be promising in adolescents with hypothalamic obesity. Further studies with larger cohorts are required in order to evaluate its longtime effectiveness for BMI and metabolic control.

P3-P310

Poland's Syndrome and Hypogonadotropic Hypogonadism

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Poland's syndrome is characterised by unilateral absence or hypoplasia of the pectoralis muscle, associated with the ipsilateral malformation of the hand. The syndrome is usually sporadic and occurs in about 1:32.000 live births. Poland's syndrome has been described associated with other abnormalities, including renal aplasia or hypoplasia, hemivertebra, Klippel-Feil syndrome and Moebius' syndrome.

In literature are reported six cases of Moebius syndrome associated with hypogonadotropic hypogonadism and only one case of Moebius-Poland syndrome associate with hypogonadotropic hypogonadism.

Here in, we report a case of a boy affected by isolated Poland's syndrome, in which we diagnosed hypogonadotropic hypogonadism disease, in adolescent age.

The patient was referred at our Department of Pediatric Endocrinology at the age of 14 years for pubertal delay and hypogenitalism. He had been born by caesarean section after normal pregnancy, AGA for birth and length, physiologic neonatal period. At born the hypoplasia of the left pectoralis muscle and the hypotrophy of the left hand had been noticed and the diagnoses of Poland's syndrome had been established.

At the first admission (chronological age of 14 years) his height was 159 cm (25 °p), his weight 58 Kg (50-75 °p). At the physical examination, the pubertal stage, according to Tanner criteria, was PH1 G1: testicular volume 1 cc bilaterally, micropenis (penile length 25 mm).

To confirm the suspected diagnosis of hypogonadotropic hypogonadism, we performed a GnRh analogue stimulation test (Decapeptyl test 100 mcg sc) (basal values: LH <0.3 mU/ml, FSH 1.3 mU/ml, T <0.025 ng/ml – after 240': LH <0.3 mU/ml, FSH 1 mU/ml, T 0.04 ng/ml) and then, an HCG stimulation test (testosterone level after stimulation 1.47 ng/ml), both documenting a subnormal response. Moreover, also the AMH value was under the normal limit for sex and pubertal stage (21.5 ng/ml). A further MRI scan of the brain showed no pathological lesions in the hypothalamus and pituitary gland, olfactory bulbs were normally represented. The boy started hormone replacement therapy with testosterone and is attaining full sexual development.

Poland's syndrome associated with hypogonadotropic hypogonadism, as in the case reported here, is very unusual. Pediatric endocrinologists should keep in mind a possible concomitant diagnosis of hypogonadotropic hypogonadism in patients with Poland anomalies and pubertal delay. Although up to now there is no evidence to connect these two abnormalities, awareness of this occurrence may lead to future cases being diagnosed.

P3-P311

Congenital Hypopituitarism Associated with Complex Cranio-vertebral Junction Anomalies

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Background: Abnormalities of cervical spine have been described in association with pituitary anomalies in the context of malformative syndromes with midline defects. Several genes are involved in the control of pituitary gland development, differentiation and function. In particular, the presence of os odontoideum has been reported in one case of pituitary hypoplasia, associated with leg anomalies, renal dysplasia and no aberrations of the BMP4, BMP2 and PTX1 genes. In another case odontoid process was reported to be associated with pituitary gland duplication. Here we describe a 7 year-old boy with pituitary stalk interruption syndrome (PSIS) and complex malformation of cranio-vertebral junction.

Presentation: This boy was admitted to our Endocrinology Unit due to a poor growth history.

Auxological evaluation showed a severe growth delay (-3.4 DS) and delayed bone age (4 years according to the Greulich and Pyle method). Physical examination revealed dysmorphic signs (short neck, low implant ears, big and stumpy hands). Neurological evaluation showed intra-rotation of right foot, motor clumsiness, slight reduction of muscle strenght in the limbs, presence of clonus on the right foot. On the light of a history of neonatal hypoglycemia and bilateral cryptorchidism, diagnosis of congenital hypopituitarism was suspected. The study of pituitary function revealed a combined pituitary hormone deficiency and therefore, a substitutive therapy with rhGH, levo-thyroxine and hydrocortisone was started. The brain MRI showed a picture of PSIS, that was associated with complex cranio-vertebral junction anomalies: presence of os odontoideum, dysmorphism of epistropheum tooth apex, median cleft of anterior and posterior C1 arc, synostosis of C2 and C3 posterior arches; at the site of stenosis the cervical cord appeared to be concentrically compressed. The child underwent urgent neurosurgery with good post-operative course. Genetic evaluation for *HESX1*, *LHX3*, *LHX4*, *PROP1*, *POU1F1*, *SOX3* and *SOX2* is ongoing.

Conclusion: In patients with PSIS and neurological involvement, cranio-vertebral junction anomalies should be suspected and, if present, rapidly treated, in order to avoid the progression toward a medullary compression. All patients with these anomalies should have genetic counseling in order to identify the specific gene alterations.

P3-P312

Premature Thelarche Followed by Acute Lymphoblastic Leukemia in a 1.5 Year Old Girl

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Introduction: Premature thelarche is considered a benign condition of breast development in prepubertal girls. It usually resolves after a certain period of time.

Materials and Methods: A 1,5 year old girl was referred to the pediatric Endocrinology department due to breast development which appeared two months prior to the visit.

Results: Upon clinical examination the patient had Tanner breast stage M2-3 bilaterally, but otherwise appeared completely healthy. Her height SDS (Standard Deviation Score) was +1,3 and her weight +1,0 SDS. Bone age was correspondent to her age, as was the ultrasound of her genitals. Two months later, she presented at the Hematology Department of the same institution with severe thrombocytopenia and anemia. Bone marrow examination confirmed the diagnosis of acute lymphoblastic leukemia. No central nervous affection was detected. She was treated for the condition according to protocols for this disease.

Conclusion: There is no evidence that these two conditions may be connected. However, we are reporting this case because it is a very rare coincidence.

P3-P313

Two cases of Non-Syndromic Congenital Unilateral Hypoplasia in One Family

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Introduction: Micromastia or breast hypoplasia is a condition which is described as postpubertal underdevelopment of a woman's mammary tissue. Breast hypoplasia may be congenital or acquired. The defect can be isolated or associated with other pathology, including syndromes and chest wall anomalies, it can also be unilateral or bilateral. Unilateral congenital breast hypoplasia is a rare anomaly of breast development, whose incidence is unclear.

Methods: We present a case of a 15 old girl referred to the Pediatric Endocrinology Department by the child's family doctor due to micromastia of the right breast. Pubertal Tanner stage was G3, she had her period at the age of 13 and the menstrual cycles were regular and normal. Her height was on the 50th percentile,while her weight was on the 75th percentile. The patient was otherwise healthy. From the family history her maternal grandmother had the same condition,which was never examined further or treated.

Results: The ultrasound of the breasts showed hypoplasia of the mammary tissue on the right breast while the other breast was normally developed (M5). Hormonal analyses showed normal estrogen and gonadotropin levels. The ultrasound of the gonads was uneventful and correspondent to her age. Also, there were no abnormalities of the chest wall. A whole exome sequencing was performed at the Genetics Department of the Technical University in Munich and it didn't show any mutations of the genes most commonly associated with this condition or any novel mutations. The most common syndromic causes for congenital breast hypoplasia, Poland's and Turner's syndrome were excluded.

Conclusion: Isolated congenital unilateral micromastia is a very rare condition with unknown incidence. Few gene mutations have been implicated as the most common culprits causative of the the non-syndromic cases. Since no mutations were detected in our case we hypothesize that other mechanisms can be responsible for the condition. Some authors have suggested that congenital unilateral hypoplasia of the breast may be caused by under-expression of the estrogen receptors in the breast, but to confirm this theory further clinical research is needed. The treatment is surgical reconstruction of the affected breast after the child reaches a certain age.

P3-P314

Klinefelter Syndrome with Ambiguous Genitalia in a Child

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Background: Klinefelter Syndrome (KS) is the most common sex chromosome disorder in males caused by additional X chromosome. It is characterized by progressive testicular failure. KS patient usually have complete male sexual differentiation without genital ambiguity. The prevalence of KS is 1 in 660 males which only 10% are detected before or during puberty, and about two third so fall men with X-chromosome polyploidies fail to be identified during their lifetime.

Objective: To report a rare case of Klinefelter Syndrome (KS) with ambiguous genitalia in a 14 months old boy, especially for improving pediatrician awareness to recognize of this disorder as early as possible

Case: Fourteen months old boy, BW 9.3 kg (WAZ < -2 SD); BH 76 cm (LAZ 0-(-2) SD); HC 44 cm (< -2 SD) visit pediatric endocrinology outpatient clinic with small penile buried beneath scrotal and hypospadias. There were gonads palpable before scrotal. The phallic length was 1.8 cm and diameter was 1 cm. Karyotyping showed 47, XXY. Genitography revealed contrast could passing through anterior and posterior urethra. Genital USG showed the right testicle lies right prescrotal and left testicle lies left prescrotal. The bone age revealed as 14 months old boy.

Conclusion: We reviewed the rare case of ambiguous genitalia associated with Klinefelter Syndrome (KS) in a child from endocrinology outpatient clinic Dr. Soetomo Hospital.

Keywords: Klinefelter; 47, XXY.

P3-P315

The Change in Growth's Velocity in Patients with Premature Puberty Receiving Treatment with Analogues of Lyuliberin

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Background: Suppression of hypothalamic-pituitary-gonadal system activity by luliberin analogues in premature sexual development of the central genesis is accompanied by a decrease in growth's velocity, sexual development and progression of bone age.

Aim: Study of the effectiveness of gonadotropin-releasing hormone agonist therapy, their influence on the physical development

Methods: 66 patients were treated by triptorelin. Idiopathic premature sexual development was identified in 40 children, hypothalamic hamartoma - 3, glial tumor - 1, organic central nervous system lesion – 15, congenital adrenal hyperplasia – 7.

Results: The use of triptorelin once daily for 28 days intramuscularly at a dose of 3.75 mg led to a significant decrease in the growth's rate. The growth rate at the 1st year of therapy with analogues of lyuliberin averaged 6.0±1,7 cm/year, which was 1.8 times lower than the growth rate before treatment. In the second year of therapy, the growth rate decreased to 4.5±0,9 cm/year, and after 2 years of treatment, it was 4.3±1,2 cm/year, which is 2.5 times lower than before the start of therapy.

Conclusions: Treatment with analogues of lyuliberin adequately suppresses the activation of the hypothalamic-pituitary-gonadal system, which is accompanied by a decrease in the rate of growth, sexual development and progression of bone age. This leads to an increase in the final growth about 10 cm, compared with untreated patients.

P3-P316

The Efficacy of Treatment in Vietnamese Children with Central Precocious Puberty

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Background: Central Precocious Puberty (CPP) may be lead to consequences such as limitation adult stature, sexual abuse, and emotional distress. GnRH agonist therapy in patients with CPP has been demonstrated in increasing adult height and improving emotional distress in puberty stage.

Objective: Evaluating the efficacy of treatment in patients with central precocious puberty after one year in Children Hospital 2, Vietnam in 7 years, from 01/2017 to 12/2016.

Methods: Cross sectional study, retrospective study 83 cases CPP which were treated minimum 1 year at Children Hospital 2 in 7 years, from 01/2017 to 12/2016.

Results: The secondary sex characteristics were almost reducing or suppressive, the menarche was disappeared in girls who had vaginal bleeding before. Mean height velocity decreased from 7cm per year to 5.4cm per year, BMI score increased significantly from 18.05 kg/to 19 kg/ Basal LH, FSH and estradiol concentration had dropped sharply after 3 months. The difference between bone age and chronological age declined from 28 months to 25 months after 1 year. Bone mineral density, Calcium and vitamin D concentration was normal after 12 months. In General, the predicted adult height after and before treatment were no different significantly. However, in patients under 6 years old, the difference of predicted adult height between pre- and post- treatment was statistically significant (156.5 -161.1 cm).

Conclusion: The secondary sex characteristics were almost reducing or suppressive. All patients had reduced height velocity and the difference between bone age and chronological age. Predicted adult height changed considerably in children under 6 years old

P3-P317

The Characteristics of Central Precocious Puberty at Children's Hospital 2 in Vietnam

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Objectives: To describe the characteristics of central precocious puberty in patients at Children's Hospital 2, Vietnam from 1/2010-12/2016.

Method: Cross – sectional analysis

Results: There were 504 cases of central precocious puberty. The mean age was 7.6 ± 1.4 years old; most of them were females (females/males: 71/1). The rate of overweight or obesity was 52.4%, accelerated height was recorded in 64.2%. The most common symptoms were breast enlargement in females (100%) and pubic hair in males (100%). The difference between bone age and chronological bone was 2.3 (1.5-3.1) years. Mean basal LH was 0.9 (0.3 – 2.2) IU/L. After aGnRH stimulation test, peak LH was 17.7 (9.4 – 35. 5) UI/L, LH reached maximum level at 60 minutes. The basal estradiol concentration at pubertal level was in 65.7% cases. The causes of CPP were idiopathic (87.7%) and hypothalamus-pituitary lesions (12.3%).

Conclusions: Precocious puberty was more common in female. Patients were usually overweight or obesity. Most common symptoms were breast enlargement in females and pubic hair in males. Most of cases were idiopathic, 15.7% caused of hypothalamus-pituitary lesions.

Keywords: precocious puberty, central, causes.

P3-P318

SIG (Special Interest Group)-ENDOPED/RUTE (Brazil): Seven Years Integrating Pediatric Endocrinology Centers Throughout the Country

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Introduction: Telemedicine, or the use of CIT (Communication and Information Technology) to deliver and/or share medical remote assistance and knowledge, is of paramount importance, mainly in large countries, with social and economic disparities, as Brazil, by means of teleconferences, webconferences, webcasts and use of a wide range of interactive technologies, helping activities of assistance and professional health education. One of the activities provided by our RUTE (University Network of Telemedicine), institution backed by our RNP (National Network of Research) with interaction of five ministries (Health, Defense, Culture, Education and Science&Technology), is the creation of SIGs (Special Interest Groups), from diverse health areas, linked directly to assistance and education at teaching health institutions (mainly hospitals), since 2007. Nowadays, 78 SIGs, with a great range of different subjects are registered, each with at least one coordination institution and three other participating institutions.

Description: The SIG ENDOPED created in the second semester of 2011, with association of eight institutions, leaded by Federal University of Rio Grande do Norte (UFRN), has been performing monthly meetings with one hour of duration. The subject of each meeting is chosen and coordinated by different member institutions in order to stimulate full participation of all members. Since its creation, there were 47 meetings, about 8 or 9 each year, ranging from discussion of selected clinical cases, updates of clinical treatment protocols, or other subjects of interest in the field of Pediatric Endocrinology. Today there are 28 centers distributed in all five regions of the country, and many discussions started at SIG meetings were useful to help updating protocols and national guidelines on further propositions to our Medical Societies (Brazilian Pediatric Society, Endocrinology and Metabolism Brazilian Society and Diabetes Brazilian Society) and Health Ministry. In the last two years, contacts with institutions in other countries (India and South Africa) have been made in order to internationalize our SIG.

Conclusion: SIG ENDOPED is a very dynamic, interactive, inclusive and convenient forum for discussion on themes of high interest in the Pediatric Endocrinology field, improving assistance, health professional education and even stimulating research,providing remote live contact between the associate institutions. Recent contacts are preparing the group for international activities.

P3-P319

The Relationship Between Prolactin and Development of Puberty in Girls with Early Breast Development

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Background: Prolactin (PRL) stimulates mammary glands and milk production in adult women. Also, high PRL level causes gonadal dysfunction by suppression of gonadotropin releasing hormone (GnRH) and luteinizing hormone (LH).

Purpose: The aim of this study was to evaluate, if any, the relationship between PRL level and development of puberty in girls with precocious breast development.

Methods: One hundred and ten girls with onset of breast development before age of eight were included in this study. Subjects were divided two groups by peak LH level after GnRH administration. They were 66 girls with precocious puberty (PP) and 44 girls with premature thelarche (PT). PRL levels were evaluated and compared between two groups. And any relationships between PRL level and clinical and laboratory parameters were investigated.

Results: PRL level was higher in PT group than in PP group (12.57±7.42 ng/mL vs. 9.66±5.18 ng/mL). There were much more girls with high PRL level in the PT group (12/44, 27.3%) than in the PP group (7/66, 10.6 %).

When we divided all subjects by PRL level, 19 girls had high PRL level (17 ng/mL) and 91 girls normal PRL level. Girls with high PRL level were shorter than girls with normal PRL level (129.8±4.9 cm vs. 132.9±4.9 cm). The ratio of Ht and mid-parental height (Ht/MPH) was also lower in high PRL group than in normal PRL group (0.80±0.03 vs. 0.83±0.03). Girls with high PRL level had higher basal LH level (1.34±2.20 IU/L vs. 0.83±0.46 IU/L) but lower peak LH level (5.83±4.65 IU/L vs. 8.84±7.52 IU/L) compared with girls with normal PRL level. The ratio of peak LH and follicle stimulating hormone (FSH) level (LH/FSH ratio) was lower in high PRL group than in normal PRL group (0.48±0.46 vs. 0.80±0.63).

PRL level had a negative relationship with Ht-SDS (r=-0.214, p=0.025) and Ht/MPH (r=-0.249, P= 0.009). There was no relationship between PRL level and peak LH level. But PRL level had a positive relationship with peak FSH level (r=0.221, p=0.020) and a negative relationship with LH/FSH ratio (r=-0.212, p=0.026).

Conclusion: More girls with PT had high PRL level than girls with PP. High PRL may suppress development of puberty in girls.

P3-P320

Central Precocious Puberty Appeared in Infancy Period in a Patient of Sotos Syndrome

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Background: Sotos syndrome is a rare syndrome; with distinctive clinical findings include typical facial appearance, learning disability; and overgrowth. Advanced bone age can be detected in some cases while precocious puberty reported only in two cases until now.

Case: A 6,5 months of age male infant admitted to clinic with neuromotor delay and macrogenitalia. He was second child of unrelated healthy parents, and birth-weight was 4200g. In physical examination: height: 75 cm (HSDS: +2,3), weight: 10.5 kg, RBMI was 90%, testicular volume 4 ml bilaterally, penis length was 6.7 cm. Mild facial dysmorphism with global developmental delay were noticed. In laboratory evaluation, high basal testosterone level (88 ng/dl), and high basal and stimulated gonadotropins (bLH: 1.56 mIU/ml, bFSH: 1.02 mIU/ml, stimulated LH: 43.3 mIU/ml, stimulated FSH: 3,65 mIU/ml) were confirmed central precocious puberty. Cranial imaging studies revealed normal pituitary gland. Bone age was 1 year.

LHRH analogue at dose of 250 mcg/kg/month was started. Because the HHG axis was not controlled efficiently, the dose of LHRHa increased to 500mcg/kg/month. At the age of 2,5 years, increase of testicular volume to 8 ml and penile length to 9 cm were detected. Bone age advanced to 4.5 years. Cyproterone acetate 50 mg/day was added to treatment. With combined treatment, patient's clinical and laboratory progression was controlled.

As his phenotype was resembled to Sotos syndrome, we performed *NSD1* analysis and detected a heterozygous mutation NM_022455.4:c.5177C>G(p.Pro1726Arg).

Conclusion: Central precocious puberty can be accompanied with Sotos syndrome, and overgrowth can be related either to syndrome itself, and precocious puberty. Treatment can also be very challenging with required high dose and combined treatment. Although we can not explain the reason of central precocious puberty in Sotos syndrome, it can be related to mutation characteristics of *NDS1*, or other underlying reasons that need to be demonstrated.

P3-P418

Clinical and Endocrinological Manifestations of Partial Ectopic Posterior Pituitary: A New Imaging Entity

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Objective: To describe six cases of possible partial ectopic posterior pituitary gland (PEPP) seen on head magnetic resonance imaging (MRI) and their associated clinical and endocrinological manifestations.

Methods: This is a single-center case series, from a tertiary public university health center in Montreal, Canada. Cases of children with possible PEPP were selected prospectively from 2005 to 2017, based on head MRI findings. Medical history, exam findings and hormonal evaluation were extracted from the medical record, and images were reviewed and interpreted by an experienced pediatric neuro-radiologist.

Results: All the cases, two boys and four girls between 8 days and 14 years old, were characterized by the presence of two midline bright spots on the thin focused T1 weighted sequences obtained with fat suppression technique. While one bright spot was located at the normal expected site of the neurohypophysis in the posterior *sella*, another was in the midline median eminence or along the normal appearing pituitary stalk above the *sella*, most likely corresponding to a partial presentation of an ectopic posterior pituitary gland. The possible PEEP was associated with different clinical phenotypes. One patient had isolated growth hormone deficiency, another had combined thyroid stimulating hormone and growth hormone deficiency, while the others had intact pituitary function at their last follow up. Of the remaining four patients, one had CHARGE syndrome, another one had motor developmental delay and one had septo-optic dysplasia without evidence of endocrinopathies to date.

Conclusions: Evaluation of pituitary function may be needed when PEPP is possibly found in the MRI. Long-term follow-up may provide additional information on others pituitary hormone deficiencies.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology P1

P1-P213

Insights In Promoter Transactivation of CBX2 Expression

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Background: The process of sexual differentiation is critical for reproduction in nearly all metazoan. Defects in any of the genes involved in either testicular or ovarian development can result in disorders of sex development (DSD). CBX2/M33 is a chromatin modifier that plays an important role in sexual development and its disorders, highlighted by the fact that M33-deficient mice have male-to-female sex reversal and loss-of-function of CBX2 causes 46, XY DSD in humans. Human CBX2 exists in two isoforms, a 532-amino acid long isoform called CBX2.1, and a second shorter 211-aminoacid isoform named CBX2.2. The promoter of these variants are unknown, however there are hints of differential expression by the isoforms in different cell lines and tissues.

Objective and Hypothesis: To characterize the CBX2 promoter in applicable cell lines using a custom reporter construct, to identify a regulatory network in gonadal development in which CBX2 takes part.

Methods: To locate the CBX2 promoter, candidate regions targeting transcription and the start of translation, were cloned as reporter inserts into the pGL4.17 Vector which lacks a promoter, requires expression of SV40 T antigen, and encodes the luciferase reporter gene luc2. The custom promoter constructs were transfected in Cos-1 cells (SV40 transformed cell type), with reporter activity established by performing a dual-reporter assay measuring firefly and *Renilla* luciferases. Subsequently, CBX2 promoter elements are dissected based on predicted binding sites and expressed in ovarian, testicular and adrenal cell lines (KGN, NT2D-1, and NCI-H295R cells respectively) to determine the regulation of CBX2 expression.

Results: Utilizing the dual-reporter assay system, we identified an optimal candidate CBX2 promoter construct that exhibited a 3.6 normalized fold change in activity when compared to a negative control ($p<0.0074$). Preliminary results indicate that this promoter construct may be applied to investigate differential transactivation of CBX2 in cell models recapitulating ovaries, testis and adrenal cells.

Conclusion: The characterization of a candidate CBX2 promoter could elucidate the inner workings of a CBX2-regulated network and its functional role as transactivator, distinct from its known function as chromatin-modifier. Further study of the impact of CBX2 activation and suppression may shed light on potential pathological mechanisms involved in DSD, and ultimately its diagnosis and management.

P1-P214

In Silico and *in Vitro* Studies of Human SRD5A2 Variants in Search for Activating Variants Explaining Androgen Excess Reveal Additional Loss of Function Variants

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Background: Androgens are steroid hormones necessary for human sex development. Testosterone (T) and the more potent dihydrotestosterone (DHT) are maybe the best known androgens, which exert their effect by binding and activating the androgen receptor. Steroid reductases 5α (SRD5As) catalyse the conversion of T to DHT in the classic androgen production pathway, or from 17-hydroxyprogesterone to 17OH-dihydroprogesterone, and androstenedione to androstanedione in alternate pathways leading to DHT. There are two enzymes with differential expression, of which SRD5A2 is expressed in reproductive organs and liver, and catalyses the reaction of T to DHT more efficiently than SRD5A1. Human *SRD5A2* loss-of-function mutations are known, and cause severe 46XY undervirilization, while gain-of-function variants have been suggested in androgen excess syndromes such as premature adrenarche, the polycystic ovary syndrome or prostate tumors, but they have not been found so far.

Aim: Therefore, we aimed to search for gain-of-function mutations in the human *SRD5A2* gene.

Methods: For that, we searched databases for candidate variants and performed bioinformatic and functional tests on selected variants. After conservation analysis of SRD5A2, a novel 3D protein model was constructed to locate the exact position of amino acids in the tertiary structure and predict their effect on protein function and substrate interaction. We then collected 116 coding SNPs in *SRD5A2* from OMIM, dbSNP, Pubmed, Clinvar, HGMD and Uniprot databases. These SNPs were ranked according to their association with phenotypes, physical location in our 3D model, and molecular dynamics simulation studies. Finally, we selected 9 coding SNPs for *in vitro* studies. These SNPs were located within or close to highly conserved areas that form the binding cavities for substrates or cofactor NADPH. SRD5A2 variants were expressed in HEK293 cells and activity to convert T to DHT was assessed and compared to wild-type.

Result: Variants R50A and P173S decreased enzymatic activity, while variants A49T, P106L, P106A, N122A, L167S, R168C and R227Q significantly reduced activity. As predicted in our *in silico* analysis, all coding SNPs affected enzyme activity *in vitro*, however none of them showed gain-of-function.

In conclusion, we provide a novel protein model for studies of SRD5A2. No gain-of-function variants were identified, but we have characterized 9 human SRD5A2 variants, which might be of clinical relevance for their enzyme activity loss. It is possible that individuals carrying these SNPs show a minor phenotype that is not yet identified. Alternatively, SRD5A1 may compensate? Genotype-phenotype studies would be able to solve this question.

P1-P215

Mutations Involving Nuclear Receptors and their Cofactors as a Major Cause of 46,XX DSD

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The genomic analysis of 46,XX individuals with testes (known as testicular Disorders/Differences of Sex Development (TDSD) or ovotestes (ovotesticular DSD (OTDSD)) supports the hypothesis that "pro-testis/anti-ovary" or "pro-ovary/anti-testis" genetic pathways exist. These children typically present with virilized genitalia due to testosterone production from the presence of testicular tissue. Many individuals with TDSD and a minority with OTDSD have a translocation of the testis-determining *SRY* gene usually onto one of the X-chromosomes, whereas a small proportion have chromosomal rearrangements associated with upregulation (gain-of-function) of *SOX* gene expression. Other rare forms of 46,XX DSD can occur due to mutations (loss-of-function) involving genes in the WNT4/RSPO1 signaling pathway. However, the etiology of majority of 46,XX DSD cases remains unknown.

Using unbiased high throughput sequencing approaches, we are generating evidence to support a key role for nuclear receptors as pro-ovary/anti-testis factors. In an analysis of 82 cases of 46,XX DSD cases, we identified recurrent mutations involving in the R92 residue of the nuclear receptor NR5A1 that are associated with the phenotype ($p=10^{-7}$) as well as recurrent mutations in the nuclear receptor *NR2F2*, which encodes COUP-TF2 (genetic association $p=10^{-8}$). Furthermore, we have identified both *de novo* mutations and rare variants in nuclear receptor cofactors, which we consider to be either pathogenic or may contribute to the development of the phenotype. This data provides further evidence of the emerging importance of nuclear receptors in specifically establishing human ovarian identity.

P1-P216

SDgeneMatch, A New Tool to Aid the Identification of the Genetic Causes of DSD

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Currently, the majority of patients with DSD do not have a molecular diagnosis. Although high throughput sequencing is having an impact on the clinical diagnosis of DSD the accurate interpretation genomic datasets of the identification of new gene mutations causing DSD is challenging. This is due to emerging evidence that DSD may be caused by mutations in many different genes and the prevalence of mutations in a single gene may be very low. As larger number of DSD patients are subject to genomic sequencing, there is an increasing concern about the ability to robustly establish causality for novel candidates. To build evidence to support causality, there is a need to share genomic data between groups. This is important because the misidentification of DSD genes will have severe consequences for the patients and their families as well as in the development of targeted gene panels for DSD diagnosis.

Within the EU COST Action DSDnet, we established a secure platform for sharing genomic data between interested groups. SDgeneMatch allows researchers to deposit lists of genes that carry one or more mutations in at least one patient sample and have these lists cross-checked with the lists uploaded by collaborators, without revealing the whole list to these collaborators. To prevent revealing any patient-specific information, only the bare minimum of information is collected by the system, which is a list of mutated genes that may be potential candidates for the phenotype. This means that it is not necessary to specify in which sample a gene was mutated or specify the type of mutation. A ‚match' occurs when two users of the system are found with a mutation in the same gene. Matches are reported to the two researchers that supplied the relevant gene identifier, and the matching gene symbol is disclosed to them. Reporting of matches is done behind the password-protected environment of SDgeneMatch, ensuring only the users that originally uploaded the match will be able to learn the gene name of the match. Other users will be made aware that a match has occurred, but will not learn the gene name.

SDgeneMatch is specific for DSD and the DSD research community is actively encouraged to submit data into the system. This should accelerate gene/mutation discovery in the field and it will lead to a more accurate ascertainment of the genes that are involved in DSD leading to a robust molecular diagnosis for DSD.

P1-P217

Reduced Androgen Receptor Expression in Patients with 45,X/46,XY Mosaicism

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Background: Individuals born with a 45,X/46,XY karyotype can present with diverging phenotypes from normal male, Turner-like to ambiguous genitalia, the latter classically being called mixed gonadal dysgenesis. No correlation between phenotype and degree of mosaicisms in the karyotype could be ascertained so far, making clinical management of these patients difficult.

Objective: To understand, if androgen action through the androgen receptor (AR) is compromised in 45,X/46,XY genital skin fibroblasts (GF).

Method: GF from 12 individuals with the clinical diagnosis mixed gonadal dysgenesis and a 45,X/46,XY karyotype were tested for AR-mRNA expression as well as AR-activity by measuring DHT-dependent induction of the AR target gene Apolipoprotein D (APOD- assay). Clinical data on external virilization as well as gonadal structures were collected when available.

Results: Six patients presented with hypospadias and a predominantly male phenotype, five patients showed ambiguous genitalia and one patient was phenotypically female. In four GF AR-activity lay below the threshold calculated for male control GF (< 2,3 fold induction; [1]). These four GF also showed a lower AR mRNA expression as compared to male control GF. However, there was no correlation between AR-expression or activity and 1) the percentage of Y-chromosome aneuploidy, 2) structural aberrations of the Y-chromosome, 3) presence or absence of Muellerian remnants or 4) gonadal development (two cases revealed one dysgenetic gonad on one side and no or one streak gonad on the other side, the other two cases showed at least one scrotal testis). In three out of the four individuals with low AR expression in their GF a HCG-test had been performed showing a low normal to normal rise in T.

Conclusion: Four out of 12 (30%) GF from individuals with 45,X/46,XY mosaicism revealed an AR-activity under the calculated cut-off using the APOD-assay. The normal T levels and the apparent undervirilization in these individuals indicate some form of androgen resistance. Our results suggest that in some cases of 45,X/46,XY mosaicism AR signaling and AR expression might be disrupted. This may modify the androgen dependent phenotype. Long-term studies are needed to analyze if this reduced AR expression is constant or changes e.g. in puberty.

Reference

1 Hornig NC et al. JCEM 2016, 101(11):4468-4477

P1-P218

Primary Gonadal Dysgenesis in Male 46,XY Patients with NR5A1 Variants Predominantly Affects Sertoli Cell Function

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Background: Steroidogenic factor 1 (encoded by the *NR5A1* gene) is a transcriptional regulator of genes involved in gonadal development and steroidogenesis. Mutations in *NR5A1* are associated with a wide phenotypic spectrum in 46,XY individuals ranging from partial/complete gonadal dysgenesis or anorchia, ambiguous genitalia, hypospadias, to infertility. However, little is known about the longitudinal course of endocrine markers for Sertoli and Leydig cell function from infancy to adolescence in these patients.

Objective: To investigate the Sertoli and Leydig cell function in 46,XY patients with an *NR5A1* variant reared as males by longitudinal analyses of the Sertoli cell markers inhibin B and anti-Müllerian hormone, the gonadotropins FSH and LH as well as testosterone.

Results: We retrospectively analyzed the laboratory results of six male 46,XY patients with *NR5A1* variants. During mini-puberty, inhibin B levels were in the low or low normal range, but variable (median 91 pg/ml, range 55-172 pg/ml). From the age of 10 to 18 years, inhibin B levels strongly decreased in all patients (median 13 pg/ml, range 3-21 pg/ml). During adolescence, anti-Müllerian hormone levels were very low as well (median 0.46 ng/ml, range 0.14-1.2 ng/ml). 3 of 4 patients who were followed during adolescence had a strong rise of FSH from a median of 9.02 IU/l (range 8.8-49.9 IU/l) to 56.1 IU/l (range 27.1-77.2 IU/l). LH increased from a median of 2.41 IU/l (range 1.03-8.8 IU/l) to 14.9 IU/l (range 7.6-48.0 IU/l). During infancy, testosterone levels ranged from 0.03 µg/l to 1.87 µg/l (median 0.48 µg/l). Interestingly, despite elevated gonadotropin levels indicating gonadal dysfunction, testosterone levels spontaneously rose into adequate levels (median of maximal testosterone 4.75 µg/l, range 2.27-7.1 µg/l) during the course of puberty.

Conclusion: Follow-up laboratory investigations may provide useful information on Sertoli and Leydig cell function in 46,XY individuals with *NR5A1* variants. Primary gonadal dysgenesis in these patients is associated with hypergonadotropic hypogonadism and low Sertoli-cell markers, but spontaneous testosterone

production during adolescence. Thus, Sertoli cell function seems to be more affected than Leydig cell function. More clinical studies are needed to better predict the future gonadal function including spermatogenesis and testosterone production, and to derive therapeutic implications for clinical practice.

P1-P219

Evaluation of Genetic Etiology in Patients with 46,XY Disorders of Sex Development: One Center Experience

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Background: Disorders of sex development (DSD) are a heterogeneous group of disorders related to sex determination and differentiation. Although several genetic abnormalities have been discovered through genetic analyses, the underlying genetic causes of 30–40% of the 46,XY DSD cases are not yet known.

Aim: To identify genetic defects in patients with 46,XY DSD.

Material and methods: Seventy-six patients with 46,XY DSD were studied. As a first step 56 patients suspected to have androgen insensitivity syndrome and 5alfa reductase deficiency according to their hormonal results are screened for *SRD5A2* and *AR* gene mutations via Sanger sequencing. Twenty two patients who do not carry mutations in these genes and 20 patients suspected to have gonadal dysgenesis or androgen synthesis defects are enrolled into the next step and 31 DSD associated genes are sequenced using in-house-designed next generation sequencing (NGS) targeted gene panel and analyzed for gross deletion/duplication with MLPA.

Results: In the first group, *SRD5A2* and *AR* gene mutations are detected 60.7% of cases. In the second group, seven previously described and 15 suspected rare variants are identified in 10 different genes within a total 19 cases, leading to our diagnostic rate to 45.2% for the second group. Highest rate of mutation is identified in *HSD17B3* gene (16.7%) which is followed by mutations in *DHH, NR5A1*, *LHCGR, POR, HOXA4, WT1, AR, ZFMP2* and *MAP3K1* genes.

Conclusion: Genetic analyses following clinical and hormonal evaluation is essential for the management of patients with 46,XY DSD with a great phenotypic and genetic heterogeneity. NGS targeted gene panel seems powerful tool to detection mutations in DSD.

P1-P220

Pitfalls in the Diagnosis of an Infant with 46,XX DSD with Congenital Adrenal Hyperplasia due to Cytochrome P450 Oxidoreductase Deficiency - The Value of Simultaneous Genetic Analysis to the Diagnosis in DSD

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Introduction: Congenital adrenal hyperplasia (CAH) is the underlying diagnosis in most newborns presenting with 46,XX disorders of sex development (DSD). Cytochrome P450 oxidoreductase deficiency (PORD) is a rare form of CAH caused by inactivating mutations in the POR gene. POR is a crucial electron donor to all microsomal type 2 P450 cytochromes (CYPs), including 21-hydroxylase (CYP21A2) and 17alpha-hydroxylase (CYP17A1). The hallmark feature of PORD is combined sex-steroid and glucocorticoid deficiency. Skeletal malformations resembling the Antley-Bixler Syndrome are present in most patients with PORD. Androgen excess in 46,XX fetuses is thought to be a consequence of an active alternative backdoor pathway to androgens, which closes down after birth.

Case report and results: Clitoromegaly, fused labia majora and a single opening was noted after term birth. The karyotype was 46,XX. Hormonal investigations showed a normal 17OHP (3.6 nmol/L) but an insufficient cortisol increase after synacthen stimulation (baseline: 210 nmol/L ; peak: 239 nmol/L), indicating glucocorticoid deficiency. Under the clinical assumption of CAH due to CYP21A2 deficiency, the patient was started on hydrocortisone and fludrocortisone replacement. No overt skeletal malformations were evident at birth, but mild midface hypoplasia and a closed fontanelle were noted at 5 months of age. Urinary steroid profiling performed by an external service lab at 7 days of age showed high amounts of 16-alpha hydroxypregnenolone, but steroid metabolites typically raised in common forms of CAH were not elevated, including 5-pregnendiol, a steroid marker metabolite commonly elevated in PORD. Next generation sequencing employing a multi-gene DSD panel revealed a homozygous mutation (p.Gly539Arg) of the *POR*gene. This mutation has been previously reported in four 46,XY DSD patients, who had no overt skeletal malformations, but were glucocorticoid and sex steroid deficient.

Summary and conclusions: This is the first 46,XX patient carrying the p.Gly539Arg *POR*mutation in homozygous state, which was shown to have a mild effect on CYP17A1 17-alpha hydroxylase

catalytic activity *in vitro*. The diagnosis of PORD via urinary steroid profiling in a clinical service lab was not achieved, although impaired 17,20 lyase activity was suggested by accumulation of pregnenolone metabolites in an early neonatal sample.

This case highlights the benefits for the management of DSD patients when employing a simultaneous approach of clinical, biochemical and genetic testing. Secondly, it emphasizes the challenges in establishing the correct diagnosis of rare steroidogenic disorders via urinary steroid profiling, in particular in neonatal samples.

P1-P221

High Mobility Group Box 1 (HMGB1) and Insulin-Like Growth Factor Binding Protein-2 (IGFBP-2) are increased, Insulin Decreased and IL-6 Unchanged in Follicular Fluid (FF) from Polycystic Ovarian Syndrome (PCOS)

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HMGB1 is a small-protein which reflects both inflammation and insulin-sensitivity. Inflammation and insulin-resistance are features of PCOS. IL-6 is important for ovarian function and can contribute to insulin-resistance. IGFBP-2 behaves like an acute-phase protein and is increased in chronic inflammation. It is also involved in the glucose-metabolism regulation and IGFBP-2 overexpression plays a protective role against insulin-resistance. Insulin functions as a co-gonadotropin modulating ovarian steroidogenesis and hyperinsulinism contributes to hyperandrogenism, a cause of arrest of follicular maturation present in PCOS. We aimed at assessing HMGB1, IGFBP-2, insulin and IL-6 concentrations and their relationships in FF from PCOS versus non-PCOS.

We enrolled, 30women(CA:34.43±0.84yr;BMI:25.92±0.99kg/m2; hirsuteN.12; amenorrhoicN.2; oligomenorrhoicN.13; regular cyclingN.15) with PCOS according to the RotterdamCriteria, and 36women(CA:35.72±0.55yr;BMI:24.08±0.79kg/m2), fertile oocyte donors, with tubarian or unknown infertility causes, with normal endocrine exams, regular menstrual-cycles, no hyperandrogenism as controls(CTRL) all undergoing the same ovarian stimulation protocol for *in-vitro-fertilization*.

HMGB1 both in FF and in serum, IGFBP-2, IL-6 and insulin in FF were assayed using specific ELISAkits. Serum estradiol(E2) at oocyte retrieval was quantified. The N.of dominant follicles(>17mm) at ultrasound was also considered. Statistical analyses was performed using SPSSv23.0.

HMGB1 in FF was higher in PCOS than in CTRL(46.09±4.25 vs 26.53±1.87ng/ml; p=0.002). IL-6 was similar in PCOS and in CTRL(11.52±1.92 vs 11.76±1.26pg/mL; n.s.). IGFBP-2 was higher in PCOS than in CTRL(719.15±37.99 vs 630.16±21.13ng/ml; p=0.030). Insulin was lower in PCOS than in CTRL(1.50±0.20 vs 3.72±0.46mU/L; p<0.001). Serum HMGB1 was confirmed higher in PCOS than in CTRL(17.47±1.84 vs 11.13±1.23ng/ml; p=0.017). HMGB1 in FF correlated with IGFBP-2(r=0.345; p=0.005) and insulin(r= -0.452; p=0.004). Insulin correlated with IGFBP-2(r= -0.361; p=0.033), and the N.of dominant follicles(r= -0.433; p=0.008).

HMGB1 both in FF and in serum and IGBFP-2 in FF were increased in PCOS, whereas insulin was decreased and IL-6 unchanged. IL-6 probably reflects other functions than inflammation. HMGB1 and IGFBP-2 reflect both inflammation and insulin concentrations. The low insulin and high IGFBP-2 in FF from PCOS confirms that insulin-sensitivity is not well understood yet in the ovary.

P1-P222

A De Novo Missense Mutation in the 4th Zinc Finger of the WT1 Gene Causes 46,XY and 46,XX DSD in Two Sibs

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The WT1 gene has a crucial role in the genesis of the bipotential genital ridge and subsequently in the specification of the Sertoli cells of testis. Mutations involving the WT1 gene are associated with a wide range of phenotypes impacting testis-determination and development including Denys-Drash syndrome, Frasier syndrome and Meacham syndrome.

Here, we describe two sibs with DSD carrying a de novo mutation in the WT1 gene. A girl was born with Prader IV intersex genitals. Cytogenetic examination revealed the a 46,XX, SRY-negative karyotype. Hormonal androgen levels were elevated and congenital adrenal hyperplasia was excluded. At three months of age explorative laparotomy identified a uterus and two macroscopically undifferentiated gonads. Histology identified testicular tissue in both gonads. At six months of age she had a feminization genioplasty. At age of 12 she underwent a bilateral gonadectomy and histological examination revealed ovotestis in both gonads. A diagnosis of 46,XX ovotesticular DSD was indicated.

A male sib was born 14 years later. At birth he presented with male external genitalia, but testes were not palpable in the scrotum nor in the inguinal canal. After birth he underwent surgery for a diaphragmatic hernia. His karyotype was 46,XY. At 2 years of age laparoscopy identified a rudimentary testis on the right side. Orchidectomy was performed on the left side and histological examination did not find any testicular tissue only pieces of funiculus spermaticus and epididymis tissue. At age 9 his FSH: 0.6 IU/L, LH <0.11 IU/L, Te< 0.43 nmol/L, E2 < 92 pmol/l hormone levels were in prepubertal range. The combination of diaphragmatic hernia with 46,XY DSD suggested the diagnosis of Meacham syndrome.

Exome sequencing revealed a de novo missense mutation of the highly conserved fourth zinc-finger of WT1 (p.Arg495Gly) in both sibs. Normal ploidy was established by qPCR.

This is the first time that mutation has been identified in the WT1, in a girl with ovotesticular DSD and her brother with 46,XY gonadal dysgenesis and hernia diaphragmatic. These cases con-

firm that mutations involving WT1 can impact on the development of both the testis and the ovary and that WT1 mutations can result in Meacham syndrome.

P1-P223

Sex-Differences in Reproductive Hormones During Mini-Puberty in Infants with Normal and Disordered Sex Development

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Context: The early activation of the hypothalamic-pituitary-gonadal axis during infancy can be used in the evaluation of infants suspected of disorders of sex development (DSD). However, few data exists on sex-specific reference ranges for these hormones during early life.

Objective: To evaluate sex-differences in reproductive hormone concentrations in serum from healthy infants in order to define sex-specific cut-off values and to apply these in infants with DSD.

Design: A cross-sectional study.

Setting: A tertiary center for pediatric endocrinology at the University Hospital of Copenhagen.

Patients or Other Participants: 1,840 healthy infants and 27 DSD patients aged 2-5 months.

Main Outcome Measures: Serum concentrations of LH, FSH, testosterone, estradiol, SHBG, inhibin B, AMH, DHEA, DHEAS, 17-OHP, androstenedione, and LH/FSH-ratio.

Results: LH and FSH concentrations showed overlap between sexes with LH being highest in boys and FSH being highest in girls. The LH/FSH-ratio separated infant boys from girls with minimal overlap at a cut-off value of 0.32. Inhibin B and AMH concentrations were markedly higher in boys compared to girls, with minimal or no overlap, respectively. In infants with Klinefelter syndrome, 45,X/46,XY mosaicism and male phenotype, and Turner syndrome, respectively, the LH/FSH-ratio matched the gender-of-rearing. However, infants with complete androgen insensitivity syndrome had LH/FSH-ratios within male range.

Conclusions: Reference ranges for reproductive hormones and LH/FSH-ratio during mini-puberty were established in this study. The classifiers that best separated sex in mini-puberty were AMH, LH/FSH-ratio and testosterone. Use of the LH/FSH-ratio may add valuable information in the work-up of infants suspected of DSD.

P1-P224

The "ExternalGenitaliaScore" to Describe External Genitalia in Male and Female Infants. A Europeanmulticenter Validation Study

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Background: The "External Masculinization Score"(EMS) is an objective method of scoring undervirilized genitalia in infants but may require further adaptation to capture the appearance of the genitalia more comprehensively across the phenotypic spectrum.

Objective: To develop and validate a non-binary, standardized score that describes the range of appearance of external genitalia.

Method: The external genitalia score (EGS), designed by WG1 of COST Action BM1303 assesses the same anatomical landmarks (urethral meatus, location of gonads, size of genital tubercle, labioscrotal fusion) as EMS, using a gradual scale from female to male (range 0-12), and a vocabulary suitable for both sexes. Intra- and inter-observer variability were studied in infants with typical (n=35) and atypical (n=74) genitalia. In a subsequent multicenter validation study, cross-sectional data were obtained in 378 full-term, 163 preterm babies and 308 infants up to 24 months with equal sex distributions, and in 74 babies with atypical genitalia (46,XY: n=69; 46,XX: n=5). EGS was compared to Prader Score (PS) and EMS. Following anogenital distances (AGD) were measured: AGDas: anus to posterior base of scrotum, AGDap: to anterior base of penis, AGDaf: to fourchette, AGDac: to anterior base of clitoris.

Results: Inter-observer reproducibility of EGS in typical and atypical genitalia is excellent, being 1 and 0,98 respectively (95%RI 0,97-0,99). Median (10^{th} - 90^{th}centile) EGS in male premature (>33 weeks) and full-term babies up to 24 months is 12 (11-12); in preterm males < 33 weeks, it is 11 (10,5-12). Median EGS in female premature and full-term babies up to 24 months is 0 (0-0). In male and female infants with variant genital development, median EGS is 9,7 (6,5-11,9), and median EMS is 9 (4,1-12). In babies with typical genitalia, median (10^{th} - 90^{th}centile; SD) AGDas/ap in males is 0,49 (0,39-0,61; 0.09), in females AGDaf/ac is 0,40 (0,31-0,48;0,07). In babies who have 46,XY DSD, median (10^{th} - 90^{th}centile;SD) AGDas/ap is 0,43 (0,28-0,57; 0.11). AGDas/ap in males with typical genitalia is significantly different from AGDas/ap in 46,XY DSD (t= 1,9, p=0,05). In babies with 46,XY DSD, AGD-ratio correlates positively with EGS (Spearman's r=0,33, p< 0,05) and with EMS (r=0,42, p<0,05).

Conclusion: EGS provides an alternative to EMS as a non-binary and reproducible tool to describe the range of external genitalia in premature and term infants up to 24 months. The AGD-ratio, a measure of prenatal androgen exposure, correlates with EGS in male infants.

P1-P225

Living with Clitoromegaly: Aqualitative Interview Study of Parent's Responses to Clitoromegaly in Congenital Adrenal Hyperplasia (CAH) with or Without Appearance Altering Surgery

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Controversy continues regarding surgery in infancy to address atypical genitalia in girls with CAH and other Disorders of Sex Development. There is no consensus to surgical approach. Interest in outcomes of the range of surgical and non-surgical interventions for genital diversity is growing. It is widely acknowledged that the multi-professional management to promote long term psychosocial adaptation of the child based partly on confident parenting is essential.

We conducted a study to provide information regarding family responses to clitoromegaly after a range of management strategies. We interviewed 27 parents of girls with CAH age <16 years. Parent interviews focussed on the behaviours and thoughts regarding their daughter's clitoromegaly during childhood. Using the pattern-based Thematic Analysis and tracking of which children had clitoral reduction surgery, feminising genitoplasty/concealment surgery and those who had had no surgical intervention at all, we explored how families respond to genital difference with and without surgery. We identify the following prominent themes and our key conclusions regarding implications.

Ignorance is bliss: Despite the recommended approach of promoting children's understanding of their condition families commonly do not discuss genital difference including its past and future treatment. Parental protective strategies ranged from: 'waiting for the right time' to 'occasional *untruths*' in response to a child's questions, creating a situation of parental perception of the child's state of bliss contrasted with hidden anxiety and worry held by the parents. Implication – parental protection could prevent meaningful psychological adaption during childhood.

No regrets: Parents recognise they had a role and responsibility in multi-professional treatment decisions, but acknowledged a dominant position from professionals regarding management. Despite divergent views across specialist centres, and the range of surgical approaches for similar presentations, the dominant parental belief is that their particular decision and treatment route was correct. Implication - This psychological process may affect patient report outcome measures.

Genital difference remains: Despite different management pathways and early surgical interventions for atypical genitalia, the parents' perceived need to 'manage' genital difference persists. Even in those instances when the child's genitals are perceived as normal-looking by the parent, the anxiety about surgery, underlying diversity and potential need for future adolescent/adult intervention(s) remains. Implication – Management of the appearance of genital difference can only address some aspects of psychological need.

P1-P226

"You Can Put Ideas into their Heads": Parental Concerns About Children's Participation in DSD Research

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It is acknowledged that children should collaborate in research about their health conditions, and DSD research has been criticised for promoting views of parents and health professionals. However parents are concerned about professionals talking to children about sensitive subjects including fertility and sexual activity. Children may have little experience of talking about their sex development. This makes direct research involving children with DSD particularly challenging.

As part of a wider qualitative interview study concerning family responses to management of girls with CAH, we asked 27 parents about the possibility of involving their children in research. We had gained ethical approval to speak to children 5-15 years, enabling us to prompt parents to consider this possibility. We proposed talking to girls with CAH about common childhood leisure activities as a non –threatening method for engaging children in research discussions. For those parents of younger children the question was more theoretical; allowing them to think about possible future research options.

Parent's concerns in relation to their daughters' research participation are summarised in the following themes:

Necessity: Although parents wanted their daughters to be able to have their questions about CAH answered, they feared taking part in research would evoke concerns prematurely.

Ending ignorance: Research participation might initiate their daughter's awareness of potential differences and cause distress.

Promoting talking: Having considered CAH for the purpose of research, their daughter might then discuss further with friends without parental guidance.

Implications: These barriers to children's participation in DSD research may also counter understanding of the diagnosis throughout childhood - a recommended aim of multi-professional clinical care.

Some parents were enthusiastic about children's involvement in research and had helpful methodological ideas including: whether the researcher should be known, research activity location; the use of standardised questionnaires; the minimum age for participation, and question design. However parents' advice was varied and contradictory, highlighting the need for careful patient and parent involvement in study design. We conclude that children's research participation needs to be flexible and involve a range of modalities.

We piloted the leisure activity questions with four girls aged 12-14years who had had variable surgical management for atypical genitalia. Only one participant acknowledged any awareness of or concern regarding genital difference. The indirect approach was most appropriate for the youngest child. We conclude that it is difficult to engage participation in DSD research when prior awareness of the genital difference is low.

P1-P227

Testosterone Levels in Newborn Boys and Girls Related to Penile Length, Anogenital Distance (AGD) and External Genitalia Score (EGS)

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Background: Testosterone levels in newborns are changing over the first weeks of life. This dynamic change is making the assessment of infants with ambiguous genitalia complicated.

The Clinical laboratory at Karolinska offer two different methods for measurement of serum testosterone, ECLIA (electrochemiluminescense **i**mmuno**a**ssay) and Liquid chromatography–tandem mass spectrometry (LC–MS/MS). It is important to evaluate these two methods in the neonatal period and the use of them in the diagnostic work-up in newborns with atypical genitalia or genital ambiguity.

Objectives: To measure testosterone in serum of newborn boys and girls, to obtain reference values of importance in the hormonal evaluation of a newborn with ambiguous genitalia.

In addition, we wanted to see if genital masculinisation could be related to the testosterone levels in boys and girls respectively.

Method: Testosterone was analysed using two methods: ECLIA and LC–MS/MS. Blood sample were obtained from 45 full-term babies, at the same time as the neonatal screening sample, day 2-3. Clinical data in 100 babies for penis and clitoris length and Anogenital distances (AGD) were collected using digital calipers. AGDas: anus to posterior base of scrotum, AGDap: to anterior base of penis, AGDaf: to fourchette, AGDac: to anterior base of clitoris.

Results: S-testosterone (ECLIA) in male full-term babies (N=20) mean 7,5 nmol/L (4,8-15,0 nmol/L). Female full-term (N=24) mean 5,1 nmol/L (2,0-7,8 nmol/L).

S-testosterone (LC-MS/MS) in male full-term babies (N=22) mean 1,9 nmol/L (0,3-4,9 nmol/L). Female full-term (N=23) mean 0,2 nmol/L (0,1–0,6 nmol/L).

Correlation between the ECLIA and the LC-MS/MS methods was moderate positive (Correlation coefficients 0,55)

Penis length (N=52) mean 3,19 cm (2,15 – 4,15cm) with no correlation between penis length and testosterone, neither method. AGDas/ap in males was 0,53 and with no correlation with testosterone.

AGDaf/ac in females was 0,43 and there was a low negative correlation between AGDaf/ac and testosterone with the ECLIA method (Correlation coefficient -0,44) and no correlation with the LC-MS/MS method (Correlation coefficient -0,25).

Conclusion: Testosterone levels were, as expected, significantly higher in the boys. The ECLIA method gave testosterone varying between 2.0 and 7.8 in the girls, most likely due to cross reactivity with adrenal metabolites. The LC- MS/MS method gave considerably lower measurements

Knowledge on the normal levels of testosterone in the neonatal period is essential and valuable for adequate evaluation when assessing babies with genital ambiguity.

P1-P228

Clinical Factors That Determine Surgical Outcome Following Hypospadias Repair

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Background: Complication rates following hypospadias surgery are variable and given that hypospadias may be associated with a genetic or an endocrine condition, hypospadias outcome may depend on several clinical factors that require exploration. Aim: To perform a systematic review of cases of hypospadias op-

erated at one tertiary centre to identify clinical determinants of optimal outcome.

Methods: Retrospective review of clinical records of all cases that were reported to have undergone hypospadias surgery according to operating theatre records at the Royal Hospital for Children, Glasgow between 2009 and 2015. Details of all relevant clinical evaluations, associated genital and non-genital malformations, timing of surgery, complications and reoperation were collected.

Results: Of 659 potential cases, 626 with complete data were included. Distal, middle, proximal and unknown type of hypospadias was reported in 422 (67%), 107 (17%), 80 (13%) and 17 (3%) respectively. Of the 626 cases, undescended testis, microphallus and bifid scrotum were recorded in 73 (12%) patients. A non-genital malformation was reported in 139 (22%) and 62 (10%) had more than one associated malformation. 38 (6%) patients had extensive genetic and endocrine evaluation and 11 (29%) of them had abnormal endocrine results pointing towards a disorder of gonadal development or androgen synthesis and 6 (16%) had a molecular genetic diagnosis consistent with a DSD. The median age at first surgical repair was 19.5 months (range 6, 195). Of the 626 cases, in 563 (90%) the surgery was single staged. At least one complication was reported in 165 (26%) of patients with fistula being the most frequent complication reported in 77 (12%). 7 (64%) cases with endocrine abnormalities had at least one complication compared to 15 (56%) cases with normal results. In the 165 cases with complications, in 40% these were manifest in the first year and in 80% within the first two years after surgery. The severity of hypospadias and existence of other malformations were associated with an increased risk of complications (p-value < 0.001), but endocrine abnormalities, type of procedure and age at primary surgical repair were not associated to outcome.

Conclusion: A quarter of cases of hypospadias may be associated with a complication and this may be more likely in those cases that are proximal or who may have additional non-genital malformations. Given that complications may present over an extended duration, there is a need for long-term follow-up, especially in those cases that are at high risk.

P1-P229

Prevalence of Hypogonadism in Prepubertal Boys with Cryptrochdism

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Introduction: Cryptorchidism has usually been managed using a surgical approach, with little attention to the underlying pathophysiology.

Objectives: to assess gonadal function before treatment in prepubertal boys with cryptorchidism.

Methods: In a cross-sectional study we reviewed all clinical charts of patients encoded with the diagnosis of cryptorchidism in the database of a paediatric tertiary hospital, between 2000 and 2017. Inclusion criteria were normal virilization and assessment at prepubertal age and before orchidopexy. Patients with other known disorders affecting the gonadal axis were excluded. Serum AMH at first visit, measured by ELISA, was used to define testicular function (Sertoli cell component). Gonadotropins were also evaluated.

Results: After sample size calculation, random samples of 124 of 1033 patients with unilateral cryptorchidism and 186 of 524 patients with bilateral cryptorchidism available in our database were analysed. Median AMH SDS was below 0 in both the bilaterally (Wilcoxon signed rank test, $P<0.0001$) and the unilaterally ($P=0.0052$) cryptorchid groups. AMH was undetectable, thus indicative of anorchidism, in 9 patients with bilateral cryptorchidism (4.8% of all patients with bilateral cryptorchidism and 26.5% of those with nonpalpable gonads). AMH levels were below the normal range (<3rd percentile for age) in 14.3% of the boys with bilateral cryptorchidism aged 1-5.9 months, 36.5% boys aged 6 months-1.9 years, 18.6% boys aged 2-8.9 years and 9.5% in boys older than 9 years. In the group with unilateral cryptorchidism, AMH levels were below the normal range in 16.7% boys 1-5.9 months, 7.1% aged 6 months-1.9 years, 7.2% aged 2-8.9 years and 6.3% older than 9 years. The prevalence of AMH below the normal range was greater in patients with bilateral cryptorchidism than in boys with unilateral cryptorchidism between 6 months and 1.9 years (Fisher's exact test, $P=0.006$) and in boys between 2 and 8.9 years (Fisher's exact test, $P=0.043$). Sixteen out of 17 boys (94.2%) with micropenis had AMH levels below the normal range. In 5, the diagnosis of central hypogonadism could be certified. Orchiopexy was performed in 151 patients. Serum AMH levels were available in 76 patients before and after surgery. A statistically significant increase was observed in AMH levels after orchiopexy. Serum gonadotropin levels were within the normal range in the vast majority of patients with unilateral or bilateral cryptorchidism independently of age (all prepubertal).

Conclusion: Hypogonadism, reflected by Sertoli cell dysfunction, is a relatively common feature at the time of diagnosis in prepubertal boys with cryptorchidism.

P1-P230

Testicular Ultrasound Measurements to Stratify Pituitary-gonadal Hormone References in a Cross-sectional Norwegian Study of Male Puberty

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Background: Recent research has demonstrated earlier testicular and pubertal development in Western boys. New ultrasound-based references of testicular growth in Norwegian boys are now available. Population specific references for FSH, LH and sex steroid hormones have not been previously available in Norwegian children and adolescents.

Objective and hypotheses: We aimed to provide an elaborate description of pubertal development in a sample of contemporary Norwegian boys, based on clinical evaluation, ultrasound determined testicular volume and hormonal levels.

Method: As part of the cross-sectional "Bergen Growth Study 2", we examined 451 boys aged 6-16 years. All boys were examined during school hours which included assessment of Tanner P-stage, ultrasound imaging of the testicular length, height and width (converted to volume), and collection of blood samples. Total testosterone levels were analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) and peptide hormones FSH, LH and SHBG were measured on Immulite 2000. Reference intervals were estimated with the GAMLSS framework within R.

Results: Reference intervals for the hormonal values based on age, testicular volume and Tanner P-stages are presented.

Conclusion: Novel and objective references for key pubertal hormones and ultrasound-based testicular volume are available to complement traditional Tanner staging for clinical assessments of individual children during the pubertal transition.

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Altered vascular Function in Boys with Hypospadias-Role of Reactive Oxygen Species

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Background: Hypospadias in boys may be associated with a lack of androgen exposure during the masculinisation programming window. As testosterone has effects on the vasculature, we assessed whether boys with hypospadias show any evidence of vascular dysfunction.

Methods: Excess foreskin tissue was obtained from boys undergoing hypospadias repair (cases) or circumcision (controls) and small arteries dissected from this tissue. Vascular contractility was assessed by wire myography in response to U46619 (thromboxane A2 analogue). Vascular smooth muscle cells (VSMCs) were cultured and generation of reactive oxygen species (ROS) was measured by amplex red and chemiluminescence. NADPH oxidase (Nox) mRNA expression was measured by qPCR.

Results: 19 cases and 22 age-matched controls were enrolled in this study (median age 1.9 (range 1.3, 12.2) years). There were 8 (42%) cases of distal, 4 (21%) of midshaft and 7 (37%) of proximal hypospadias. Endocrine and genetic evaluation did not reveal an underlying disorder of sex development in the cases and there were no differences in clinical cardiometabolic or biochemical parameters between the cases and controls. Arteries from cases demonstrated increased constriction to U46619 compared to controls (Emax: 175.6 vs 66.3 $p<0.001$), an effect inhibited by the ROS scavenger N-acetylcysteine (NAC). VSMC superoxide anion (5.3 fold) production and H_20_2 (3.3 fold) levels were increased in cases compared to controls ($p<0.05$). Expression of Nox5, a major ROS-generating oxidase in vascular cells, was increased in cases (2.6 fold, $p<0.05$). Exposure of vessels to testosterone increased vasoconstriction to U46619 (Emax: 66.3 to 124.6 $p<0.001$) in controls, but not in cases. Incubation with NAC abolished the testosterone-induced vascular effects. Vascular hypercontractility in boys with hypospadias was associated with reduced endothelium-dependent and –independent vasorelaxation, compared with controls.

Conclusions: These novel data, from a unique cohort of patients, demonstrate that small arteries from boys with hypospadias exhibit increased vascular contractility and decreased vasorelaxation with associated increased Nox-derived ROS generation. The functional significance of vascular dysfunction in these boys is unclear, but may play a role in immediate surgical outcome as well as altered long-term cardiovascular risk.

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Gonadectomy for Adults With DSD Conditions In The International Disorders of Sex Development Registry

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Introduction: Depending on the underlying diagnosis, Disorders of Sex Development (DSD) can be associated with an increased risk of germ cell cancers. To date, however, knowledge regarding the indications and timing of gonadectomy is lacking.

Methods: The International-DSD (I-DSD) Registry was interrogated for anonymised information regarding the diagnosis, karyotype, sex of rearing and timing of gonadectomy, if undertaken, of all individuals of any karyotype who were over the age of 16 years at the time of search and who had a disorder that may lead to long-term hypogonadism namely a disorder of androgen action; androgen synthesis; gonadal development or a non-specific disorder of undermasculinisation (NSDUM).

Results: At the time of search, 2,141 cases were accessible on the I-DSD Registry. A total of 614 (29%) met the above study inclusion criteria. Data regarding gonadectomy were available in 520 (85%). Of these, 158 (30%) (median age 24 yrs (range 17, 72)) were registered as male while 362 (70%) were female (median age 28 yrs (16, 90)). Gonadectomy was performed in 315 (61%) cases. Females had gonadectomy at a later median age of 14 yrs (0.3, 68) compared to median age of 5 yrs (0.1, 54) in males (p=0.047). Table 1 demonstrates the frequency and median age at time of gonadectomy for each condition. Gonadectomy was performed later in

Table 1. (for Abstract no P1-P232)

	Females with gonadectomy (%)	Age at gonadectomy females (yrs, range)	Males with gonadectomy (%)	Age at gonadectomy males (yrs, range)
Complete androgen insensitivity synd	123/154 (80)	15 (0.3,68)	0/0 (0)	-
Complete gonadal dysgenesis	55/69 (80)	15 (0.3,21)	2/7 (29)	5 (4,5)
NSDUM	6/6 (100)	14 (3,26)	3/22 (14)	9 (6,10)
Partial androgen insensitivity synd	26/29 (90)	12 (1,24)	3/41 (7)	32 (10,54)
Partial gonadal dysgenesis	23/26 (88)	2 (0.3,21)	15/51 (29)	1 (0.1,13)
17β hydroxysteroid dehydrogenase def	25/25 (100)	11 (0.5,21)	0/1 (0)	-
5α reductase def	11/14 (79)	6 (2,17)	0/5 (0)	-
Other	16/39 (41)	16 (1,21)	7/31 (23)	17 (10,26)

both males (median 15 vs 4 yrs, p=0.0004) and females (median 17 vs 8 yrs, p<0.0001) after the publication of the 2006 consensus statement on the management of DSD conditions.

Conclusions: Not only does the rate of gonadectomy vary from one diagnosis to another, it also seems that gonadectomy is performed at a later age than previously. A substantial proportion of young men and women with a range of DSD continue to retain gonads into adulthood.

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Phenotypic and Genetic Assessment of Boys Witha Suspected XY Disorder of Sex Development

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Introduction: Among Disorders of Sex Development (DSDs), XY DSD, represents the most challenging group in terms of identifying a diagnosis.

Objectives: The aim of the study was to determine the prevalence of biochemical and molecular genetic tests in a cohort of boys with XY DSD and to collate the phenotypes of patients with results of laboratory investigations and presence of associated abnormalities.

Methods: New and existing cases of XY DSD who had endocrine and/or genetic evaluation during 2016 and 2017 were identified. Information on clinical assessment including family history, appearance of external genitalia, biochemical and molecular genetic investigations and associated abnormalities was obtained from the medical records.

Results: 52 patients with median age of 0.9 years (range, 0.01, 17.91) and median external masculinization score (EMS) of 9 (2.5, 12) were identified. A positive family history of DSD was present in 10 (19%) children. Of these 52 boys, associated malformations (AM) were found in 27 (52%) with 6 (12%) having a known genetic syndrome. The median EMS of the boys who had associated malformations (AM) was also 9 (2.5, 12). Endocrine assessment revealed an abnormality in 14 (27%) with a median EMS of 8.75 (2.5, 12). The range of endocrine abnormalities consisted of a disorder of gonadal development (DGD) in 10 (19%) and LH deficiency (LHD) in 4 (8%). In the remaining 38 (73%) cases without any endocrine abnormalities who were categorized as a non-specific disorder of under-masculinization (NSDUM) the median EMS was also 9 (3-11). Molecular genetic investigations were completed in 34 (65%) cases and a genetic abnormality was found in 9 (26%). Of the 29 XY DSD boys (NSDUM,19; DGD,8; LHD,2) who had array-CGH, copy number variants (CNVs) were reported in 6 (21%) (NSDUM,4; DGD,1; LHD, 1) with a median EMS of 10 (8–11). Sanger sequencing of seven common causative genes in 22 (NSDUM,16; DGD,5; LHD,1) boys identified variants in 3 (14%) (NSDUM,3) with a median EMS of 3 (3–9) and these were detected in *HSD17B3*.

Conclusions: The severity of under-masculinization of external genitalia in XY DSD boys seems to be unrelated to the presence of endocrine and array-CGH genetic abnormalities and is not associated with concomitant morbidities. A comprehensive diagnostic strategy that includes a more extended genetic approach requires further exploration.

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Pediatricians' Attitudes and Beliefs Towards Transgender Persons

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Introduction: Pediatricians are becoming key figures for gender dysphoric persons, as the number of children seeking information or treatment for gender dysphoria rises. Puberty suppression and affirming approach, have been shown to improve both psychological functioning and physical outcome. However, recent data show that most children referred were too old to receive this treatment. One barrier that can preclude appropriate care is pediatricians' attitudes towards transgender. Little is known about physicians' attitudes in general, and pediatricians' attitudes in particular were not previously assessed.

Aim: To assess the attitudes and beliefs of pediatricians toward transgender people, and to examine associations of demographic and occupational characteristics with these attitudes.

Methods: The transgender attitude and belief scales questionnaire (TABS) was administered to 355 pediatricians. TABS consists of 29 items in three domains: human value, interpersonal comfort and sex/gender beliefs. Answers range from 1-7 on Likert scale, and were analyzed accordingly: favorable attitudes (6-7) and unfavorable (1-5). Demographic and occupational information was analyzed.

Results: The final study cohort comprised 221 (62%) females, 132 (37%) males and 2 who defined themselves as others; 223 (63%) were senior pediatricians and 132 residents; 254 (72%) work in hospitals, and 101 work in the community; 274 (77%) defined themselves as secular and 290 (75%) were born in western countries. Most pediatricians held favorable attitudes in all domains; 94% in human values, 85% for interpersonal comfort domain and 57% in the sex/gender belief domain. In multi variant analysis pediatricians who scored less favorably had distinct demographic characteristics for all segments. Specifically, in the sex/gender belief domain, male gender was associated with two fold increased odds of unfavorable score (odds ratio (OR), 2.1 95% confidence interval (CI) 1.3-3.5) compared to females. Secular pediatricians

and those born in non-western countries had 10 fold (OR, 10.3 95% CI 4.5-23.5) and 1.5 fold (OR, 1.5 95% CI 0.8-3.0) odds ratio for unfavorable scores respectively. We found no differences between seniors and residents nor between pediatricians working in hospital compared with those working in the community.

Conclusions: There is still stigma towards transgender persons among pediatricians. The medical community should take measures to promote positive attitudes to make treatment more attainable for transgender adolescents.

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Diagnosis of Adolescent Polycystic Ovary Syndrome (PCOS) According to the 2018 International Evidence-Based Guideline for the Assessment and Management of PCOS

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The diagnosis of Polycystic Ovary Syndrome (PCOS) during adolescence is controversial with adult diagnostic features overlapping with normal physiological events that occur during puberty.

The aim of international evidence-based guideline was to promote accurate diagnosis, optimal consistent care, prevention of complications and improve patient experience and health outcomes.

Extensive international health professional and patient engagement informed the priorities and core outcomes for the guideline. International nominated panels including women with PCOS, multidisciplinary team of health care professionals (across 44 societies and 71 countries), researchers and an evidence synthesis and translation team developed the guideline that was funded and led by Australia.

The evidence-based guideline development followed international best practice involving 60 systematic and narrative reviews and applying full Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework to reflect quality of the evidence, and consider feasibility, acceptability, cost, implementation and the strength of recommendations.

Adolescent recommendations for PCOS diagnosis aimed to avoid over diagnosis, misdiagnosis and delay and under diagnosis; and include:

1. Irregular menstrual cycles are:

– in the first year post menarche, a normal part of the pubertal transition

– >1 to <3 years post menarche: <21 or >45 days

– >3 years post menarche to perimenopause: <21 or >35 days or <8 cycles per year

– >1 year post menarche >90 days for any one cycle

– Primary amenorrhea by age 15 or >3 years post thelarche

When irregular menstrual cycles are present a diagnosis of PCOS should be considered and assessed according to the guidelines.

2. Clinical hyperandrogenism should focus on hirsutism using scoring tools, not on mild to moderate acne that is common in adolescence, or alopecia. Where clinical hyperandrogenism is not present, biochemical hyperandrogenemia testing is appropriate using high quality assays.

3. Pelvic ultrasound and anti-mullerian hormone measurement are not recommended for PCOS diagnosis during adolescence.

4. Exclusion of other disorders that mimic PCOS is required in all women but particularly in those with amenorrhea and severe phenotypes.

For adolescents who have features of PCOS but do not meet diagnostic criteria, an "increased risk" could be considered and reassessment advised at or before full reproductive maturity, 8 years post menarche. This includes those with features of PCOS before contraceptive pill commencement, those with persisting features and those with significant weight gain.

The value and optimal timing of assessment and diagnosis of PCOS should be discussed with the individual patient, taking into account diagnostic challenges at this life stage and psychosocial and cultural factors.

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Identification and Analysis of the Genetic Causes of Premature Ovarian Failure (POF) in a Cohort of Adolescent Girls

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Introduction: In human, the development of the embryonic gonads represents a complex process involving a large number of genes, some still unknown. Specific pathways have a crucial role for the normal ovarian development, the germ cell genomic stability and hormonal maintenance. These pathways' dysregulation can lead to POF, clinically manifesting as the absence of pubertal onset and/or amenorrhea.

Objective: To identify candidate genes responsible for POF, in a cohort of adolescent girls.

Methods: A total of 55 adolescent girls were included in this study. All patients made blood tests for the analysis of karyotype, FMR1 gene and array CGH.

Results: Among the 55 patients, 37 girls were diagnosed as POF associated with known disorders: 35 girls with Turner Syndrome (1 mosaicism; 22 miscellaneous karyotypes; 12 monosomies); 1 girl with BPES; 1 girl with APECED. The remaining 18 girls were classified as isolated POF. Among these, the array CGH analysis showed: a frameshift variant on 9q21.13 **(gene PCSK5)** in 4 patients; a missense variant on 16p13.2 **(gene PMM2)** in 1 patient; a deletion on 8q23.1 **(gene ZFPM2)** in 1 patient; a missense variant on 15q26.1 **(gene POLG)** in 1 patient.

PCSK5 encodes for a convertase responsible for the cleavage of different proteins, such as the proAMH. AMH is known to be essential in follicologenesis, so: variants that we revealed can led to PCSK5 dysfunction, responsible for POF? In literature, there are no reports regarding this association, so further studies are needed to examine the cause-effect relation.

Regarding the **PMM2** gene, our patient was a carrier for the missense variant R141H. In literature is reported one family whose individuals were compound heterozygous for PMM2 mutation but unaffected by the metabolic disease. A female in this family had been diagnosed with POF at 26 years.

ZFPM2 is known to be implicated in gonadal development. In literature ZFPM2 mutations were associated with 46, XY sex reversal case reports. In literature, there are no case reports regarding the association between ZFPM2 and POF, but certainly it could be implicated in the pathogenesis of disease.

POLG encodes for the polymerase of the mitochondrial genome. Mutations in this gene have been associated with a variety of clinical features, including PEO, ataxia and epilepsy. In literature, are described families affected by PEO, carrying a POLG mutation, presenting also a POF disease.

Conclusion: This study supports the importance of genetic analyses to identify the etiology of POF.

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Premature Ovarian Insufficiency in Girls Caused by Autosomal Microdeletions: 3 Case Reports

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Objectives: Premature ovarian insufficiency(POI) is mostly considered X chromosome abnormalities in child.Few of POI cases are associated with autosomal abnormalities.This study was to identify new genes involved POI in three girls.

Methods: 3 girls who came to the hospital because of no menstruation were investigated.They were 14, 15, and 14 years old. They did not find any breast tissue in their physical examination.Clinical data, sex hormones, abdominal ultrasonography, chromosome karyotype analysis and Chromosome microarray analysis(CMA) was done.

Results: Patient 1was a 14-year-old girl. Her height was 147cm, weight 33kg,. Sex hormone values LH: 35.05mIU/mL(1.50-9.30mIU/mL), FSH: 105.6mIU/mL(1.4-18.1mIU/mL),E2:17.3pg/mL(0-44.5pg/mL),T:19.6ng/dL(241.0-827.0ng/dL), PRL: 14.1ng/mL(2.1-17.7ng/mL), PRGE 0.55ng/mL(0.28-1.22ng/mL), DHEAS 144.6μg/dL (34.5-568.9μg/dL). Androstenedione 1.1ng/mL (0.6-3.1ng/mL). The abdominal ultrasound showed that the uterus was 1.9 * 0.7 * 1.2cm^3, the cervix was about 1.5cm long, and the intima was thin. Chromosome karyotype:46, XX. CMA: Del 15q25.2. Patient 2 was a 15-year-old girl. Her height was 153cm, weight 53kg, breasts have not yet developed with normal height growth and no significant wide nipple spacing or neck web phenomenon, no obvious neurological development behind. Sex hormone values LH: 24.29mIU/mL, FSH: 87.1mIU/mL, E2:18.2pg/mL,T:34.7ng/dL, PRL: 17.9ng/mL, PRGE<0.21ng/mL. DHEAS 97.1μg/L. Androstenedione 0.6ng/mL. The abdominal ultrasound showed that the uterus was 1.4 * 0.5 * 1.3cm, the cervix was about 1.7cm long, and the intima was thin. Chromosome karyotype:46, XX. CMA: Del 19p13.3. Patient 3 was a 14-year-old girl. Her height was 136.4cm, weight 38.5kg, breasts have not yet developed, had been in sluggish growth for 11 years. Sex hormone values LH: 17.02mIU/mL, FSH: 61.3mIU/mL, E2: 16.3pg/mL,T:11.9ng/dL, PRL:11.3ng/mL, PRGE<0.21ng/mL. The abdominal ultrasound showed that the uterus was 1.4 * 1.4 * 0.6cm, the cervix was about 1.9cm long, and the intima was thin.Chromosome karyotype:46, XX. CMA: Del 16P11.2.

Conclusions: All the 3 patients were adolescent girls, clinical diagnosis was POI. The presence of microdeletions in 15q25.2, 19p13.3 and 16P11.2 was confirmed by CMA detection. Compared with adult patients with POI, the proportion of chromosomal aberrations in adolescent POIs is significantly higher. Not only common Turner syndrome but also autosomal abnormalities should be noted, and CMA is a powerful weapon for finding autosomal minute mutations. It is recommended that young POI routinely perform CMA examinations.

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Effect of Intrauterine Growth Restriction on Ovarian Follicle Pool

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Introduction: A low oxygen and/or nutrient supply to the fetus, resulting in intrauterine growth restriction (IUGR), can affect gonadal development of the offspring and have a potential impact on fertility. Epidemiological studies on subjects born small for gestational age (SGA), as a surrogate measure of IUGR, have reported contradictory results. Data derived from animal models of placental insufficiency are limited.

Objective and hypotheses: To investigate the effects of placental insufficiency induced by uterine artery ligation (UAL) on the postnatal rat ovary.

Methods: Sprague-Dawley rats underwent UAL at day 19 of gestation. Offspring were sacrificed at 5, 20 and 40 days post-partum (d*pp*), representative of infancy, childhood and peri-pubertal period. At sacrifice, ovaries were excised and weighed. One gonad *per* animal was fixed in 4% PFA and used for histological evaluation. Follicles were counted and classified in three sections *per* ovary after H&E staining. The second gonad was snap frozen in liquid nitrogen and stored at -80°C until processed for RNA extraction. Gene expression of 90 genes was analyzed by TaqMan® Low Density Array. Serum AMH was measured by ELISA.

Results: A lower number of total and primordial follicles was detected in 5 and 20 d*pp* old IUGR animals compared to controls. The number of follicles was no longer different at 40 d*pp*, suggesting a compensatory reduction in the rate of the physiological follicular attrition occurring during pre-pubertal period. Fur-

thermore, IUGR modified the expression of 23 genes involved in different cellular functions, e.g. proliferation, metabolism and angiogenesis. AMH serum levels were not significantly different in the experimental animals compared to controls, although reduced levels were noted at all ages.

Conclusions: This is the first study investigating the effects of placental insufficiency on the postnatal female gonad. The ovarian follicle pool was affected in the IUGR rats up to the prepubertal age, but this effect did not persist in older ages. Different genes involved in fundamental cellular processes were affected by fetal hypoxia at all ages, suggesting that long term alterations occur as a consequence of IUGR. Further analyses are needed to elucidate later effects of IUGR on ovarian function and fertility lifespan.

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Sustainability of Estradiol Drug Concentrations in Cut Matrix Patches; A Study of Different Brands with Potential Use for Pubertal Induction

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Background: The estimated estradiol (E_2) dose required for pubertal induction in hypogonadal girls is about 1/10 of the adult dose. Previous studies have shown that it is possible to provide an individualized and physiological dose for pubertal induction by cutting the patch into smaller pieces. However, the manufacturers do not guarantee stability or utility of cut E_2 patches, primarily designed for postmenopausal women, and have no interest in that evaluation.

Objective: To assess the distribution of E_2 drug over the surface area on different brands of patches and test sustainability of cut pieces.

Methods: Four different E_2 matrix patches available in Europe were tested; all guaranteed by the manufacturer to sustain until expire date by storage in its sachet <+25C or <+30C.

1. Oesclim® 25µg (Mylan Technologies). Rectangular (11 cm^2), containing 5mg E_2.

2. Estraderm MX® 50µg (Merus Labs). Square-shaped (22 cm^2), containing 1.5mg E_2.

3. Estradot® 50µg (Novartis). Rectangular (5 cm^2), containing 0.78mg E_2.

4. Systen® (=Evorel®); 50µg (Janssen-Cilag International). Square-shaped (16 cm^2), containing 3.2mg E_2.

Oesclim, Estraderm and Systen patches were cut into eight parts while Estradot (small patch) was cut into two parts. Patch pieces were put back into respective sachet and sealed by hand. Half of the sachets were put in plastic bags and sealed. The patches were stored at room temperature (+20-22C) or at +35C in heating cabinet for up to 1 month. The E_2 drug was extracted from the patch in a solution of ethyl acetate n-hexane, serially diluted and determined by RIA. A CV below 20% was considered as an acceptable variance in E_2 concentrations between cut pieces.

Results: E_2 drug concentrations were evenly distributed on Oesclim, Estraderm and Systen surface area. Storage in +20-22C or +35C up to 1 month did not affect the E_2 drug amount. E_2 in Estradot patch however, was not affected by storage in +20-22C, but in +35C E_2 decreased with 33% (±15%) in sealed patches and 60% (±13%) in cut patches, during 1 month storage. Storage in plastic bags gave the same results as storage without.

Conclusion: Sustainability of cut Oesclim®, Estraderm® and Systen® patches was achieved for at least 1 month in room temperature or +35C. The Estradot® patch was too small to properly cut into small pieces and not sustainable in warm climate.

P1-P240

Serum Anti-Mullerian Hormone (AMH) Concentrations and Reduced Appendix Testis Estrogen Receptor Expression in Cryptorchidism

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Objective: AMH causes fetal paramesonephric duct regression and is involved in testicular development and function. Sertoli cell AMH remains high during childhood until puberty. The appendix testis (AT), a remnant of the paramesonephric duct, contains both androgen and estrogen receptors. AT androgen receptors have been reported to play a role in embryonic testicular descent. The AT is commonly resected during orchiopexy and abdominal surgery as possible torsion in the future may cause an acute scrotum. Our study aimed to assess AMH concentrations together with the expression of AT androgen and estrogen receptors in cryptorchidism.

Methods: The study included 52 boys, 31 patients with cryptorchidism (PC) and 21 healthy control boys with orthotopic

testes who underwent surgery for hydrocele. Plasma AMH was measured using a chemiluminescent enzyme immunoassay. The appendix testis was surgically resected from all the boys studied. AT androgen and estrogen receptor expression was assessed with immunohistochemistry using the monoclonal antibody R441 for the androgen receptors and monoclonal antibody MAB463 for the estrogen receptors. For the estimation of the receptors' expression the Allred Score method was used. Statistical analysis was performed with Mann-Whitney και Spearman's rs tests.

Results: AMH concentrations showed statistically significant differences between patients with high (HC) and those with low cryptorchidism (LC) (p=0.019){median=4.7ng/ml, interquartile range (IR) =14.0 ng/ml for HC and median=19.8 ng/ml, IR=19.4 ng/ml for LC}. Estrogen receptor expression was lower in cryptorchid patients' AT compared to controls (p=0.036). The expression of the AT androgen receptors, though lower in PC, did not present statistically significant differences compared to the controls (p=0.248). In the PC there was a highly positive correlation (rs=0.80) between the expression of the estrogen and androgen receptors (p<0.0001).

Conclusions: Our study suggests that there is an inverse correlation between plasma AMH concentrations and cryptorchidism severity. It is also of interest that the expression of the androgen receptors of the appendix testis was not significantly different between the patients with cryptorchidism and controls, while the expression of the estrogen receptors in the children with cryptorchidism was significantly lower. Our results suggest that the expression of the AT estrogen receptors, and not only the AT androgen receptors as previously reported, may possibly play an important role in the descent of the testes to the scrotum.

P1-P241

The Comparisons of the Adult Height Gain and the Menarchal Age of the Girls with Central Precocious Puberty after Gonadotropin Releasing Hormone Agonist Alone and Those Treated with Combined Growth Hormone Therapy

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Purpose : To investigate the outcomes of GH therapy combined with GnRH agonist for short girls who diagnosed with idiopathic CPP compared to whom treated with GnRH agonist alone.

Methods: We performed retrospective reviews, among 1636 patients managed for CPP, collected data of the 166 girls with CPP treated with GnRHa for 36 months or more from January 2002 to December 2016. We divided groups of patients received GnRHa alone (Group A, n=135) or GnRHa combined GH (Group B, n=31). Height, predicted adult height (PAH), bone age(BA) were recorded at the times of initial treatment with GnRHa, 1, 2, 3 years after initial GnRHa, the cessation of GnRHa, and the final adult height. We assessed the yearly changes in PAH SDS, MPH SDS and final height gain SDS. The menarchal ages of 166 girls were recorded.

Results: The mean age of patients at initial treatment was 7.89 years-old. The duration of GnRHa in group B was longer than group A (44.25 ± 7.33mo in Gr. A vs 49.58 ± 11.35mo in Gr. B, p=0.017). MPH (target height) were 159.25 ± 3.51cm in group A and 156.61 ± 3.39cm in group B. The height at the initiation of treatment were 129.34 ± 5.18cm and 123.12 ± 5.13cm in group A and B. PAH before treatment was significantly higher in group A (150.76 ± 3.69cm vs 146.44 ± 3.56cm, p<0.001). The duration of GH treatment was 39.23 ± 16.94 months. The timing of initiation of GH therapy was 19.19 months after start of GnRHa. Height at the end of treatment were 148.99 ± 4.27cm and 148.61 ± 3.67cm in group A and B. BA at the end of therapy were 11.83 ± 0.51 and 11.71 ± 0.52 in group A and B. The annual increment of PAH SDS was higher in the group B than group A (0.63 ± 0.52 vs 0.88 ± 0.57 at first year, p=0.02; 0.52 ± 0.34 vs 0.79 ± 0.51 at second year, p=0.008). The height gain SDS that is the difference between NFH SDS and initial PAH SDS was significantly higher in group B (2.5 ± 0.75 vs 2.92±1.02, p=0.048). The mean menarchal age were 13.1 ± 0.99 vs 13.18 ± 0.58 (p=0.755). The interval time to menarche were not significantly different between two groups.

Conclusions: The patients who were treated combined GH with GnRHa showed faster growth and had more additional height gain.

P1-P242

AMH Level of Infants with Premature Thelarche and Possible Relationship between AMH and Mini-Puberty

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Background/Aims: AMH levels of mini puberty are higher than prepubertal period. In this study we investigated AMH levels in infants with premature thelarche who are presumed to have exaggerated mini puberty due to inadequate/late suppression of pubertal activation.

Methods: Fifty five female infants between 3 months and 3 years of age with premature thelarche were enrolled in the study and 49 healthy girls in the same age group were included in the study. Bone age, pelvic ultrasonography(USG) findings and AMH level of the patient group and serum AMH level of the control group were evaluated.

Results: Serum AMH levels of premature thelarche (med:1.66 min-max:0.15-7.28 ng/ml) were significantly lower than the control group's (med:2.46 min-max:0.60-8.49 ng/ml)(p:0.015). AMH and FSH were negatively correlated (r:-0.412 p:0,002) in infants with premature thelarche.

Conclusion: This is the first study to investigate AMH levels in infants with premature thelarche. It was concluded that AMH may play a role of suppressing pubertal findings during the mini-

puberty period and decreased of AMH may cause premature thelarche in infants as a result of exaggerated mini-puberty because of detection of AMH levels in infants with premature thelarche less than healthy controls and a negative correlation between AMH and FSH.

P1-P243

Circulating Makorin Ring Finger Protein 3 Levels Predict Central Precocious Puberty in Girls

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Background/Aim: Puberty is a mysterious process about which much is as yet unknown.MKRN3 is involved in regulating the initiation of puberty by inhibiting gonadotropin releasing hormone (GnRH) secretion. This study evaluated the serum level of MKRN3 and investigated its diagnostic usefulness in girls with central precocious puberty (CPP). Changes in the MKRN3 concentration during GnRH agonist (GnRHa) treatment were also analyzed.

Methods: In total, 41 girls with CPP and 35 age-matched prepubertal girls were enrolled. Serum levels of MKRN3 were measured in patients and normal controls and compared. Patients were then treated with GnRHa, and their MKRN3 and gonadotropin concentrations were measured every 6 months for 1 year. A receiver operating characteristic curve analysis was performed to assess the value of MKRN3 in diagnosing CPP.

Results: The MKRN3 concentrations were much lower in the patient group than in the control group, 521.00 ± 608.50 and 1282.24 ± 791.26 (pg/mL), respectively (p = 0.005). At an MKRN3 cutoff value of 932.91 pg/mL, the sensitivity for differentiating CPP was 83.9% and the specificity was 88.8%. The gonadotropin concentrations were significantly decreased, while the MKRN3 concentrations were unchanged, during GnRHa treatment in CPP girls. There was no significant correlation between MKRN3 and gonadotropin levels in CPP girls.

Conclusions: The circulating MKRN3 concentrations were lower in precocious puberty patients than in normal controls. GnRH agonist treatment did not seem to affect the MKRN3 concentrations in the precocious puberty patients. The measurement of serum MKRN3 may be helpful in diagnosing CPP.

P1-P244

Polycystic Ovarian Syndrome in Adolescents: Characterising the Clinical Phenotype and the Role of Precision Medicine

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Background: Polycystic ovarian syndrome (PCOS) is the most common hormone disorder in adolescent and young adult females, affecting 4-20% of the population. PCOS is associated with metabolic dysfunction, pro-inflammatory processes and mood disorders. Despite this, it is poorly understood in younger adolescents, and diagnosis and management remain challenging.

Objectives: To better understand the clinical phenotype of PCOS in adolescents. Subsequently, we will undertake proteomic and metabolomic (omic) profiling of urine to identify novel non-invasive biomarkers of PCOS.

Method: In this prospective longitudinal study, females aged 12-19 years meeting NIH diagnostic criteria for PCOS were recruited from adolescent endocrine and gynaecology clinics (July 2016-November 2017). At baseline and annual follow-up, pituitary, adrenal and ovarian hormones were analysed by radioimmunoassay and mass spectrometry. Anti-müllerian hormone, inflammatory and metabolic markers were measured including an oral glucose tolerance test. Psychometric questionnaires, menstrual records, pubertal assessment, anthropometric parameters and trans-abdominal pelvic ultrasounds were undertaken. Urine samples were obtained for shotgun omic profiling using Electrospray-Ionisation Quadrupole-Time-of-Flight Mass Spectrometry.

Results: To date, 37 participants have been recruited (median age 15.0 years, range 12.6-18.3 years), and 17 have completed their 12 month follow-up. Clinical signs at presentation included acne (89%), hirsutism (78%), acanthosis nigricans (49%), obesity (57%; BMI Z score >2) and overweight (24%; BMI Z score >1). Two-thirds of participants had symptoms of depression or anxiety but only one-third were known to mental health services. Metabolic dysfunction was common at baseline; 88% of participants had an elevated body fat percentage, 24% had hypercholesterolaemia or hypertriglyceridaemia, 29% had impaired fasting glucose or impaired glucose tolerance, one had undiagnosed type 2 diabetes and 62% had insulin resistance. AMH was elevated in one-third of participants (median AMH 34.1pmol/l, range 5.0-116.0pmol/l) and three-quarters had an elevated free androgen index. Elevated inflammatory markers (CRP/ESR) were present in 40% participants. Only three participants had ultrasonographic evidence of PCOS and a further quarter had equivocal results.

Conclusion and Future Directions: Diagnosing PCOS in adolescents remains challenging as acne and irregular menstrual cycles are common, and ultrasonographic diagnosis of PCOS is suboptimal. However, prevalence of mental health disorders and

metabolic disease is high. Therefore, accurate diagnosis and early intervention are imperative. Whilst promising biomarkers, including AMH have been noted, our omic analysis aims to identify a wider range of novel non-invasive biomarkers. Subsequently, we aim to create a clinically translatable assay to aid diagnosis and management of this common adolescent condition.

P1-P245

Thyroid Function in Central Precocious Puberty Girls

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Objectives: Obesity is a well-known risk factor for central precocious puberty (CPP). Recently, elevated thyroid stimulating hormone (TSH) were reported in obese youth. However, few data regarding the relationship between CPP and TSH are available. The aim of this study was to evaluate thyroid function in CPP girls and the relationship between CPP and serum TSH concentration.

Methods: This is a retrospective cross-sectional study. A total 1,247 girls aged 6-8 years who underwent gonadotropin-releasing hormone (GnRH) stimulation test were included. Medical records of all subjects were reviewed. Subjects were classified into CPP (n=554) and control (n=693) groups according to the results of GnRH stimulation test. Subclinical hypothyroidism was defined as elevated TSH with normal free T4 (TSH ≥5.0 mIU/L and free T4 ≥0.8 ng/dL). Characteristic and laboratory data between CPP and control groups were compared. Correlations of characteristic and laboratory data with TSH concentration were evaluated.

Results: There were no significant differences in age, height, height standard deviation score (SDS), insulin-like growth factor binding protein (IGFBP)-3 and IGFBP-3 SDS between CPP and control groups. Bone age, bone age advance, alkaline phosphatase, insulin-like growth factor (IGF)-I, IGF-I SDS, basal and peak luteinizing hormone (LH) and basal and peak follicular stimulating hormone (FSH) were significantly higher in CPP than in control group. Weight SDS and body mass index SDS were significantly higher in control than CPP group. Serum TSH concentration of CPP group was significantly higher than that of control group (3.19±1.55 vs. 2.58±1.34 mIU/L, p<0.001). Serum free T4 concentration of CPP group was significantly lower than that of control group (1.38±0.14 vs. 1.44±0.18 ng/dL, p<0.001). Among all subjects, 149 girls (11.9%) had subclinical hypothyroidism. The prevalence of subclinical hypothyroidism was higher in CPP group compared to control group (15.7 vs. 8.9%, p<0.001). TSH concentrations were positively correlated with age, height, weight, BMI, bone age, alkaline phosphatase, IGF-I, IGF-I SDS, basal LH, peak LH and basal FSH. Multiple linear regression analysis showed that age (β=0.574, p<0.001) and peak LH (β=0.016, p=0.021) were independent predictors of serum TSH concentration.

Conclusion: Subclinical hypothyroidism in CPP girls should be associated with pubertal LH elevation.

P1-P246

Clinical Phenotypes and Mutation Spectrum of Patients with Isolated Gonadotropin-Releasing Hormone Deficiency in a Single Academic Center

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Background: Isolated gonadotropin-releasing hormone (GnRH) deficiency (IGD) is caused by a deficiency in GnRH production, secretion or action. IGD is a highly heterogeneous disorder with wide phenotypic spectrum including Kallmann syndrome (KS) with anosmia and normosmic idiopathic hypogonadotropic hypogonadism (nIHH). More than 30 different causative genes have been identified in several studies. However, there are no data on the prevalence, clinical characteristics, and molecular spectrum in Korea. Therefore, this study was performed to investigate the phenotypic and genotypic spectrum in patients with IGD in Korea.

Methods: This study included 41 patients from 40 families diagnosed between January 1995 and December 2017. Clinical and endocrine characteristics were retrospectively analyzed including cryptorchidism, micropenis, anosmia, associated anomalies, family history, and laboratory findings. Mutation analysis was performed using targeted gene panel for known 69 IGD genes (n = 33) or whole exome sequencing (n = 8).

Results: KS was predominant in men (M:F = 24:0) compared to patients with nIHH (M:F= 10:7). The mean age at presentation was 14.5 ± 5.0 years (range, 4.7–21.3 years) in KS including two prepubertal males with isolated anosmia and 17.5 ± 2.2 years (range, 13.7–22.5 years) in nIHH (P = 0.015). Two pre-pubertal males presented with anosmia and aplasia of the olfactory bulbs at 8.1 and 5.8 years, respectively. The other patients presented with delayed puberty or primary amenorrhea. Non-reproductive features were found in 9 patients with KS [hearing defect (n = 4), renal anomaly (n =1), cleft lip/palate (n =1), heart defects (n = 3)] and 5 patients with nIHH [hearing defect (n = 2), renal anomaly (n =1), syndactyly (n = 2)]. Among 40 families, rare sequence variants were identified 8 probands with KS and 7 probands with nIHH, respectively. *FGFR1* (5/40, 12.5%) was the most common, followed by *CHD7* (3/40, 7.5%), *ANOS1* (2/40, 5%), *TACR3* (1/40, 2.5%), *GNRHR* (1/40), *SOX3* (1/40), and *PROKR2* (1/40).

Conclusions: KS was predominant in males, and they presented earlier than those with nIHH. The prevalence of non-reproductive features were not different between patients with KS and nIHH. Two prepubertal males with anosmia should be followed up to initiate timely hormonal replacement therapy. Overall, genetic diagnosis was possible in 37.5% of probands with IGD with 13 pathogenic or likely pathogenic variants and two variants of uncertain significance.

P1-P247

Evaluation of Hormonal Profiles and Autoantibodies Against Sperm and Leydig Cells in Patients After Testicular Torsion Treatment

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Background: Proper endocrine function of testicles is essential for the healthy development of children and for adult life.

Methods: Hormonal profiles of patients (aged 1-18 years) were evaluated several years after surgical testicular torsion treatment. Blood samples were obtained between 11a.m and 1p.m. to measure serum levels of FSH, LH, AMH, testosterone, VEGF-A total, IGF-1, IGFBP-3 and autoantibodies against sperm and Leydig cells.

Results: Levels of FSH in patients after testicular torsion incidents were often higher than those in control group but still within the normal range. In the group of youngest boys AMH levels were normal or significantly lower than in the control group. Levels of the testosterone, VEGF-A, IGF-1, IGFBP-3 were normal for patients' age. No sperm and leydig cells autoantibodies were found in the serum.

Conclusions: Due to testicular damage, FSH secretion is higher to compensate the loss of testicular function therefore the seroidogenesis was unaffected. Testicular torsion did not cause chronic autoimmunological process and did not affect vasculogenesis or IGF-1 axis. It seems that lower AMH levels in the youngest boys group can be a primordial abnormality – testicular torsion appearing in those patients may be secondary to inproper testicular function. Futher investigations are needed.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology P2

P2-P338

Physical Assessment in Chinese children with 5a-Reductase Type 2 Deficiency

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Background: 5α - reductase type 2 deficiency (5αRD) is an autosomal recessive hereditary disease which has an incidence of 11.2%-15.5% among population with 46, XY DSD (disorders of sex development).

Objective: To study the growth pattern in Chinese pediatric patients with 5αRD.

Subjects: Data were from 187 patients with 5αRD (age from 0-16 years old, with homozygous or compound heterozygous mutations in the SRD5A2 gene) who visited 8 pediatric endocrine centers from Jan, 2010 to Dec, 2017. Children with 46, XY DSD without hormone treatment and those with testicular dysfunction were also selected as a positive control group.

Methods: Height, weight and other relevant data were collected from the multicenter hospital registration database. Hormone was tested by enzyme enhanced chemiluminescence assay; BA was assessed by G-P. Growth curve was constructed based on λ-median-coefficient of variation method (LMS).

Results: Compared to normal boys, higher height standard deviation scores (HtSDS) were observed in 5αRD children who were <1-year-old (*p=0.002, 0.048,* respectively), and higher weight standard deviation scores (WtSDS) in those < 6-month-old (*p=0.012*). Then HtSDS and WtSDS showed lower than those of normal boys of the same age when > 2-year-old. Furthermore, compared to testicular dysfunction 46, XY DSD, the HtSDS in 5αRDs was significantly higher (*P=0.003*), while WtSDS was lower in 5αRD patients without significant difference. Additionally, the ratio of bone age over chronological age (BA/CA) was lower than 1 in children with 5αRD and with testicular dysfunction 46, XY DSD.

Conclusion: The children with 5αRD had a special growth pattern. Their body length was longer in 0~5 months group, and then its growing slowed down leaving children shorter than normal boys after the age of 2 years old. The bone age was delayed in 5αRD children. This may provide a chance for androgens treatment in young age 5αRD boys for their micropenis.

P2-P339

Results of Exome Sequencing in Disorders of Sex Development

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Disorders or Differences of sex development (DSD) are a heterogeneous group of congenital conditions, involving variations of chromosomal, gonadal, or anatomical development. Diagnosis is based on clinical, biochemical, imaging and genetic evaluation. In recent years knowledge about genetic causes has increased, mainly due to improved genetic techniques. In this study we investigated the yield of exome sequencing in our patients with DSD.

Patients and methods: Genetic investigations are performed by karyotyping as a first step, followed by additional DNA analysis in case of 46,XX or 46,XY. Based on biochemical and imaging results and family history either a DSD genepanel (containing 53 genes) is used, or targeted gene-sequencing (by direct Sanger sequencing) is performed. Exome sequencing is performed using Illumina HiSeq by BGI-Europe.

Results: Since the introduction of exome sequencing in our DSD expertise center (2014), exome sequencing with the DSD ge-

nepanel was performed in 64 patients; of which 19 external referrals. Of the 45 internal referrals, 9 children were 46,XX, 35 46,XY and 1 child with 45,X/46,XY karyotype.

In children with 46,XY, homozygous or compound heterozygous *SRD5A2* mutations were found in 3 patients. *NR5A1* variants were found in 2 patients (1 de novo, 1 maternally inherited; both considered likely pathogenic). A pathogenic *AR* mutation was found in 1 patient, and a *DMRT1* variant was found in 1 patient (possibly pathogenic). (Likely) pathogenic variants were thus found in 13% of patients (6/45).

In 46,XX DSD cases, 2 patients had a heterozygous *CYP17A1* mutation.

In the 19 external samples 1 *NR5A1* variant of unknown inheritance was found, 1 patient with homozygous *CYP17A1* mutations, 1 patient with homozygous *HSD17B3* mutations, 1 patient with homozygous *DHCR7* mutations, and 1 patient with a *WT1* mutation; all considered pathogenic.

In total, exome sequencing revealed a likely pathogenic cause in 17% (11/64).

In the same period pathogenic mutations were found with direct sequencing in: *SRY* gene (46,XY DSD), *SRD5A2* (46,XY, compound heterozygous mutations), *DHCR7* (46,XY, homozygous mutations). In an additional 11 patients with 46,XX DSD and a strong suspicion of CAH, bi-allelic *CYP21A2* mutations were found.

Conclusion: In DSD exome sequencing is a valuable tool as a first-step diagnostic tool, but in selected cases when phenotype and biochemical tests suggest a specific genetic defect direct DNA sequencing can be appropriate. Early identification of a genetic cause is important for optimal management of the patient.

P2-P340

Awareness is the Key: Heavy Delay in Diagnosis of 17-β-Hydroxysteroid-Dehydrogenase III Deficiency (17bHSD3D) and Other Insights and Conclusions from a Cohort of Ten 17bHSD3D Patients in Germany

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Background/Objective: 17bHSD3D is a rare genetic disorder that leads to disorders of sex development (DSD) in 46,XY patients. Phenotype at birth ranges from unsuspicious female genitalia to micropenises. Besides molecular genetic testing no reliable lab parameters have been established for pre-identifying patients through basal steroid-levels or hCG-testing. This bares the risk of under-, mis- or late diagnosis. Further, little research has been performed on psychological wellbeing, gender identification and gender related behaviour of affected patients. We aim to share insights from our cohort of 17bHSD3D patients in these fields of interest.

Method: Blood hormone levels from 10 17bHSD3D patients from Nordrhein-Westfalen, Germany were collected for signs of possible patterns in steroid profiles. Information on time to diagnosis was drawn from case histories. Semi-structured interviews with patients and parents were performed for information on psychological wellbeing and gender identity.

Results: Mean age at diagnosis of DSD and 17bHSD3D were 4,3 and 10,9 years respectively. 5 patient's steroid profiles were determined before gonadectomy and commencement of hormonotherapy and thus could be considered for evaluation, resulting in sample size too small to draw definitive conclusions. It remains noteworthy that all patients with gonads showed androstendion and estrone levels above tanner-related reference values. This may be approached for further research. Basal testosterone/androstendione-quotient was below 0,62 regardless of gonadectomy.

As of April 2018 5 semi-structured interviews were conducted, 3 are still pending and 2 patients did not wish to be interviewed. All 5 were declared as female. 2 now identify themselves as male and 3 as female. However, 2 female-identifying patients showed male gender related behaviour and were less confident about their gender. One male-identifying patient continues to struggle with his gender, after his begun gender reassignment during early adolescence.

Conclusion: This highlights the relevance of gender neutral upbringing of 46, XY 17bHSD3D patients to allow development to both male and female gender. Further gender reassignment should be deferred until 18 years for a more deliberate decision to be possible. An average 6-year delay between diagnosis of DSD and 17bHSD3D emphasizes the need for increased awareness among physicians as well as clear diagnostic procedures for 17bHSD3D to allow for swifter diagnosis thus reducing burden for patients and family through the limbo of unclear etiology. Further, our interviews showed that patients may present with gender dysphoria before diagnosis of DSD, thus physicians should consider DSD and hence 17bHSD3D in these patients too.

P2-P341

Evaluation of Three Patients with 46,XY Gonadal Dysgenesis due to Desert Hedgehog Gene Mutations

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Background: Desert Hedgehog (*DHH*) gene acts on early testicular development, testis cord formation and differentiation of fetal Leydig cells. It also has a role in nerve sheath formation. *DHH* gene mutations is a very rare cause of 46,XY gonadal dysgenesis (GD). Gonadal tumors and peripheral neuropathy have been associated with *DHH* mutations.

Aim: To present three patients with 46,XY GD due to novel homozygous *DHH* mutations.

Patients and methods: Targeted next-generation sequencing of three patients by in-house designed DSD gene-panel.

Results: First patient (one of the siblings) presented at age 1 year with penoscrotal hypospadias [external masculinization score (EMS) 5], bilateral inguinal testes, Müllerian structure evident on biopsy, no response to HCG, raised as female initially and con-

verted to male at 5 years of age. Second patient (the other siblings) presented at age 14 days with severe micropenis, bilateral inguinal testes (EMS 2), no Müllerian structure. Testosterone response was normal to HCG and the patient was raised as female. Gonadectomy revealed gonadal dysgenesis with loss of Leydig cells with intratubuler germ cell neoplasia. Third patient presented at age 19 days with penoscrotal hypospadias, bilateral inguinal testes (EMS 6), penile size 2 cm, and basal testosterone at 4 months of age was 1.48 ng/ml, no Müllerian structure, low AMH and raised as male. Consanguinity was present in all.

In two siblings, a novel homozygous c.114G>A mutation in exon 3 of the *DHH* gene was predicted to cause nonsense type alteration (p.Trp382*). In other patient two missense variants in homozygous form were shown (c.71G>C in exon 1 and c.1063C>T in exon 3).

None of patients had any clinical signs of neuropathy but detailed neurophysiologic evaluation has not been performed.

Conclusion: *DHH* gene mutation should be analyzed in patients with 46,XY gonadal dysgenesis for diagnosis and the presence of potential neuropathy and gonadal tumors. *In vivo* studies are needed to further delineate the phenotype genotype relation.

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In-silico Gene-protein Analysis and Clinical Phenotype Characterisation of Three Novel *NR5A1*/ SF1 Gene Mutations Presenting with 46,XY DSD

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Background: Disorders of sex development (DSD) due to mutations in the *NR5A1* (SF1) gene result in a highly variable phenotype.

Objective: To report the clinical phenotype and the molecular / structural characteristics of the gene-protein product arising from three novel mutations of the NR5A1 (SF1) gene found in patients presenting with 46,XY DSD

Method: Phenotype determined from interrogation of clinical case notes. Interpretation of DNA-protein molecular interactions were modelled *in-silico* using PyMOL Molecular Graphic System. Mutation effect and structural analyses verified using *PolyPhen2; MutationTaster, SIFT, LRT and SAAP* software *programmes.*

Results: Case 1. Mutation (heterozygous) Q329X. Karyotype 46XY. Female presented age 14yrs with primary amenorrhoea, no breast development, hirsutism, clitoromegaly (6cm) and narrow blind-ending vagina. Bilateral inguinal gonads and absent uterus detected. Basal serum testosterone (T)= 20.6 nmol/l. Mutation results in a truncated SF1 protein at ligand binding domain.

Case 2. Mutation (heterozygous) G22D. Karyotype 46XY - confirmed prenatally. Female appearance at birth with normal sized clitoris. Bilateral palpable labial gonads and absent uterus. Post-HCG T= 10.1 nmol/l. Mutation alters DNA binding domain site configuration.

Case 3. Mutation (heterozygous) A280E. Karyotype 46XY. Female presented age 14yrs with isolated pubic hair development (onset age 8 yrs), clitoromegaly (3cm) and lack of other pubertal development. Rudimentary uterus detected. Basal T= 4.8 nmol/l. Mutation located within central protein core and alters folding. Familial gene screening detected that her father was mosaic for mutations A280E and A280V, whilst her sister (46,XX; currently age 9yrs) was heterozygous for A280E.

In all cases, no adrenal dysfunction has been demonstrated to date. All underwent bilateral gonadectomy and female sex assignment. Histology of the gonads showed testicular characteristics in all cases, with no evidence of malignancy. *In-silico* bioinformatic analyses confirmed all mutations were pathogenic.

Discussion: We report 3 novel NR5A1 mutations presenting with 46XY DSD and variable degrees of virilisation. *In-silico* molecular and structural analyses confirm the mutations to be highly pathogenic. Case 3 also highlights a sibling with a 46XX karyotype with the same mutation. The clinical significance of this for the sibling is uncertain, and raises specific challenges with respect to provision of counselling, predicting clinical prognosis and future management.

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Clinical, Biochemical, Structural and Functional Characterization of a Novel P450 Oxidoreductase Mutation Causing Virilization in a 46,XX Patient

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Background: Cytochrome P450 oxidoreductase (POR) deficiency (PORD) is a form of congenital adrenal hyperplasia (CAH) and results in steroid-production loss from cytochrome P450 proteins. Mutations in *POR* cause mild to severe forms of CAH with/ without bone malformation symptoms resembling Antley-Bixler syndrome. We report a novel *POR* Arg550Trp mutation identified in a 46,XX patient with signs of aromatase (ARO) deficiency. Child (first pregnancy) and mother presented signs of virilization from 6th month. Mother had elevated T at 5th day that returned to normal at 4th month. Daughter was born with fused labioscrotal

folds (genital tubercle 1.5 cm with urethral opening, Prader 3). Ultrasound revealed presence of uterus and ovaries. Sequencing of *CYP19A1* gene did not reveal any defects and candidate-gene screening revealed compound heterozygous novel mutations c.70_71delTC/p.Leu25PhefsTer93 and c.1648C>T/p.Arg550Trp in *POR*. At 8y adrenal function is normal except for slightly elevated 17-OH-progesterone.

Methods: We analyzed the ability of POR wild-type (WT) and Arg550Trp to reduce ferricyanide, MTT, cytochrome c and activity towards the drug and steroid metabolizing cytochrome P450. POR WT and Arg550Trp were expressed and produced as recombinant proteins in bacteria (*E. coli* C41(DE3)) and combined with recombinant P450 proteins and small molecule substrates for enzyme assays. The CYP19A1 was produced in *E.coli* JM109 cells with chaperons GroEL and GroES for folding and purified by metal chelate column chromatography.

Results: We found severe effects of Arg550Trp mutation on activities with different substrates. Arg550Trp showed 41% of the WT activity in cytochrome c and only 7.7% activity towards reduction of MTT. A 2.75 fold increase in Michaelis constant (Km) was observed in ferricyanide reduction assays compared to WT POR. Further ongoing assays with ARO activity (D4A to E1) and change of NADPH in assays will provide detailed information.

Conclusion: Arg550Trp is located in the NADPH binding region of POR. Binding of NADPH is crucial for electron transfer in POR and supply of redox equivalents to partner proteins and small molecules. Computational analysis predicted instability in the NADPH binding region of POR, which may affect ARO activity to a higher degree than other partner enzymes because ARO requires 6 molecules of NADPH per reaction cycle compared to 2 molecules for other cytochrome P450 partners of POR. Therefore, an adverse effect on ARO activity due to Arg550W mutation in POR is predicted. This mutation combined with p.Leu25PhefsTer93 explains the patient phenotype of PORD.

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Copy-Number Variations of the Human Olfactory Receptor Gene Family in Patients with Macromastia and Prepubertal Gynecomastia

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Background: Aromatase excess syndrome(AEXS)(OMIM 139300) is a rare condition characterized with gynecomastia in boys and macromastia in girls. Estrogen excess in boys can lead to prepubertal and pubertal gynecomastia, bone age progression and short adult stature. While most of girls are usually asymptomatic, there are few reported female patients with excessive breast growth, early puberty, menstrual irregularities, and short adult stature. Male and female children with AEXS have shown heterozygous structural mutations in *CYP19A1*, leading to increased activity of aromatase enzyme and consequently excessive estrogen production.

Aim: Investigation of Copy Number Variations (CNVs) in *CYP19A1* and other pathway related genes in patients with prepubertal gynecomastia and macromastia.

Subjects and Methods: Patients who were followed with AEXS diagnosis (6 male patients with prepubertal gynecomastia and 7 female patients with macromastia).

Clinical and hormonal findings of the patients at diagnosis and follow-up were reviewed retrospectively. Oligonucleotide array comparative genomic hybridization (a-CGH) was performed (Agilent Technologies, Inc., Santa Clara, CA, USA) according to manufacturer protocol. Data were analyzed with the use of Agilent Genomics Workbench, with data aligned to the Human Genome release 19 (hg19). Predicted pathogenic CNVs is searched and group of genes 8*CYP19A1, TNFAIP8L3, AP4E1, GLDN, DMXL2, TMOD3, SEMA6D, SCG3, CGNL1, ESR1,* and *PTEN)* are specifically investigated.

Results: The median age of patients at presentation was 13 (min-max: 12-22.1) years in female patients and 8.9 (6.3-12.7) years in male patients. Three males had gynecomastia and two males had macromastia history in their families. Four females had a history of macromastia in the family. Median BMI SDS was 1.6 (0.6-3.6) in female and 1.6 (0.2-2.4) in male patients. Median bone age was 15 (13-18) years in females and 11.5 (5-14) years in males. Median estradiol (E2) level was 96.8 (25.8-357) pg/ml in females and 19.5 (11.4-64.3) pg/ml in males. Median E1 level of males was 22 (10.8-30) pg/ml. No mutation was detected by a-CGH technique neither in *CYP19A1* nor investigated genes. But, interestingly, we detected a 65.172 kb deletion in olfactory receptor gene cluster *OR4P4, OR4S2, OR4C6* (CHR 11q11.1) in four females and in 2 males (46.2%). Whereas, in our a-CGH cohort we detected the same type of deletion in 34 out of 988 cases (3.4%).

Conclusion: No association *CYP19A1* CNVs revealed in our cohort. Increased frequency of olfactory genes region deletion in our cohort requires further attention if obesity associated genes may play role in development of gynecomastia and macromastia.

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Histopathologic Characterization of Patients with 46,XX Testicular and Ovotesticular Disorders of Sex Development

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Disorders of sex development (DSD) are those congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. The aim of this study was to characterize the histology of 46,XX DSD prepubertal gonads.

We studied 25 gonads of fourteen 46,XX DSD patients. The age of biopsy/gonadectomy was 1.17 (0.08-4.17) years (median

and range). Molecular studies confirmed the absence of *SRY* by PCR and/or MLPA in blood samples of all patients and in DNA from gonads from 8 patients. General gonadal histology was assessed on H&E stained sections from each sample by two double blinded specialists and the findings were classified as testicular, ovarian or ovotesticular parenchyma, undifferentiated gonadal tissue (UGT) and gonadoblastoma (GB). Immunohistochemical (IHC) analysis was used to identify Sertoli cells (SOX9), ovarian follicular cells (FOXL2), somatic cells (INHIBIN B), pluripotent germ cells (OCT3/4) and steroidogenic cells (HSD3B2 and CYP17A1).

Twenty one gonads (corresponding to 12 patients) showed ovotesticular characteristics and 4 (2 patients) showed only testicular parenchyma. No histological alterations were found in the ovarian parenchyma. Testicular parenchyma showed signs of dysgenesis in all cases (seminiferous tubules inside the tunica albuginea) with significantly thick basal membrane (in some cases) and scarce germ cells.

Regarding the patients with ovotestis, in 2/12 the first biopsy showed only testicular tissue and a second biopsy (performed 10 years later due to clinical characteristics of feminization) revealed ovarian tissue as well. Moreover, 3 cases presented UGT and in 2 other patients GB was found.

IHC analysis of SOX9 and FOXL2 confirmed the presence of testicular or ovarian parenchyma, even in apparently undifferentiated structures. OCT3/4 was positive in 6 gonads (3 patients): 4 with UGT features (2 patients) and 2 with the presence of GB (1 patient). HSD3B2 and CYP17A1 revealed the presence of active steroidogenic cells. Expression of inhibin B, SOX9 and FOXL2 in UGT and GB was found.

A careful histological analysis is crucial for the diagnosis. Nevertheless, the addition of several IHC markers is important to achieve a thorough characterization of the gonads. Interestingly, in all testicular parenchyma signs of dysgenesis were found. It is noteworthy that a second biopsy in 2 former testicular cases revealed the presence of ovarian parenchyma. Considering the histopathological findings in early childhood, a close clinical follow up of patients with a specialized DSD team is suggested.

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Current Medical Care of Children and Adolescents with Disorders/Differences of Sex Development in Switzerland

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Introduction: Since 2000 understanding of biology of sex development increased tremendously thanks to genetic research. This lead to new classification for persons with disorders/differences of sex development (DSD) based on genetics, and guidelines from the UK recommend revising medical care for persons with DSD by setting up interdisciplinary DSD teams. In Switzerland, persons with DSD asked for better care, stimulating the Swiss National Ethics Commission in 2012 to recommend improved treatment of DSD persons. We aimed to describe the current situation of medical care of DSD in Switzerland.

Methods: A questionnaire was sent to pediatric endocrinologists of eight hospitals in Switzerland who were either part of the Working Group DSD of the Swiss Society for Pediatric Endocrinology and Diabetology (AG DSD SGPED) or committed to set up a DSD cohort. We asked them to estimate numbers of treated DSD persons, indicate specialists involved in DSD care and report DSD-related research projects.

Results: The eight clinics cover >85% of all newborns in Switzerland. Each year, around 24 newborns and 24 children and adolescents were diagnosed with complex DSD, e.g. ambiguous genitalia. In total, the eight clinics care for about 750 children with a DSD diagnosis according to the Chicago consensus classification. Of those, 90 had complex DSD, 130 congenital adrenal hyperplasia, and 130 Turner syndrome.

Most clinics used the UK guidelines and 7/8 had established interdisciplinary DSD-teams including specialized pediatricians from many areas, geneticists, general psychologists or social coun-

selors. Only few clinics had specialized psychologists, social counselors, nurses, or ethicists.

Young adults with DSD were transitioned to adult medicine at age 16-25 years, but it was unclear who can provide the optimal care for them, because there were hardly any adult physicians specialized on DSD.

All participating clinics indicated to establish a Swiss DSD cohort, and several clinics had their own research projects, including basic science, ethics and epidemiology.

Conclusion: We identified gaps in psychological care, in the collaboration with adult medicine and with associations of DSD individuals, and in epidemiological monitoring of DSD. Few clinics had already included specialized psychologists in their DSD team. The new Swiss DSD cohort will help to answer open questions on epidemiology of DSD in Switzerland.

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Clinical, Laboratory and Molecular Genetic Findings of Patients with 17ß-Hydroxysteroid Dehydrogenase 3 Deficiency

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Background: 17ß-Hydroxysteroid Dehydrogenase3 **(**17b-HSD3) deficiency is a rare autosomal recessive disorder, caused by a mutation of the *HSD17B3* gene. The phenotypic spectrum ranges from normal-appearing female external genitalia to microphallus with hypospadias and variable degrees of genital ambiguity. 17b-HSD3 deficiency phenotype is variable, leading to misdiagnosis especially with partial androgen insensitivity syndrome and 5alfa reductase deficiency.

Aim: We aimed to evaluate clinical and laboratory features of ten patients with *HSD17B3* mutations and phenotype/genotype correlation.

Patients and Methods: Data of 10 46,XY patients with *HSD17B3* mutations were reviewed retrospectively.

Results: Ten patients were identified from seven pedigrees. Range of age at presentation was 0.5-17.3 years old. Only one patient presented in early infancy. Presenting symptoms were inguinal hernia and masses in six patients and hirsutism, primary amenorrhea in three patients and hypospadias and cryptorchidism in one patient. All patients were from consanguineous families. Six of the nine patients had female appearance of external genitalia and three patients had mild cliteromegaly or a prominent clitoris and one patient had penoscrotal hypospadias and cryptorchidism at presentation. All patients except one were raised as female. Müllerian structures were absent in all patients. Five of seven mutations were reported previously (c.[139A>G];[704T>C], c.[182G>A];[182G>A], c.[277+4A>T];[277+4A>T], c.[277G>A];[277G>A], c.[607-1G>A];[607-1G>A]. Two mutations are first time reported in this study (c.[167C>T];[167C>T], and c.[639_640 insA];[639_640 insA].

The median testosterone/androstenedione ratio after a short hCG stimulation test was evaluated in five patients and ratio of four patients was <0.8. Bilateral gonadectomy were performed in all patients reared as female. The histopathology of the gonads was consistent with testis and spermatic cord and no malignancy was seen.

Conclusion: 17b-HSD3 deficiency presents with a wide spectrum of clinical findings. There seems to be no phenotype/genotype correlation. Molecular diagnosis guide families for differential genetic counseling.

P2-P348

Revisiting the Diagnosis: Next Generation Sequencing (NGS) Identifies Concurrence of PAIS in a Previously Reported Case of Klinefelter Syndrome (47,XXY) with Hypospadias

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Background: Klinefelter syndrome (KFS) is a sex chromosomal disorder characterised by hypogonadism, progressive testicular failure, gynaecomastia and learning difficulties. Genital anomalies are rarely observed in KFS. Androgen insensitivity has been previously postulated, but not proven to cause genital ambiguity in KFS. Androgen receptor (*AR)* gene defects are reported in AIS, but have not been reported in children with KFS with mild hypospadias. We describe a novel p.Phe795Tyr (c.2384T>A) mutation in the *AR* gene affecting two male siblings of which one had concurrent KFS.

Case report: Case 1: A term infant born to consanguineous parents of Asian origin presented with penoscrotal hypospadias, bifid scrotum and bilateral palpable testes at birth. Investigations showed normal electrolytes and androgen profile. Chromosome analysis revealed 46,XY karyotype. Molecular analysis of the *AR* gene was performed using a NGS 32-gene DSD panel plat-

form, and DNA sequencing revealed a novel hemizygous mutation p.Phe795Tyr (c.2384T>A) in the *AR* gene.

Case 2: The older sibling presented with genital ambiguity (mild hypospadias and micropenis) at birth. Chromosome analysis diagnosed KFS (47,XXY)which was considered to account for his hypospadias. He underwent surgical repair at 1 year of age. The gonadotropins were elevated. This case was previously reported as association of genital anomalies in KFS. The finding of *AR* gene mutation in his brother (Case-1) triggered molecular genetic analysis. The same hemizygous missense variant p.Phe795Tyr (c.2384T>A) in the *AR* gene was identified as in his brother, confirming partial androgen insensitivity syndrome (PAIS).

This mutation has not been previously described in the literature. The PAIS phenotypes of these two siblings suggest that normal *AR* is partially functional. Furthermore, X-inactivation studies conducted showed a random X inactivation pattern with no evidence of skewed X-inactivation in case-2. The X-inactivation status is confirmed only in lymphocytes, which may not be representative of other tissues. Given that the variant was identified in both the index Case-1 and his affected brother (Case-2), this increases the likelihood that the variant is the cause of the clinical features of undervirilisation seen in this family. Despite the use of dihydrotestosterone gel to enhance penile growth, there was limited clinical response. He further received adequate psychology input to support his emotional well-being.

Conclusion: This report emphasizes the importance of considering concurrent finding of PAIS in KFS with ambiguous genitalia. It also highlights the significance of NGS panel in revisiting the diagnosis of DSD.

P2-P349

A 46,XX Female with WT1 Mutation, Congenital Nephrotic Syndrome and a Complex Disorder of Sex Development

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Background: The Wilms tumor suppressor gene 1 (WT1) is essential for kidney and gonadal development.WT1 gene mutations are associated with two syndromes called Denys-Drash (DDS) and Frasier (FS) that clinically overlap and differ in the type of mutation and in the age at nephropathy onset.In 46,XY subjects WT1 mutations are associated with steroid-resistant nephrotic syndrome (NS), Wilms tumor, disorder of sex development (DSD) with dysgenetic gonads and gonadoblastoma risk.On the contrary, the impact of WT1 gene on the genital development of 46,XX subjects is not clear.

Case Report: We report the case of a girl with chronic kidney failure due to steroid-resistant congenital NS. Biopsy at onset evidenced mesangial proliferative glomerulonephritis with focal-segmental glomerular sclerosis. Due to end-stage renal disease, peritoneal dialysis was started in the first months of life. The child received kidney transplantation when she was 3, with acute rejection at the age of 5. Regular hemodialysis was started when she was 12.Chromosomal analysis revealed a normal 46,XX female karyotype.Mutational analysis of WT1 gene identified the heterozygous mutation c.1097>A, producing the amino acid change Arg366His. This mutation had been described in 46,XY patients with Denys-Drash syndrome.At the age of 14, the girl was referred to endocrinological observation for primary amenorrhea despite a complete pubertal development (Tanner stage 5).Weight was 44 kg (25th centile), height 161.4 cm (50-75th centile), BMI 16.9 kg/mq (10-25th centile).Bone age corresponded to chronological age.She showed androgenetic alopecia and voice deepening. Endocrine tests showed pubertal gonadotrophins(FSH 8.8mU/ml, LH 3.6mUI/ml),with estradiol 92.8pg/ml, testosterone 190.2ng/dl and anti-mullerian hormone 1.3ng/ml.Basal and post-ACTH adrenal androgens were normal.Pelvic ultrasound showed bilateral dysgenetic gonads in the inguinal canals, uterotubaric agenesis, vaginal atresia and urogenital sinus.Gonadectomy was then performed and histological examination showed hypotrophic ovaries with cystic follicles and interstitial fibrosis.

Discussion: WT1 knockout mice lack gonads in both sexes, suggesting a role of the gene in the formation of the genital ridge, an early stage of development in which the gonad is still undifferentiated.Nowadays, little is known about the role of WT1 in the development of the female reproductive system.Sporadic cases of 46,XX females are reported with a WT1 mutation and minor abnormalities such as streak ovaries or bicornuate uterus.To our knowledge, this is the first report on a 46,XX female presenting heterozygous WT1 mutation, congenital nephrotic syndrome, and a complex DSD associated with gonadal dysgenesis.

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Psychological Gender Features and Social Abilities and in Adolescent Girls – Influence of Obesity and Hyperandrogenism

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Background: Both, obesity and hyperandrogenism are the conditions that can influence many different health domains, also may affect the mental and social wellbeing components of subject's life.

Study Objective was to evaluate whether body weight status and clinical hyperandrogenism may influence social competencies and psychological gender features in adolescent girls.

Design & Participants: In 104 adolescent girls clinical evaluation and hormonal profile were done, psychological gender inventory (PGI) and social competencies questionnaire (SCQ) [assessing social abilities in three aspects: Intimacy (I), Social Exposure (SE), Assertiveness (AS)] were performed. According to BMI percentile and clinical features of hyperandrogenism (hirsutism, menstrual disturbances), subjects were divided into four subgroups: G1 – 24 non-obese girls, without hyperandrogenism (mean age 16.8±0.8yrs; mean gynecological age 45.0±9mo; BMI z-score 0.1±0.9); G2 – 18 obese girls, without hyperandrogenism (mean age 16.5±1.4yrs; mean gynecological age 58.5.0±22.0mo; BMI z-score 2.2±0.5), G3 – 30 non-obese hyperandrogenic girls (mean age 17.1±0.7yrs; mean gynecological age 50.0±8.0mo, BMI z-score 0.6±0.8) and G4 – 32 obese girls with hyperandrogenism (mean age 16.7±0.8yrs; mean gynecological age 47.0±16.5mo, BMI z-score 2.3±0.6).

Results: There were no significant differences in all parts of SCQ and PGI between the study and control groups. The feminine woman type dominated in all groups, in G3 and G4 masculine woman type appeared more often than in G1 and G2 (13.3% and 12.5% vs. 4.0% and 0.0%, respectively). In G4 positive relationship between BMI z-score and SCQ (r=0.4, p=0.03) was found. In G1 the relationship was opposite (r=-0.5, p=0.03). Hirsutism correlated negatively with SCQ (r=-0.5, p=0.02), I (r=-0.5, p=0.02) and AS (r=-0.5, p=0.02) only in G1; in other groups this relationship was insignificant. In G4 higher testosterone level was associated with lower SCQ (r=-0.5, p=0.008) and AS (r=-0.5, p=0.003). In G2 testosterone concentration correlated positively with SCQ (r=0.6, p=0.01), SE (r=0.5, p=0.02) and AS (r=0.6, p=0.02).

Conclusion: In adolescent girls body weight status and clinical features of androgen excess can be associated with some aspects of social competences and psychological gender features, facilitate or disturb social and psychological subject's functioning.

P2-P351

Two Unrelated Cases of Severe Insulin Resistance Due to Insulin Receptor Mutation Discovered During Adolescence

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Introduction : Severe insulin resistance due to insulin receptor mutation is usually diagnosed at the neonatal period (Donohue and Rabson-Medenhall syndromes), or later in a type A insulin resistance syndrome. We report here two cases of insulin receptor mutation whose presenting signs were less noticeable.

Observation : A 13-year-old girl was referred for short stature (Height -2.5 SDS) with SGA (birth length 44.5 cm, at gestational age 41 weeks). Clinical examination was normal, pubertal stage was A2P3 S3. The glycemic nadir was 3,7 mmol/l, and GH peak was 8 ng/mL during the insulin tolerance test. All the investigations were normal, and the short stature was attributed to idiopathic SGA. At the age of 16, she was seen for acanthosis nigricans and primary amenorrhea. Pubertal stage was A4P4S4, and Ferriman score was 4. Pelvic ultrasound showed ovaries of 10 and 8 cm^2. Testosterone level was 1.43 ng/mL. During OGTT, she had very high levels of fasting and insulin peak: 708 pmol/l and 52087 pmol/l, respectively. The family history found a hyper androgenic clinic in the mother and acanthosis nigricans in the 13-year-old brother (height -1 SDS). A compound heterozygote mutation in the insulin gene was found in the index case and in the brother : exon 11 and exon 14.

A 16-year-old girl (Height 156 cm, Weight 50 kg) consulted for hirsutism and secondary amenorrhea. Ferriman-Gallwey score was 7. Family history found a 13-years sister with acanthosis nigricans and hirsutism, two female cousins with PCOS, and an aunt with acanthosis nigricans. Fasting insulinemia in the girl was 1800 pmol/l. A mutation in the insulin receptor has been identified in the index case: exon 17 c.3164c>T, and molecular studies in the family are underway.

Conclusion : In short stature with SGA as well as in familial cases of PCOS, we suggest to routinely measure fasting insulinemia, as it may lead to the diagnosis of pathological insulin resistance due to insulin receptor mutation.

P2-P352

A Systematic Review of Reported Outcomes for Hypospadias

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Introduction: The outcome of hypospadias is considered to be primarily dependent on the underlying aetiology, its surgical management and the duration of follow-up. However, currently, there is little consensus on what set of parameters are essential and clinically feasible for assessment of outcome.

Aim: To facilitate the development of a core outcome set for hypospadias by assessment of the range of outcomes reported in boys undergoing surgery.

Methods: Using the terms "outcome" and "hypospadias", pubmed was searched to identify randomised controlled trials, case controlled trials, case series, and prospective cohorts reporting on short and long term outcomes in males with hypospadias published in the English language from 2008 to 2017. All publications reporting on outcomes in males after primary surgery were included as were mixed series with cases after primary and redo surgery. All reported outcomes were systematically extracted by a single person and a subset verified by a second person.

Results: Of 878 publications, 274 met the eligibility criteria. Although 70 different outcomes were reported, only 18 (26%) were

reported in more than 10% of the publications. On categorization into four age groups, based on the age of the patient at the time of reported outcome, the majority of studies examined short-term outcome (1-5 years n=133 (49%), 6-10 years n=65 (24%), 11-16 years n=33 (12%), and >16 years n=36 (13%), unclear n=7 (2%)). Overall, urethrocutaneous fistula was most commonly reported (n=236 publications (85%)), and this was consistent across all ages. Among boys aged 1-5 and 6-10 years, meatal stenosis, dehiscence, and urethral strictures were next most frequent (n=94 (71%), n=87 (65%), n=56 (42%) and n=38 (59%), n=35 (54%), n=36 (55%) respectively). In the older age categories, there was an increasing frequency of other reported outcomes including cosmesis, meatal shape/location and genital skin changes (11-16 years, n=16 (49%), n=19 (58%), n=7 (21%), and >16 years, n=20 (56%), n=21 (58%), n=12 (33%)). Outcomes reflecting sexual health, erection, and relationship status including paternity were reported in the >16 year olds (n=22 (61%), n=21 (58%), n=12 (33%)). Redo surgery was reported similarly across age groups (n=76 (27.2%)).

Discussion: The current study identifies the range of parameters that are measured to assess outcome and the extent of consensus. This review can be used to inform the development of a core outcome set that can be applied as a standardized assessment tool in a routine clinical setting in an age dependent manner.

P2-P353

Young Transgender People's Attitudes to Fertility Preservation and Practice

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Background: GnRH analogue and subsequent oestradiol treatments are indicated to alleviate gender dysphoriain adolescent male to female young people (MtF; transgirls). Side effects include impairments in gonadal histology that may cause infertility or biological sterility. Current guidelines encourage professionals to address potential infertility risk and fertility preservation options with transgender youth and their families before starting these treatments.

Purpose: The aim of this study was to examine fertility preservation uptake and rate of sperm banking success among transgirls seen in our paediatric endocrine clinic.

Methods: This is a retrospective study of young people with DSM IV codes for gender dysphoria attending the Gender Identity Development Service (GIDS) endocrine clinic. Between 2015 and 2017, 179 transgirls were referred to the GIDS endocrine clinic. Fertility counselling was documented. YP could also choose to opt for professional fertility clinic counselling.

Results: 60 MtF (34%) requested referral to our fertility laboratory. Mean age at referral was 16.4 (±1.9 years). 13 transgirls were younger than 15 years (13.4 ±0.8) and 47 were 15 years and older (17.2 ±0.9).

Conclusions: Our cohort of transgirls had a good rate of sperm banking success, regardless of their age. Interestingly lack of clarity regarding the future use of sperm samples among young participants decreased as the group got older.

If fertility preservation is handled sensitively in young transgirls, a high success rate can be obtained and should therefore be considered early in the transition process. Developmentally appropriate fertility counselling is essential in in this population. Guidelines and specific pathways are needed.

Table 1. (for Abstract no P2-P353)

	<15 years n:13		≥15 years n:47	
Hormonal treatment status	No treatment started	9	No treatment started	31
	Hormone Blocker	-	Hormone Blocker	10
	Cross sex hormones	-	Cross sex hormones	1
	No data	4	No data	6
Fertility preservation counselling	11 (85%)		36 (75%)	
Fertility preservation uptake	10 (77%)		28 (58%)	
Age at sperm banking	13.4 years (±0.8 SD)		17.2 years (±0.9 SD)	
Mean number of visits (SD)	1.9 (±1.1 SD)		1.4 (±0.6 SD)	
Future use of sample	Unsure 10 (69%)		Unsure 18 (38%)	
	Surrogacy/IVF/Partner 1 (8%)		Surrogacy/IVF/Partner 15 (31%)	
	N/A 2		N/A 15(31%)	
Sperm banking in referred	Successful	7 (54%)	Successful	26 (54%)
	Unsuccessful	2 (15%)	Unsuccessful	7 (15%)
	Declined	2 (15%)	Declined	8 (17%)
	Waiting list	-	Waiting list	4 (8%)

P2-P354

Etiology of Disorders of Sex Development in Kenyan Children and Adolescents

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Objective: The purpose of this study was to describe baseline data on etiological diagnosis of Disorders of Sex Development (DSD) in Kenyan children and adolescents.

Methods: This retrospective study included 71 patients diagnosed with DSD who presented at ages 0-19 years from January 2008 to December 2015 at the Kenyatta National (KNH) and Gertrude's Children's (GCH) Hospitals.

Results: Thirty-nine (54.9%) children had karyotype testing done. The median age (IQR) of children with reported karyotypes and those without was 3.3 years (1.3-8.9) and 8.3 years (3.6-12.1), respectively (p = 0.021). Based on the new DSD nomenclature 19 (48.7%) of karyotyped children had 46,XY DSD and 18 (46.2%) had 46,XX DSD. There were 2 (5.1%) children with sex chromosome DSD. Among the 71 patients, 10 (14.1%) patients had a diagnosis of ovotesticular DSD based on histology results and 8 (11.3%) were diagnosed with Congenital Adrenal Hyperplasia (CAH) based on the presence of müllerian structures and elevated 17-hydroxyprogesterone levels. One of these patients had salt-wasting CAH. A diagnosis of 5α-reductase deficiency was made in 2 patients based on normal testosterone (T) levels, low or normal dihydrotestosterone (DHT) levels and a high T/DHT ratio after human Chorionic Gonadotropin (hCG) stimulation test. One patient was diagnosed with Partial Androgen Insensitivity Syndrome based on a 46,XY karyotype, absence of műllerian structures and normal T and DHT response to hCG stimulation. Twenty-four patients underwent genitoplasty/ urethroplasty while 9 patients underwent orchidopexy. Two patients with ovotesticular DSD who were assigned male gender underwent oophorectomy while one with ovotesticular DSD assigned a female gender underwent bilateral gonadectomy. No patient was found to have a gonadal tumour.

Conclusion: The commonest cause of DSD was ovotesticular DSD in contrast to western studies which found CAH to be more common. Investigation of DSD cases is expensive and needs to be supported. We would have liked to do molecular genetic analysis outside the country but local regulations made it impossible. A network for detailed diagnostics in resource limited countries would be highly desirable

P2-P355

Adiponectin as a Marker of Peripheral Insulin Resistance in Adolescents with Polycystic Ovarian Syndrome (PCOS) and as a Tool to Suspect Insulin Receptor Defects

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Background: Decreased serum adiponectin levels are associated with obesity and peripheral insulin resistance (IR). PCOS is characterized by hyperandrogenism and chronic anovulation and frequently is associated to IR. Some defects of Insulin Receptor have been proposed as mechanisms to explain ovarian hyperandrogenism in PCOS.

Objectives: To explore adiponectin levels in adolescents with PCOS and to evaluate if adiponectin would identify potential patients with hyperandrogenism associated to defects in the insulin receptor or its intracellular signal pathway.

Patients and Methods: Prospective cross-sectional study. Twenty PCOS adolescents (16.4±2 years) diagnosed according to AES criteria and 10 healthy normal cycling adolescents (16.0±1.5 years) were studied. Fasting glucose, insulin, adiponectin, androgens (total and free testosterone, androstenedione), were measured. HOMA-IR > 2.5 was used a surrogate of IR.

Results: 11/20 (55%) PCOS patients showed IR (4 with normal BMI and 7 with high BMI). There were no differences between patients with or without IR in hirsutism score, menstrual cycle abnormalities or in the grade of hyperandrogenemia. Adiponectin levels in PCOS patients with increased BMI and insulin resistance were lower than in both PCOS and controls with normal BMI (ANOVA on way $p<0.05$).

Significant inverse correlations between adiponectin, BMI ($r= - 0.79$, $p<0.001$) and HOMA-IR ($r= - 0.53$, $p=0.02$) were observed in patients with PCOS. Two patients with high adiponectin levels were excluded from the regression model as bivariant outliers. Both had unexpectedly high levels of adiponectin in spite of having the highest values of HOMA-IR. In one of them, a novel heterozygous missense variant in the tyrosine kinase domain of INSR was identified (NM_000208.3 (INSR): c.3449T>C (p.Leu1150Pro)). This variant is classified as likely pathogenic applying ACMG guidelines. Molecular study of insulin receptor gene from the other patient is currently under process.

Conclusions: Adiponectin levels are negatively associated with BMI and the severity of peripheral insulin resistance, while serum androgens do not seem to be related to them. Unexpectedly high levels of Adiponectin in patients with PCOS who exhibit insulin resistance should lead towards molecular studies to rule out insulin receptor defects.

P2-P356

Diagnostic Experiences and Concerns in Adolescents with Polycystic Ovary Syndrome

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Many women with polycystic ovary syndrome (PCOS) have a delayed diagnosis after seeing multiple health care providers for their symptoms impacting on their physical and emotional well-being (1). In adolescent girls, PCOS diagnosis is even more controversial and challenging than in adult women yet there have been no studies in adolescents evaluating diagnostic experience, their knowledge and concerns. We aimed to evaluate diagnostic experience and concerns regarding PCOS in an adolescent population.

Adolescents aged 12-19 years with a confirmed PCOS diagnosis recruited from specialist clinics (Women's and Children's Hospital (Adelaide) completed a validated questionnaire (1) and a community sample of adolescents with PCOS recruited via Polycystic Ovary Syndrome Association of Australia (POSAA) and Health Consumer Alliance of South Australia completed the same questionnaire.

Twenty four girls (mean (SD) age 17 (1.7) years, menarche 12.1 (1.3) years, 15 Caucasians, 8 Asians and 1 Aboriginal) completed the questionnaire. Two had a mother diagnosed with PCOS.

Whilst the majority of the adolescents were diagnosed in less than 1 year from their first doctor's visit for PCOS symptoms (16 [66.7%] 9:<6 months and 7:6- 12 months), a third of the adolescents were diagnosed after 1 year (4 after 1 year, 4 after 2 years). 17 adolescents saw ≤2 health professionals before diagnosis was made and 7 saw >2.

The majority of the adolescents were satisfied with the diagnosis experience (5: very satisfied and 14 satisfied) and satisfied with PCOS information received at diagnosis (12 very satisfied and 8 satisfied). The majority of the adolescents were satisfied with information provided at diagnosis in relation to lifestyle, medical therapy and long term complications but not in relation to emotional support and counselling.

The most common key features of PCOS identified by participants as the most important to them were irregular menstrual cycles (14 [58.3%]), excess hair (13 [54.1%]) weight gain (10 [41.7%]), and difficulties losing weight (8 [33.3%]).

The preferred method of support by adolescents was educational materials (87.5%) followed by patient forums (55.0%) and a consumer website (42.1%). Twenty agreed that education was more important than a change in the condition's name.

This is the first study evaluating diagnosis experiences in adolescents with PCOS and showed that in contrast to adult women the majority of adolescents are satisfied with diagnosis experience and information received. Delayed PCOS diagnosis also occurs during adolescence.

Reference

1. Gibson-Helm M et al. J Clin Endocrinol Metab 2017.

P2-P357

Impact of Hydrocortisone Treatment on Clitoral Size During First Year of Life in Girls with Congenital Adrenal Hyperplasia (CAH)

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Objective: Early genital surgery has been the routine practice in virilized girls with severe forms of CAH for many years. During the last decade studies have shown genital surgery to have unsatisfactory effects on genital sensation and sexuality, and the current practice with early surgery has been questioned by patients and support groups as well as by clinicians and researchers. As surgery has been postponed in only few girls, published data on the effect of hydrocortisone treatment on clitoral size are sparse. We aimed to investigate the effect of hydrocortisone treatment on clitoral size during the first year of life.

Methods: Six girls with CAH due to 21-hydroxylase deficiency were investigated at birth before start of treatment with hydrocortisone, and when vaginoscopy was performed at a mean age of 0.7 years (range 0.4 – 1.0). Clitoral length and width were measured and the clitoral index was calculated from the product of the length and the width, and expressed as square millimeters. Anthropometric measurements were taken and body surface area (BSA) was calculated. To evaluate clitoral size in relation to general growth clitoral index per square meter BSA was calculated. Hydrocortisone and fludrocortisone dosages at time of vaginoscopy were recorded.

Results: The changes in clitoral length (26,3 mm (range 19,0 – 32,0) vs. 25,7 mm (range 12.0 – 35.0), p=0.674), width (10,3 mm (range 8.0 – 15.0) vs. 7,5 mm (range 5.0 – 10.0), p=0.066) and clitoral index (273,3 mm^2 (range 152 - 384) vs. 201,7 mm^2 (range 60 – 320), P=0,116) were not significant.

There was a significant reduction in clitoral index per m^2 BSA (1264 mm^2/m^2 (range 709 – 1909) vs. 534 mm^2/m^2 (range 140 – 967), p< 0.05). The mean Hydrocortisone dose was 11.2 mg/m^2 BSA/day, (range 9.3 – 12.6), and the mean Fludrocortisone dose was 199,0 $microgram/m^2$ BSA/day (range 58 – 453).

Conclusion: In this small observational study Hydrocortisone treatment with regular recommended dosages was sufficient to prevent clitoral growth during the first year of life. Clitoral index showed a significant decrease per square meter body surface area, indicating that clitoromegaly becomes less marked as the girls grow.

P2-P358

Persistent Mullerian duct syndrome: Rare But Important Aetiology of an Inguinal Hernia and Cryptorchidism in Boys

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Background: Anti-Mullerian hormone (AMH), secreted by immature Sertoli cells, provokes the regression of male fetal Mullerian ducts. Loss of function mutations in genes coding AMH (*AMH*) or its receptor (*AMHRII*) lead to the persistent Mullerian duct syndrome (PMDS) which is characterized by the presence of uterus, fallopian tubes, cervix and vagina in otherwise normally virilized 46,XY males. Typical clinical features along with plasma AMH levels and genotyping establish the diagnosis of PMDS. However, surgical management and long-term follow up of these patients is challenging.

Case Reports: We present 4 cases with PMDS presented with a cryptorchidism and inguinal hernia (Table). Inguinal exploration for cryptorchidism or inguinal hernia by laparoscopy revealed incidental findings of Mullerian remnants. Biopsies taken from gonads in each patient revealed testicular tissue with a variable degree of immaturity. The biopsy of Mullerian remnants did not reveal any malignancy. All patients were genotypically male. Clinical and genetic characterization of the patients is presented in Table. We opted a single stage laparotomy to split the fundus of the uterus in the midline to release testes and to avoid damaging vas deferens or the deferential artery during orchidopexy. The postoperative course was uneventful.

Conclusion: PMDS serves as a remarkable management dilemma due to 2 main complications namely infertility and cancer. The surgeon should bear in mind that a cryptorchidism and inguinal hernia in presence of Mullerian duct structures in male phenotypes should suggest PMDS. The management of PMDS cases is far more complicated than the ones with isolated cryptorchidism and/or an inguinal hernia. Long-term reproductive and endocrinological surveillance is warranted.

P2-P359

Clinical, Hormonal and Metabolic Profile in Adolescent Girls Treated with Gonadotropin Releasing Hormone Agonist for Idiopathic Central Precocious Puberty

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Background: Gonadotropin-releasing hormone analog (GnRHa) is the gold standard treatment for central precocious puberty (CPP). In recent years, increased prevalence of polycystic ovary syndrome (PCOS) has been reported in girls treated with GnRHa for CPP. Attributes of PCOS overlap normal pubertal changes, making the diagnosis of PCOS during adolescence controversial.

Table 1. Clinical and genetic characterization of the patients with PMDS (for Abstract no P2-P358)

Patient	Age of presentation	Signs/symptoms at presentation	Other anomalies	FSH (mIU/mL)	AMH concentration	Gene/mutation	Reference
I	26 days	Bilateral inguinal hernia, bilateral cryptorchidism	-	2.47	<0.1 ng/ml (45-266)	*AMH* c.G301A, p.(Gly101Arg) (homozygous)	*Three families from West Turkey, Pakistan and India
2	8 yr 9 mos	Unilateral inguinal hernia, bilateral cryptorchidism	-	0.8	138.5 ng/ml (33-60.2)	*AMHRII c.1510C>T, p.(Arg504Cys) (homozygous)*	*Two PMDS patients from Germany and Italy
3	1 yr 6 mos	Bilateral inguinal hernia, bilateral cryptorchidism	-	0.46	0.02 ng/ ml (45-266)	*AMH c.1577C>T, p.(Cys526Phe) (homozygous)*	novel
4	3 yrs 8 mos	Bilateral inguinal hernia, bilateral cryptorchidism	-	2.88	0,02 ng/ml (45-266)	*AMH c.1673G>A, p.(Gly558Asp) (homozygous)*	novel

*Picard JY, et al. Sex Dev 2017;11:109–125.

Aim: To assess the metabolic profile, the prevalence of PCOS and describe its phenotypes as function of different combination of diagnostic criteria in young girls treated with GnRHa for CPP.

Methods: We evaluated 22 girls treated with GnRHa for CPP, who were at least 2 years after menarche and had attained near final height. We assessed auxological parameters, lipid profile, markers of insulin resistance, androgen levels, and the prevalence of PCOS and PCOS phenotypes.

Results: GnRHa-treated patients attained predicted final height. Mean standard deviation score (SDS) for height was -0.39±0.7 *versus* target height (SDS). Mean gynecological age at evaluation was 3.06 ± 1 years. Among PCOS criteria, hyperandrogenemia was found in 38% of patients, 33% had clinical hyperandrogenism, 24% had menstrual disturbances (oligomenorrhea, secondary amenorrhea), and 28% percent had polycystic ovary morphology on ultrasound examination. A total of 19% of cases had PCOS according to *Pediatric Endocrine Society 2015* consensus on PCOS diagnosis during adolescence; according to *Rotterdam criteria*. 33% of girls had PCOS. No predictive factors of PCOS were found at the time of ICPP diagnosis in our series. Among clinical, metabolic and hormonal parameters, the differences between non-PCOS and PCOS girls were at the limit of statistical significance. Only LH values were statistically significant between the 2 groups

Conclusions: Patients with CCP treated with GnRHa need to be followed-up for PCOS in adolescence in order to establish whether the condition persists in young adulthood, due to its implications on fertility and metabolic complications.

P2-P360

Spontaneous Pregnancies in Female Survivors of Childhood Hematological Malignancies Post Allogeneic Haemopoietic Stem Cell Transplantation

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Background: With improved treatment and survival of childhood hematological malignancies, the issue of fertility in survivors has become an important domain of holistic care. Haemopoietic stem cell transplant (HSCT) survivors were reported to have reduced fertility as compared to siblings, with 4/170 adult female allogeneic HSCT survivors achieving successful pregnancy.[1] Of 532 female survivors, median age of 17.8 years at HSCT, who had TBI conditioning, 13 pregnancies were reported.[2] More recent study reported 10/92 female survivors of childhood/adolescent HSCT achieved pregnancy, but 38% had non-malignant diagnoses.[3] The data on spontaneous pregnancy in female survivors underwent HSCT under 18 years for malignancies is still lacking.

Aim: To describe the proportion and characteristics of female HSCT survivors who had spontaneous pregnancy with live birth despite a period of documented post-treatment primary or premature ovarian failure, with stratification into TBI and non-TBI groups.

Methods: Retrospective review of all the female survivors of childhood hematological malignancies who had allogeneic HSCT at the Royal Children Hospital between 1985 and 2011. Girls under 18 years and those who described themselves as never sexually active were excluded from analysis.

Results: Seven of forty-four female survivors reported spontaneous pregnancy resulting in live birth. Twenty-five women had received TBI and high dose cyclophosphamide (either as conditioning prior to HSCT or as part of previous chemotherapy), with three reporting pregnancy resulting in live birth. Nineteen of forty-four received busulfan and high dose cyclophosphamide, with four reporting live birth. Median age at HSCT in those who had a pregnancy was 15.5 years for TBI women and 11.5 years for the non-TBI women. Median age at pregnancy was 28.5 years and 26.5 years in TBI and non-TBI groups respectively. Mean time from HSCT to pregnancy was 12 years and 15 years in TBI and non-TBI groups respectively. At conception, 3 women were using oral contraception, 2 were on hormone replacement therapy and 2 were not taking any hormonal supplements when pregnancy was confirmed.

Conclusion: We found a higher proportion of female HSCT survivors having spontaneous pregnancy than reported in previous predominant adult cohorts, and the overall proportion of pregnancy was higher in the non-TBI group. However, findings are limited by small sample size.

References

1 Carter A et al. Bone Marrow Transplant. 2006 Jun;37(11):1023-9.
2 Sanders JE et al. Blood. 1996 Apr 1;87(7):3045-52.
3 Vatanen A et al. Eur J Endocrinol. 2013 Dec 27;170(2):211-8.

P2-P361

Towards an Integrated Approach to Diagnosis of 46,XY Disorder of Sex Development

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Background and objective: Given phenotype variability as well as limited utility of conventional endocrine investigations in reaching the diagnosis in a 46,XY patient suspected of a disorder of sex development (DSD), there is an increasingly stronger argument for considering targeted genetic sequencing at an earlier stage of the evaluation process. This study focused on identifying the relationship between clinical examination, endocrine and radiological assessment, as well as the result of targeted 46,XY DSD gene panel.

Methods: The study group consisted of 35 patients, 21 (60%) were raised as boys and 14 (40%) were raised as girls. External ap-

pearance of the genitalia was described by the external masculinization score. The endocrine investigations assessing hypothalamic-pituitary-gonadal axis including AMH and Inhibine b (Gen II ELISA assay, Beckman Coulter, Diagnostic Systems Laboratories, Inc., USA) were performed. The assessment of internal genitalia (presence or absence of uterus, localization of undescended gonads) was undertaken by transabdominal ultrasound examination. Targeted gene panel sequencing was performed (TruSight One gene panel, Illumina, Inc., San Diego, CA USA) on the MiSeq (Illumina) and 54 known diagnostic genes implicated in 46,XY DSD were selected for evaluation (Saphetor, Lausanne, Switzerland).

Results: Findings from an integrated approach established a definitive diagnosis in 12 patients (34%), three boys (out of 21, 14%) and nine girls (out of 14, 64%). In all those cases raised as girls and suspected of a disorder of androgen action or disorder of androgen synthesis (n, 9), the agreement with the results of genetic tests was complete. However, in those raised as boys (n, 21), the genetic analysis led to identification of at least one variant of uncertain significance in more than half of them (n, 12; 57%) mainly due to incomplete consistency between the genetic and conventional tests. Due to targeted massive parallel sequencing oligogenic variants were identified in 29% (10 out of 35) of patients.

Conclusions: Due to discrepancy between the genetic tests and the detailed phenotypic assessment, especially in patients raised as boys, as well as the presence of multiple oligogenic variants, the targeted genetic sequencing should be performed alongside other investigations.

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Mini-Puberty in Boys with Inguinal Cryptorchidism

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Background: The period of 0 – 6 month of life is a short window for postnatal testicular maturation and the diagnostic of reproductive disorders.

Objective: To evaluate the functional condition of the hypothalamo-pitutary-gonadal axis in 1–3 months boys with cryptorchidism.

Method: 51 boys ages 1–3 months with cryptorchidism were examined: group 1 – 30 boys with unilateral inguinal retention testes and group 2 – 21 boys with bilateral inguinal testes. Control group consist of 40 healthy boys ages 2–3 month. Methods: orchiometriya, ultrasound and hormonal tests – gonadotropins, testosterone and inhibin B serum levels by immunoenzyme assays;

Results: In group 1 scrotal testicular 2.3±0.46 cm^3 was like as control group (P=0.8). Hormonal tests results showed the increase of the LH serum level in 24% and the increase of FSH in 40%. The testosterone – 4.0 [3.0; 5.4] nmol/l and inhibin B – 380 (344; 422) pg/ml remained normal. In group 2 inguinal testes were found by ultrasound. Hormonal tests revealed different results: a) normal LH, FSH, testosterone and inhibin B level in 11 (52%) patients; b) increase the LH – 7.8 [6.0; 11.1] IU/l and FSH 15.9 [8.8; 19] IU/l (p=0,0007) level, normal testosterone – 5.0 (1.3; 5.4) nmol/l and decrease inhibin B level 96 [48; 97] IU/l (P=0.023) in 6 (28,6%) boys; c) low LH - 0,08[0,05; 0,12], FSH serum level, low testosterone and inhibin B – 39 [28; 43] (p=0.003) in 4 (19,4%) boys.

Conclusion: subclinical testicular disorders were revealed in 40% 1 – 3 month patients with unilateral inguinal cryptorchidism and 28,6% with bilateral inguinal cryptorchidism; the hypogonadotropic hypogonadism was diagnosed – in 19,4% boys with bilateral inguinal cryptorchidism.

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The Human Genital Tubercle Is Steroidogenic Organ at Earlypregnancy

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It is generally accepted that androgens produced by fetal Leydig cells (FLC) control proper masculinization of the male external genitalia. Here, we hypothesized that the human genital tubercle (GT) has potential to synthesize androgens independently of FLC at early pregnancy. We observed that human GT of both genders have capacity to synthesize steroids of the Δ4, Δ5 and alternative pathway of DHT synthesis including the androgen itself. The presence of steroids in the GT was associated with the expression of corresponding steroidogenic enzymes. Levels of steroids and the expression of steroidogenic enzymes were similar in the GT from male and female fetuses. In contrast to the GT, the human fetal testis synthesized DHT from testosterone but not via the alternative pathway. Our findings strongly suggest that the human GT at early pregnancy can synthesize DHT via the alternative pathway, which may play an important role in organogenesis of the urethra.

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Transgender Medicine Is a Significant Part of Paediatric Endocrinology

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Background: Paediatric transgender individuals are reported, as adults, to be disproportionately affected by barriers to care, mental health problems, suicide, violence, discrimination, poverty, and HIV compared to the general population possibly due to stigma and discrimination (1). Knowing the denominator of people at risk is necessary for assessing the incidence of diseases, setting medical priorities and goals, and advocating for care programs (1).

Objective: The purpose of this survey is to underline the importance of transgender medicine as a part of paediatric endocrinology.

Materials and Methods: We studied a cohort of 35 paediatric transgender individuals since the opening of our centre in 2014 until 2018.

Results: A total of 35 trans-children and trans-adolescents from 6.9 up to 19 years of age were enrolled in the survey, all recruited at our centre by referral from sexologists, paediatricians and self-referral (Figure 1).

34% of the paediatric transgender patients aged 19.8 ± 2.9 years (SD) were male-to-female (MtF) and 66% female-to-male (FtM) gender dysphoric. 46% of all patients were started on cross-sex hormonal treatment (CHT) within one to three years after initial presentation, 8% in the MtF group and 65% in the FtM group, respectively. Patients not yet started on CHT are intended to do so after indications are fulfilled according to treatment guidelines (2). Hormonal treatment in the MtF group consisted of estradiol and cyproterone acetate (CPA) and in the FtM group of testosterone undecanoate and Leuprorelin (3). In one patient gender-confirming surgery was performed at the age of 20.9 years.

Discussion: The total number of transgender patients in our center equals to 517, 481 adult individuals older than 21 years and 35 patients up to 21 years of age. When relating these numbers to a recent epidemiologic publication from San Francisco (4), we detected less than roughly ¼ of these patients in the city of Hamburg. The difference can partly be explained by additional centers in our metropolitan region.

We started cross-sex hormonal treatment as early as possible according to treatment guidelines and national legislation.

Conclusion Diagnostics, treatment and professional attendance of paediatric patients with gender dysphoria should be in the hands of an experienced team consisting of paediatric endocrinologists, psychologists, psychiatrists, gynaecologists, urologists and paediatric surgeons. Transgender individuals should undergo the transition from adolescence to adulthood best when paediatric endocrinologists are having consultations together with adult endocrinologists.

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Prospective Investigation of the the Influence of Triptorelin Treatment on Body Weight and Body Mass Index of Girls Who Were Diagnosed with Idiopathic Precocious Puberty or Early Puberty

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Background: Gonadotropin-releasing hormone agonists (GnRHa) have been widely used to treat patients with central precocious puberty (CPP). Several studies have investigated changes in body composition in patients with CPP following GnRHa treatment. But the results are inconsistent. This study aimed to investigate the influence of GnRHa treatment on the weight and body mass index (BMI) of girls who were diagnosed with idiopathic CPP or early puberty (EP).

Methods : Patients who were younger than 8 years of age at diagnosis were classified as CPP and patients aged between 8 and 9 years at diagnosis were classified as EP. Of 89 patients 22 were diagnosed with CPP and 67 were diagnosed with EP. The patients were treated with triptorelin for 1 year. Changes in weight and body mass index were monitored prospectively. The patients were grouped according to pretreatment weight status into normal weight, overweight, and obesity.

Results: Significant changes were observed with respect to weight standard deviation score (SDS) and BMI SDS after 6 months and 1 year of treatment, respectively. Depending on the degree of obesity, normal weight group showed significant increments of BMI SDS.

Conclusion : Weight SDS and BMI SDS increased in triptorelin acetate treated patients significantly as a whole group. BMI SDS increased significantly in the normal weight group after 6 months and 1 year of triptorelin treatment.

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Genetic Etiologies and Gender Outcomes of Patients with Disorders of Sex Development Presenting with Asymmetric Gonads

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Purpose: Patients with mixed gonadal dysgenesis (MGD) and ovotesticular disorders of sex development (DSD) usually present with asymmetric gonads. Differential diagnosis of these conditions is based on karyotype and pathological findings of gonads. However, it is difficult to determine sex of rearing and to predict long-term outcomes. This study investigated the clinical features, karyotype, sex of rearing, and pubertal outcomes of patients with MGD and ovotesticular DSD.

Methods: This study included 17 patients with DSD who presented with asymmetric gonads. Presenting features, karyotype, sex of rearing, and pubertal outcomes were reviewed retrospectively.

Results: All 17 patients presented with asymmetric gonads in the neonatal period. They manifested labioscrotal deformity (58.8%), hypospadias (52.9%), clitoromegaly (23.5%), and micropenis (11.8%). Eight patients with a dysgenetic gonad and a testis were diagnosed with MGD; karyotype was 45,X/46,XY in 7 (87.5%) and 45,X/47,XYY in one patient (12.5%). Nine patients with a coexistence of testicular and ovarian tissues were diagnosed with ovotesticular DSD; karyotype was 46,XX in 6 (66.7%), 45,X/46,XY in 2 (22.2%) patients, and 46,XY in one patient (11.1%). Mullerian duct remnants were found in 15 of 17 patients (88.2%). Fifteen patients underwent unilateral gonadectomy; 11 of them raised as males and 4 patients were reared as females. The remaining 2 patients underwent bilateral gonadectomy and raised as females. Six of 8 patients with MGD (75%) were raised as males, while 5 of 9 patients with ovotesticular DSD (55.6%) were assigned as males. Two patients with MGD and two with ovotesticular DSD reached pubertal age. Among them, one phenotypic male with MGD and two with ovotesticular DSD showed spontaneous puberty. The

remaining one female with MGD showed hypergonadotropic hypogonadism and have been treated with estrogen replacement therapy. One male-assigned patient with ovotesticular DSD was confused about sexual identity at age 20 years and changed gender as a female, despite her karyotype of 46,XX.

Conclusions: DSD with asymmetric gonads could manifest wide phenotype of external genitalia and karyotypes. Pathological findings of gonads are necessary for differential diagnosis of MGD and ovotesticular DSD. Further studies are needed to establish appropriate treatment strategies and gender outcomes.

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A Rare Form of Ovotesticular DSD: Diagnostic and Management Challenges

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We report mosaic triploidy 69XXY/46XX in ovotesticular DSD which poses significant diagnostic and management questions.

CASE: A baby born to non-consanguineous parents after a normal pregnancy, presented with atypical genitalia including significant clitoromegaly, a urethral opening in the anterior perineum and a normal vaginal opening. Bilateral masses were noted in the labio-scrotal folds. Pelvic ultrasound identified a normal uterus however the gonads could not be characterised as ovaries or testes. The blood karyotype was 46XX. Androgens and urine steroid profile were normal. Inhibin B and anti-Mullerian hormone results, at 149ng/L and 280.2pmol/L respectively, were abnormal for a child with a 46XX karyotype. These results suggested 46XX ovotesticular DSD.

A female sex of rearing was decided in conjunction with parents and further investigations undertaken.

A 30-gene DSD panel identified a heterozygous sequence variant c.389C>T in the *NR5A1* gene. Heterozygous variants in the *NR5A1* gene have recently been described in association with 46, XX ovotesticular DSD but as this variant was subsequently identified in her father its relevance was unclear.

The role of gonadal biopsy was discussed and as the child had inguinal herniae, an examination under anaesthetic was undertaken. The left ovary appeared normal and was not biopsied. Normal Mullerian structures were confirmed and no Wolffian structures were present. The right gonad however appeared bilobar and abnormal, and biopsy demonstrated clearly demarcated ovarian and testicular histology. Cytogenetic testing showed mosaicism for a triploid 69XXYand 46XX cells within the right gonad.

The presence of the Y chromosome in the abnormal gonad was thought to be sufficient explanation for virilisation, rather than the *NR5A1* variant. Two possible mechanisms were postulated for this apparently localised triploidy: either the foetus was initially triploid with subsequent trisomic rescue in some cells, or a chimera resulting from two sperm fertilising one ovum.

Optimal management of the gonads remains a significant question. Her atypical right gonad is likely to cause virilisation and may pose a risk of malignancy in the future. These factors and poor fertility potential, support its removal, but the management of the left ovary is controversial. It appears normal with potential for fertility, but has an unknown risk of malignancy. A biopsy carries risk of injury compromising future fertility and could yield only localised information. The decision currently is to watch and undertake surveillance of the left ovary, however the optimal surveillance method and long term management remains a concern.

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A Case of Gonadal Dysgenesis Due to a Novel Homozygous Mutation in NR5A2 Gene

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Background: Steroidogenic factor (SF1, NR5A2) regulates multiple genes known to be involved in gonadal development, adrenal development, steroidogenesis, and gonadotroph development. Heterozygous mutations in the NR5A1 gene have been described in association with mild to severe gonadal dysgenesis with or without adrenal failure. Homozygous mutations are rare and have also been described in association with gonadal dysgenesis with or without adrenal failure.

Case vignette: We report a 18-year-old patient of normal female phenotype with absent breast development and primary amenorrhea. Stage of puberty was Tanner B1, PH 3. There was no axillary hair. Serum concentrations were low for estradiol, low for testosterone, low for AMH, and low for Inhibin B. These findings suggested gonadal dysgenesis. Unexpectedly LH and FSH were within the normal range. In addition, endocrine evaluation showed low adrenal androgens, whereas ACTH testing revealed normal cortisol response. Karyotyping revealed 46, XY. Pelvic ultrasound showed no mullerian structures and no gonads. Genetic examination was performed and revealed a novel homozygous mutation in the NR5A1 gene (c.1048C>T; p.Arg350Trp). This mutation has an allele frequency of < 0,0001 according to ExAC and gnomAD and has, to our knowledge, not been described in the literature. Prediction programs for a possible pathogenicity SIFT and PolyPhen classify this mutation as „deleterious" and „probably damaging". Both parents are heterozygous for this mutation and phenotypically normal and healthy.

Conclusions: Homozygous SF 1 mutation can be responsible for sex reversal with normogonadotropic hypogonadism and low adrenal androgens.

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Assessment of Initial Investigation Requested in Adolescents with Menstrual Disorders

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Backround: Menstrual disorders are common among the adolescent girls. We examined the initial investigations performed in adolescents, presenting with frequent, heavy or painful periods. Although, usually abnormal uterine bleeding (AUB) in adolescent women is attributable to immaturity of the hypothalamic-pituitary-ovarian axis, underlying conditions such as coagulation disorders and anemia should always kept in mind. However, neither the laboratory nor the ultrasound investigation reveals any pathology related to AUB or dysmenorrhea.

Objective: To assess the value of laboratory and sonographic findings in girls with menstrual disorders, attending an adolescent gynecologic clinic. Data were collected on clinical presentation and investigation requested and results were available.

Results: 134 patients were identified, presenting either with dysmenorrhea or heavy bleeding or combination of both, during an 8 month period. Patients with oligomenorrhea were excluded. Average age was 14, 9 years. Most of the patients experienced regular menstruation, whereas, there was a significant proportion (19, 9%) mentioning irregular periods.

59 patients (44%) had a full blood count test, however only in 10 cases there was a remarkable decrease in hemoglobin value. Of note, none of the remaining mentioned any symptoms of anemia. 46 girls had had thyroid testing within normal range, except one case of hypothyroidism.

4 patients had known blood clotting disorders (ITP and Von Willebrand) who surprisingly were not anemic. Coagulation tests had already been held in 13 other girls, revealing no pathology.

In terms of imaging, 62 patients had a scan (46,2%). 9 girls had typical PCOS appearance (6,7%) and other 5 (3,7%) had other incidental u/s findings unrelated to menstrual disorders.

There were 13 girls with severe learning difficulties which contributed negatively to their general condition.

Another girl with persistent pelvic pain was diagnosed with endometriosis after laparoscopic investigation.

Conclusions: Ultrasound scans are currently a key component in the diagnosis of abnormal uterine bleeding. This study suggests that they do not finally contribute to the management and diagnosis of causes hidden behind menstrual disorders in adolescence. Ultrasound and clotting investigation should be kept only for menstrual disorders refractory to medication.

Overmedicalization and overinvestigation may cause anxiety for the girl and family but also has cost to health care service. Taking detailed history is essential and may prevent rigorous investigation. Adolescent health education is determining to create awareness regarding menstrual disorders. Reassurance that menstrual disorders in adolescence are a normal and transient condition should be offered by primary physicians.

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Persistent Müllerian Duct Syndrome in Twin Brothers Caused by a Novel Mutation in the AMHR2 Gene

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Background: Persistent Müllerian Duct Syndrome (PMDS) needs to be considered in boys (46, XY) presenting with bilateral cryptorchidism or unilateral cryptorchidism associated with an inguinal hernia. Anti-Müllerian hormone (*AMH)* gene as well as Anti-Müllerian hormone Receptor (*AMHR 2)* gene mutations have been identified in PMDS boys.

Aim and methods: To report a novel mutation in the *AMHR 2* gene in monochorionic diamniotic (MCDA) twin boys with different anatomical presentation of PMDS. The *AMHR 2* gene analysis was performed by Sanger sequencing.

Results: After 36 weeks of an uneventful gestation, the MCDA twin brothers were born with a normal birth weight and length. Both consanguineous Turkish parents were healthy, but both their two older daughters had been diagnosed with an unexplained retinitis pigmentosa. Bilateral cryptorchidism without penile abnormalities was noted at birth in both boys. Since intra-abdominal testes were suspected at ultrasound in the first week of life, no further examinations were performed at that moment. At referral to the pediatric endocrinology department at the age of 14 months because of persisting cryptorchidism, both infants had an identical body weight of 7.93 kg (-0.86 SDS) and a body length of 79.5 cm (+0.18 SDS). Physical examination revealed apart from cryptorchidism, a synophrys and slight hypertrichosis in both children. Serum testosterone level increased respectively up to 5.98 µg/L and 6.21 µg/L and serum dihydrotestosterone to 0.50 µg/L and 0.56 µg/L three days after single dose of 2500 IU of hCG.

Boy 1 had a normally developed scrotum and a penile length, but at laparoscopic exploration, a crossed fused ectopia of the left testis was found. *Boy 2* had an underdeveloped scrotum and at surgical exploration a hypotrophic vas deferens without testicular fusion and a remainder of a fallopian tube was found.

Additional genetic investigations demonstrated a normal 46, XY karyotype and a homozygous mutation c.1473C>G p.(Asp491Glu) in the *AMHR2* gene in both boys. This variant is classified as likely pathogenic on the base of prediction programs and a pathogenic effect of a known other variant within the same amino acid (Asp491His).

Conclusions: A novel but similar *AMHR 2* gene mutation was found in non-identical twin brothers, presenting with a different anatomical variant of PMDS, a crossed testicular ectopia in one boy and a female Mullerian remnant structure in the other.

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No Difference in Cognitive Performance or Gender Role Behaviour in Men with and Without Hypospadias

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Background: Hypospadias is a common malformation of male external genitalia, resulting in urethral displacement with different severity. Male genital development occurs during fetal development when also the brain is developing rapidly. Genital development is dependent on androgen effect, and androgens also have impact on gender development. We here explore whether hypospadias are associated with variation in other aspects of sex typical development.

Objective: The aim of this study was to investigate whether hypospadias is associated with differences in performance on cognitive tests and/or self rated gender role behaviour.

Participants: Eighty-six men with hypospadias participating in a medical follow up study were compared to male and female controls from the general population.

Procedure: Cognitive tasks previously shown to yield group level sex differences and questions regarding self reported retrospective gender role behaviour in childhood were administered either at an outpatient clinic visit or via online participation.

Results: The cognitive performance of men and women in the control groups differed significantly in the expected directions. Men and women also differed on gender role behaviour in childhood. There were no significant differences between men with and without hypospadias on any of the measures. Men with proximal hypospadias performed slightly lower on many of cognitive tasks.

Conclusion: Hypospadias in general, is not associated with differences in performance on cognitive tests that typically yield sex differences or with altered gender role behaviour in childhood. Further studies are needed in boys and men with proximal hypospadias.

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Assessment of the Gonadotrophin–Gonadal Axis and Sertoli Cell Function in Partial Androgen Insensitivity Syndrome

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Androgen insensitivity syndrome (AIS) is the largest single entity that leads to male under-masculinization. Although adequate serum concentrations of testosterone exclude a defect in testosterone biosynthesis, a low testosterone value at baseline does not always exclude PAIS. Anti-Müllerian hormone (AMH), also called Müllerian inhibiting substance or factor, is secreted in high amounts by the immature Sertoli cell; it is negatively regulated by testosterone.

Objective: To study the value of measuring basal and human chorionic gonadotropin (HCG) stimulated testosterone level, Dihydrotestosterone, anti-mullerian hormone (AMH) and Inhibin levels in 9 prepubertal children with the final diagnosis of partial androgen insensitivity syndrome (PAIS)

Design: Retrospective study of patients in Alexandria University Ped Endocrine clinic, Alexandria, Egypt. Patients included 9 cases of PAIS (mean age = 8.2 months ± 2.3) A single dose HCG stimulation protocol was used (1500U/m2). Measurements included pre-HCG and post-HCG serum testosterone values, serum DHT values, and serum AMH and inhibin were measured and analyzed.

Results: The mean testosterone rise following fixed dosage of HCG was 94.5 times the basal value. 5/9 patients had low basal testosterone. The mean stimulated testosterone: DHT ratios were 11.3. AMH was High to normal in 8/9 patients and Inhibin was high to normal in 7/9 patients and low in 2/9 patients.

Conclusion: Basal testosterone may not be raised during early infancy in patients with PAIS; however testosterone rise after HCG stimulation is adequate. The elevation of serum AMH and inhibin level appears to be an interesting marker of androgen resistance in sexually ambiguous male infants.

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Prevalence and Ethiologic Factors of Hirsutism in Adolescents

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Aim: To investigate the prevalence of hirsutism among adolescents using the modified Ferriman-Gallway (FG) Scale and to determine etiological factors in childen with hirsutism.

Materials and Methods: The study was in 2380 female adolescents aged 12-18 years. The modified FG score was used in the diagnosis and monitoring of hirsutism. Scores of 8 or above were regarded as hirsutism. Two hundred thirty-three volunteers determined as having hirsutism were invited to hospital.

Results: Screening revealed a prevalence of hirsutism among the 2378 patients of 9.8%. Mean FGS score of the 233 cases identified as hirsutism was 10.86 ± 3.6. Mean FGS score in the remaining 2145 cases was 2.08 ± 2.1. Mean FGS was higher in the cases with hirsutism, and the difference was highly significant (p=0.00). Acne was present in 45.9% of the hirsutism group but in only 27% of the screening group, the difference being significant (p=0.001). Hair loss, one of the findings of hyperandrogenemia, was present in 59.7%of the cases of hirsutism and 51.1% of the non-hirsutism group. The level was significantly higher in the hirsutism group (p=0.016). Mean age at menarche of all menstruating cases was 13.1±1 years. Mean age at menarche in the hirsutism group was 12.8±1.1 years, and 13.2±1 years in the non-hirsutism group. The difference in mean age at menarche between the hirsutism and non-hirsutism groups was significant (p=0.001). Menstrual cycle was irregular in 24.8% of the hirsutism group and regular in 75.2%. In the non-hirsutism group, cycles were irregular in 15%of case and regular in 85%. The difference between the two groups was significant (p=0.001). Mild hirsutism was determined in 85.7%of

cases, moderate hirsutism in 12% and severe hirsutism in 0.5%. IH was determined in 52 cases (54%), PCOS in 43 (38.5%) and NCAH in 1 (1%).

Conclusion: Studies reported a high prevalence of PCOS, while we determined a higher prevalence of IH. All patients presenting with hirsutism should be investigated in detail and the cause determined.

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Evaluation of Serum Anti-Mullerian Hormone and Androstenedione Levels in Adolescents Girls with Menstrual Irregularities

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Aim: Oligo- or amenorrhea is one of the most important features of polycystic ovary syndrome (PCOS). Anti-Mullerien Hormone (AMH) plays an inhibitory role in follicular development and contributes to hyperandrogenism in PCOS. Our aim was to assess differences in serum AMH and androstenedione levels, and clinical characteristics between adolescent girls with and without oligomenorrhea.

Participants and Methods: Sixty-eight adolescent girls with oligomenorrhea were included in the study. Sixty-four adolescent girls without menstrual irregularities also studied as a control group. All adolescent girls in this study were menarche at least 3 years ago. Oligomenorrhea was defined menstrual periods occurring at intervals of greater than 35 days, with only four to nine periods in a year. Anthropometric indices and the presence of hirsutism were assessed. Blood sample was drawn for serum AMH and androstenedione levels in the follicular phase. Transabdominal pelvic ultrasound (TPU) was performed to all participants.

Results: Mean age of the participants was 17.06±0.95 years. Serum AMH and androstenedione levels in adolescent girls with oligomenorrhea were significantly higher compared with those without oligomenorrhea ($p<0.001$ and $P=0.022$, respectively). Menarcheal age did not differ significantly between the two groups ($p=0.956$). There was no significant difference between the two groups in terms of anthropometric parameters ($p>0.05$). The frequency of hirsutism in the girls with oligomenorrhea was 27.9%, whereas it was 5.9% in the control group. 61.8 % of girls with oligomenorrhea had polycystic ovarian appearance in TPU. It was also 27.9% in control group. There was positive correlation between Body Mass Index (BMI) and androstenedione levels (r: 0.269, p:0.022).

Conclusions: Hirsutism and polycystic appearance in TPU which are important components of PCOS are more common in adolescents girls with oligomenorrhea. Adolescent girls with oligomenorrhea have higher androstenedione and AMH levels than girls with regular menstruation. The high AMH level is one of the diagnostic criteria for PCOS. High androstenedione level is a sensitive marker of hyperandrogenemia, one of the PCOS criteria. High androstenedione levels are associated with high BMI values.

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Could Basal AMH Replace hCG Stimulation Test in XY Disorder of Sex Development Cases

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Background: Traditionally, the standard endocrinological evaluation of 46, XY DSD cases is based upon measurement of testosterone, dihydrotestosterone and androstenedione and their ratios either in mini-puberty or under human chorionic gonadotropin (hCG) stimulation. However, this method is of limited value in reaching definite diagnosis in many cases. More recently, there is a growing appreciation of the value of assessing Sertoli cell function because the most active compartment of the prepubertal testis is the seminiferous tubule compartment, in which Sertoli cells secrete hormones like anti-mullerian hormone (AMH) and inhibin B.

Objectives:

- Evaluation of the role of single sample of basal AMH and inhibin B as a tool for investigating the presence and function of the pre-pubertal testis without the need for hCG stimulation test.
- Reaching the best and simplest diagnostic approach for such cases in our endocrinology clinic within the available resources and investigations.

Methods and subjects: We studied 33 cases through a whole year. The patients underwent hormonal evaluation of gonadal function, including basal testosterone, FSH, LH, AMH, and inhibin B and hCG stimulation test besides imaging studies.

Results: There were varieties of diagnoses among our subjects. Basal AMH was within normal ranges for age in the majority of cases (69.7%) with a mean of 100.55 ± 75.54. There was a significant correlation between basal AMH and testosterone increment after hCG stimulation. A positive relation was found between AMH and inhibin B. Cases with primary gonadal failure had undetectable AMH and inhibin B and high FSH on the other hand.

Conclusion: Measurement of AMH is highly informative about the presence and function of testes. Although, that cannot obviate the need for hCG test. In cases with anorchia, it might substitute the need for invasive procedure as laparoscopy.

Sex Differentiation, Gonads and Gynaecology or Sex Endocrinology P3

P3-P321

Gonadal Tumor Incidence in Patients with Disorders Od Sex Development Containing Y Chromosome or Y-Derived Sequences - Experience from One Clinical Center

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Background: Risk of developing germ cell tumors (GCTs) in disorders of sex development (DSD) patients with karyotypes contain Y-chromosome or it's material (Y) increase with age. The appropriate timing for prophylactic gonadectomy in these patients is still controversial.

Aim: to analyze the gonadal tumor incidence and histological assessment of gonads in DSD (Y) patients who were treated in a single institution between 1997 and 03/2018.

Patients/Methods: 43 SD (Y) patients' data from one center in the last twenty years were analyzed: 16(37.2%) with 45,X/46,XY, 25(58.1%) with 46,XY and 2(4.65%) with 46,XX/46,XY.

Results: 29(67.4%) patients were reared as female (F), 14(32.6%) as male (M) (Table). Gonadectomy was performed in 22(51.2%) patients: in 7/10 45,X/46,XY TS patients (age 7.65±5.33 yrs), in 2/5 males with 45,X/46,XY (at age 4.66±5.31 yrs), in 5/9 with AIS (age 11.98±7.0 yrs) and in 8/8 with GD (age 13.04±5.64 yrs). The TS 45,X/46,XY patients experienced the shortest delay between diagnosis and surgery. In one CAIS patient the earlier gonadectomy resulted from testicular torsion.

40 gonads were histopatologically evaluated, of which 12 (30%, 7 patients) tested GCTs positive. Gonadoblastoma was found in 3/14 gonads of TS patients and in 6/15 gonads of patients with GD. Additionally in 3 gonads of GD patients dysgerminoma was discovered. Leydig-Sertoli cell tumor was described in 2/9 AIS gonads (in one patient). Carcinoma embryonale, with Yolk sack tumor (on the basis of gonadoblastoma) was found in 1 gonad of 46,XY GD F patient. With the exception of the last patient, there were no evident clinical/laboratory indicators of gonadal tumor risk in DSD (Y) patients.

Conclusion: The overall GCTs risk was 30% and 46,XY GD carried the highest risk. Further search for useful clinical/lab markers of individual tumor risk is urgently needed.

P3-P322

New Method of Surgical Correction of Female Hypospadias in Girls with Disorders of Sex Development and Stenosis of Artificial Introitus

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Introduction: Female hypospadias (FH) is one of disorders of sex development signs (DSD). Short and wide urethra that opens into the vagina predisposes to occurrence of recurrent infection of urinary tract, vaginal voiding and postoperative narrowing of artificial vaginal introitus (AVI).

Aim: Improve the results of correction FH with stenosis AVI using reintroitoplasty separating the urinary and genital tracts in patients with DSD.

Materials and methods: Proposed method for the correction of FH in girls with DSD after primary introitoplasty is a modification of the "pull-through" vaginoplasty described by Hendren in 1969. In lithotomy position, posterior wall of the urogenital sinus (UGS) was mobilized without its dissection to the level of vaginal confluence. The vagina was cut off the confluence site, mobilized from the UGS and "pulled through" to the perineum. Then the UGS defect was sutured in transverse direction. New AVI was formed from mucosa flaps, previously incised on the vestibule. Mucosa under the external UGS opening used as a Passerini-like flap that was anastomosed with the anterior vaginal wall. Side and back new AVI walls were created from two lateral mucosa flaps of the vestibule and a special way of prepared vagina. We operated five patient with FH in combination with stenosis AVI and follow up them in three months. The artificial meatus opens separately

Table 1. (for Abstract no P3-P321)

	DSD 45,X/46,XY	DSD 46,XX/46,XY	DSD 46,XY			
n	11	5	1	1	17	8
Age of diagnosis mean (SD) [yrs]	5.82(5.0)	4.51 (4.49)	0.02	0.71	10.06 (6.98)	0.23 (0.35)
F/M rearing	F	M	F	M	F	M
Diagnosis (n)	TS (10) GD (1)	GD (5)	in progress	in progress	*AIS(9)* *GD(7)* *CAH (1)*	*PAIS/5AR?(1)* *GD (1)* *PAIS ?(5)* *Ohers (1)*

from the vagina with wide introitus. All patients were found of urinary continence and satisfaction of the aesthetic and functional result.

Conclusion: The proposed method correction FH with stenosis AVI makes it possible to separate the urinary and genital tracts using UGS as the urethra, and the mucosal flaps of the vestibule for re-creation of the new AVI, and improve the results of surgical treatment of patients with DSD and hypospadias.

P3-P323

Novel Mutation in Two Related 46, XY Phenotypic Females with 17β-Hydroxysteroid Dehydrogenase 3 Deficiency

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Introduction: Deficiency of 17β-hydroxysteroid dehydrogenase 3 (17β-HSD3) enzyme encoded by *HSD17B3* is a rare cause of disorders of sex development (DSD). The phenotype associated with 17β-HSD3 deficiency in 46, XY individuals is variable, ranging from predominantly male external genitalia with micropenis and hypospadias to completely female external genitalia. The diagnosis and management of this enzymatic defect is very challenging. **Case Presentation:** Case 1. A 1.6-year-old girl born to first-cousin parents presented after surgical repair of bilateral inguinal hernia, where testes with Wolffian duct elements were identified in the inguinal pouches. Karyotyping revealed a 46, XY male genotype. LH level was mildly elevated (3.1 mIU/mL). hCG stimulation test demonstrated a subnormal increase in testosterone level and a low stimulated T/Δ4A ratio of 0.44 consistent with *HSD17B3* mutation. Her parents decided to raise her as a girl and therefore, bilateral gonadectomy was performed. Case 2 (aunt of case 1). A 27-year-old female presented with primary amenorrhea. On examination, she had a male appearance with severe hirsutism, male hair balding, clitoromegaly of 3 cm and bilateral palpable inguinal mass of 2 mL. Abdominal computed tomography scan confirmed two abdominal masses. Karyotype was 46, XY. Elevated LH of 24 mIU/L and FSH of 36 mIU/mL with elevated testosterone of 3 ng/mL (normal range for male, 2.4-8.3) were found. She decided to continue as a female and express her female gender identity, and therefore bilateral gonadectomy with vaginoplasty were undertaken. Gonadal biopsy revealed Sertoli cells without spermatogenesis with diffuse hyperplasia of Leydig cells and hyaline fibrosis of the tubule walls. In the left testis, a non-invasive seminoma of 1.7 cm was shown. The phenotype of both patients with low T/Δ4A ratio (less than 0.8) raised the diagnosis of 17β-HSD3 deficiency. Sequencing of *HSD17B3* identified a novel homozygous missense mutation, Thr81Pro, in both patients. The challenging nature of this diagnosis, and the difficulties involved in sex assignment decisions and gender dysphoria in 17β-HSD3 deficiency will be discussed. Our findings emphasize the importance of high awareness of this rare enzymatic defect and the role of molecular analysis in early diagnosis, as well as in the management and sex assignment decision in 17β-HSD3 deficiency.

P3-P324

Challenges in Managing 46, XY Partial Gonadal Dysgenesis in Saudi Arabia

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Background: Partial gonadal dysgenesis is a rare 46, XY Disorder of sex development (DSD) characterized by a varying degree of testicular dysgenesis, ambiguous genitalia, and persistence or absence of regression of Müllerian structures. Many studies examined the challenges in presentation and gender assignment regarding the genital features, genetic mutations and histopathological risks of dysgenetic gonads. More recently some studies described the long-term outcome of patients reared as males. In the Middle East, cultural aspects might also influence the parents' choice of gender assignment.

Case Report: We report on a Saudi newborn with 46, XY chromosomes, presence of the „sex-determining region of Y chromosome" (SRY) gene, inguinal gonads, fallopian tubes, uterus, common urogenital sinus, and ambiguous genitalia with a micro phallus like structure and perineal hypospadias giving 8-9/12 of external masculinization score (EMS). Gonadal biopsy revealed virtually normal testicular tissue in both gonads. Her 1-year-old sister, born in district settings with limited resources, had a similar presentation at birth and was treated for labial adhesions in surgery clinics with unsuccessful attempts of dilatations. She is found to be a copy/paste of the baby sister clinically and genetically.

Discussion: Parents were extremely anxious of gender reassignment in the older sister. Psychosocial and cultural pressures heavily influence parental decision making in this neck of the wood. XY DSD girls would potentially have a very gloomy future of sexual life. This would support raising these patients as males in such communities but not necessarily gender reassignment that could be more stressful to parents. However, a trial of testosterone therapy proving response of peripheral tissue and to avoid a concomitant pathology of androgen insensitivity is worth prior to final assignment if possible. Although, consideration of long-term outcomes in children with these disorders mainly affect the decision of gender assignment and reassignment, however, psychosocial pressures on parents also have a major role in this perspective. Removal of the gonads during surgery anticipating development of gonadal tumors has to be taken into consideration. While in the past, female sex assignment was commonly recommended

for such patients, raising them in a male gender role is now more considered.

Conclusion: Parents should be involved in the decision that is ultimately based on extensive analysis of the individual case. Extensive counseling and support to parents help them to take a decision in the best interest of the patients despite all of psychosocial pressures.

P3-P325

A Paternally Inherited *NR5A1* Mutation in a Case of 46,XY Partial Gonadal Dysgenesis

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Steroidogenic factor-1 (SF1), encoded by *NR5A1*, plays a central role in sex development, steroidogenesis, and reproduction in both males and females. *NR5A1* mutations have been described in a diverse spectrum of disorders of sex development (DSD). We report on a case of XY Partial Gonadal Dysgenesis with paternal inheritance of a *NR5A1* variant. A 17-year-old girl was referred to us due to primary amenorrhea and absence of secondary female sex characteristics. She was born at term to healthy unrelated parents after an uneventful pregnancy with a birth weight of 3085 g and length 51 cm. Her neuromotor development was normal, there were no significant health problems and family history was unremarkable. On physical examination weight was 87.5 Kg and height 184 cm. She had a 3-cm phallus, a female urethra and a vaginal opening; no gonads were palpable, and pubertal stage was B1P3. Karyotype was 46,XY, there were high FSH and LH concentrations, low estradiol, low serum testosterone and no accumulation of testosterone precursors. Müllerian derivatives could not be identified on pelvic ultrasound and pelvic MRI. She was subject to bilateral laparoscopic gonadectomy and pathology revealed bilateral dysgenetic testes. Estrogen replacement therapy for puberty induction was initiated and vaginal dilation will be performed in due time. Sequencing of *NR5A1* revealed a heterozygous 17-bp deletion (c.268_285 p.M98Gfs*44) in exon 4. This mutation, which is located in the DNA binding domain of SF1, was inherited from her father. Adrenal function was evaluated in both of them, with normal results. Most *NR5A1* mutations in patients with a 46,XY DSD are heterozygous and may be inherited from the mother in a sex-limited dominant manner. However, paternal inheritance has also been reported in a few cases where the father was unaffected or presented a milder phenotype. These findings add further complexity to genetic studies of *NR5A1* in DSD and point out to the need to perform sequencing of all family members of a patient with a *NR5A1* variant, irrespective of genetic sex and phenotype.

P3-P326

Clinical Presentation and Characteristics of DSD in Kenyan Children and Adolescents

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Study Objective: To describe the clinical presentation and characteristics of DSD in Kenyan children and adolescents.

Methodology: This retrospective observational study was carried out at Kenyatta National hospital and Gertrude's Children's Hospitals involving 71 patients age 0-19 years with DSD enrolled in the clinics between January 2008 to December 2015.

Results: The mean age at the time of diagnosis was 2.7 years with a median of 0.4 years. Physical measurements showed that 25 participants (39.7%) had weights below -2 SDs, and 20 participants (44.4%) had height below -2 SDs. 16% of these children were born prematurely.53% were from Nairobi. One child was managed for severe malnutrition. There was no evidence of abandonment or neglect

Of the 16 children, 12 (75%) had normal blood pressure and 4 (25%) were hypertensive. Among the hypertensive patients, one had anorectal malformation and congenital talipes equinovarus while other patients had sex chromosome DSD and disorder of testosterone biosynthesis. Among the 7 patients with CAH, 4 were normotensive. Among 58 patients, 6 (10.3%) reported genital ambiguity in family. Five (15.2%) patients had family history of infertility. History of parental consanguinity was present in 3 (12.5%). Among 60 patients, 2 (3.3%) had been exposed to drugs during antenatal period. Out of 59 patients, 50(84.7%) were delivered in hospital. There was family history of infant deaths in 9 (30%). 95.7% of the patients presented with symptoms of DSD at birth.77.5% presented with ambiguous genitalia alone while 15.5% presented with ambiguous genitalia and other symptoms. 60% of these patients had a Prader Score of 3. while 39.7% had prader score ranging from 4 to 6. Ambiguous genitalia was initially observed by the mother in 32 (51.6%) and by healthcare provider in 28 (45.1%) patients. Thirty-six (50.7%) patients were initially assigned a male gender while 31 (43.7%) reared as females. 23.9% of patients had gender reassignment at final diagnosis.

Conclusion: Patients with DSD may present at a wide age range varying from the first day of life to late adolescence. Ambiguous genitalia was initially observed by the patient's mother in majority of cases despite a high rate of delivery in hospital.This may be due to the fact that midwives and primary healthcare doctors are not trained on this and there is no national guideline for diagnosis and management of DSD. There is a need of intensifying training on DSD at primary and secondary level of healthcare centers

P3-P327

Evolutive Profile of Pauci-Symptomatic Forms of Mc Cune Albright Syndrome

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In young girls, the occurrence of secretory ovarian cysts may be the first manifestation of Mc Cune Albright Syndrome.

We reported the evolutive profile of 8 patients with peripheral precocious puberty (PP) with (n = 5 cases) or without metrorrhagia (n = 3). On the first episode, they were 3.8 years old (range 2.5 to 7.25 years), the average diameter of the ovarian cyst was 38.5 mm (range 25 to 88 mm), the mean estradiol level was 32.5 pg/ml (range 3 to 160), mean AMH level was 3.35 ng/ml (range 1.9 to 8.7). 2 patients had café-au-lait spots (cases 4 and 7). No patient had bone lesions detected on the holoskeleton and no patient had detected GSa protein mutation by peripheral blood analysis. Five patients underwent cystectomy, GSa protein mutation was positive on the follicular fluid in 4 cases. The cyst spontaneously regressed in 3 cases. The rates of E2 and AMH level were not correlated to the diameter of the cyst. The recurrence of the cyst was noted once (case 7 at 4 yrs), twice (case 4 at 7 and 10 yrs) and 6 times (case 1 at 3, 4, 6, 7, 9 and 11 yrs). This girl with 6 recurrences (case 1) was followed until the age of 27 yrs, she had no other recurrence after 11 yrs.

Mc Cune Albright syndrome is a sporadic disease with unpredictable evolution. Only follow-up is essential because there is no predictive factor of recurrence at the initial diagnosis.

P3-P328

A 45X0/46XY Girl Diagnosed with Prepubertal FSH Elevation

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Aim: The 45,X/46,XY karyotype is rare with an estimated incidence rate of less than 1/15.000 live births. It represents from Turner females to phenotypically normal males with varying degrees of genital ambiguity. Although, high gonadotropin levels have been described in 0-5 years old girls with Turner syndrome, high FSH level is not well known finding in prepubertal girls older than 6 years.

Case: A 6y 8m girl presented with lipomastia. She was born 3720 gr via section and her background was normal. Although her height is normal (height: 116.4 cm (-0.57SD), weight: 26.8 kg (+1.17SD), BMI: 19.7 kg/m^2 (+1.73SD), MPH: 170 cm (+1.05SD)), her height SDS was 1.5 SD lower than MPH SDS. Also she has long palpebral fissure and prominent eyes as her father's. The system examination was normal with breast T1 (lipomastia), pubic T1. On laboratory tests, FSH: 16.7U/L, LH: <0.1U/L, E2: <5pg/mL, BA: 6y10/12-7y10/12, PAH: 154.9-148.8 cm, pelvic USG: uterus 29x5x10 mm, RO:13x4x7 mm, LO:10x5x6 mm. Karyotype analysis (blood) was detected 45X0[22]/46XY[82]. FSH levels decreased 8.2 U/L one month later. Gonadectomy was planned.

Conclusion: Elevated FSH level expects in 0-5 years old children with 45X0 Turner syndrome, but it can be also seen in prepubertal girls.

P3-P329

About a Case of Leydig Cell Tumor Associated with Central Precocious Puberty

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Background: Leydig cell tumor (LCT) is a rare testicular tumor developing from male gonadal interstitium and most common type of testicular sex cord-stromal tumor. Its incidence is about 1%–3% of all testicular neoplasms. In children only few cases had been reported and are associated with pseudo puberty.

Case report: We report a case of a 4 years old boy admitted to our unit for management of precocious puberty which started one year ago with increase in penis length and pubic hear. At four years his height was 130cm (+3SDS), weight 28 Kg (+3SDS), he has no dysmorphic face, acne and hoarse voice. Genital examination found a G3P2 Tanner stage with right testis volume of 6cc and left of 3cc.Hormonal assay showed luteinizing hormone (LH) levels at 0, 5 U/l; normal human chorionic gonadotropin level <1 m IU/ml; alpha-fetoprotein (AFP) level at 0.76 IU/ml; serum testosterone at 1.9 ng/ml; 17OHP at 1,04ng/ml. TSH at 2,4µUI/ml, FT4 at 12 pg/ml. Testicular ultrasound found an hypo echogenic lesion of 12,5x6 mm in the right testis with irregular limits. MIR confirm the nodule of 15x6mm which appear in isosinal T2 and enhanced gadolinium. The patient underwent right orchiectomy. Histological section show polygonal cells with abundant eosinophilic cytoplasm and prominent nucleoli arranged in sheets and nodular pattern corresponding to LCT.

One and three months later, we note the persistence of signs of precocious puberty with morning erection and increase of left testis volume to 6cc. LH level was 2,58 U/L and testosterone 2,85ng/ml confirming central puberty. Hypothalamic-pituitary MIR was normal. Precocious puberty with" priming phenomena" due to long term testosterone secretion by the LCT has been evoked. The patients was treated with LH-RH analogues (TRIPTORELINE 3,75mg) every 28 days which induce good evolution with decrease of testicular volume and testosterone levels (0,12ng/ml).

Conclusion: This case report a rare testicular tumor (LCT) revealed by precocious pseudo puberty followed by central puberty with priming phenomena. This underlines the interest of a rigorous follow-up after tumor resection.

P3-P330

Gender Dysphoria

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Purpose: To assess the prevalence in 2017 and elucidate the well-being of youngsters with gender dysphoria.

Background: Gender dysphoria is described as a strong and persistent feeling of being born in the wrong sex. Often the feeling is associated with impaired ability to function in everyday life, found in children, adolescents and adults. For adolescents with gender dysphoria, puberty is an additional mental strain that can lead to depression, anxiety and social isolation.

Method: With a descriptive study design, we aim to evaluate the quality of life perceived by all the youngsters referred to the university clinic of Queen Silvia Children´s Hospital 2017 for endocrine treatment.

Results: Twenty three youngsters (14 female/9 male) with an age of 11-17 years were referred to the endocrine clinic for gender dysphoria. All "male to female" were treated with GnRH-analogue for a median period of 9 months before follow up visit and final diagnosis. By interview with a nurse most reported they had perceived low quality of life and in half of them diagnosed with depressive symptoms. After GnRH analogue treatment they were satisfied stopping further sex developing with less symptoms of depression and anxiety in their everyday life.

Twenty of the youngsters started with cross-sex hormone treatment during the year when they fulfill all criteria's for gender dysfhoria.

Conclusion: Appropriate care improved quality of life in most youngsters seeking for gender dysphoria.

P3-P331

GnRH Analogues and Cross-Sex Hormonal Therapy: Side Effects in Transgender Youth

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Background: Transsexuality during childhood/adolescence is a complex condition usually ending in dysphoria (GD). The prevalence of transgenderism is increasing in Pediatrics. In the process of sexual reassignment, a correct pharmacological treatment and the knowledge of possible consequences are necessary.

Objective: The objective of this study is to present the evolution of the physical and analytical characteristics and side effects in Transgender children and youth with pubertal blockade (PB) and/or cross-sex hormones (CSH).

Method: 102 patients (age ranged from 5.8 to 16.1 years) with GD are followed in the Endocrinology Unit of a tertiary hospital during 3.1 years. 52% are biological women (female to male -FtM- group) and 48% biological men (male to female -MtF- group).

Results: GD is present from early childhood in 85% and persists in all patients nowadays. 66 patients are treated with GnRH analogues (the onset of treatment ranges from 9.8 to 16.3 years). 36 patients receiving cross-sex hormonal treatment, initiated between 14.8 and 16.4 years (19 cases FtM, 17 cases MtF). GnRH agonists (monthly/ quarterly) were used for PB, observing LH <0.5 mUI/ml at 3 months after the start of treatment. Erections stopped in all MtF after the first dose. The menstruation disappeared in the FtM with monthly preparation after the first dose, if the preparation was quarterly they presented one or two menstrual cycles. As for CSH, 17β-Estradiol (oral / transdermal) and PB were used together in MtF. In FtM we used Testosterone Cypionate (intramuscular/ subcutaneous) associated to PB only during the first year. About FtM analytical evolution, hematocrit increased and higher total cholesterol was observed. Physical changes observed in the physical examination and side effects are also described.

Conclusion: GD management should be multidisciplinary, requiring a correct diagnosis of GD by mental health specialist and it is necessary the application of standardized therapeutic protocols. Pharmacological treatment in transsexual subjects involves anthropometric, physical and metabolic changes; long-term studies are needed in Pediatrics.

P3-P332

Klinefelter Syndrome with Low Gonadotropin Levels

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Background: Klinefelter syndrome (KS) is the most common cause for hypergonadotropic hypogonadism. Patients with 47,XXY karyotype often have increased gonadotropin levels at early puberty, which stay high during adolescent and adult life due to hyalinisation of seminiferous tubules of testes. We report a clinical case of 47, XXY KS patient with low gonadotropin levels.

Clinical case: A boy was referred to an endocrinologist at the age of 12,5 years due to overweight and small testis. Physical examination revealed: height 158.4 cm (SDS=0.58), BMI=23.23 kg/м2 (SDS=+1.38), Tanner stage 1 with no signs of eunuchoid body shape. The testis were soft and the testicular volume was 1 ml. Bone age was 13 years (G&P). Levels of LH (0.2 U/l), FSH (1.8 U/l) were estimated as normal, while basal (0.6 nmol/l) and stimulated (4.5 nmol/l after HGH stimulation test) testosterone levels – as low. The patient was found to have normal levels of 8:00 cortisol (415,3 nmol/l), free T4 (15,3 pmol/l), thyroid-stimulating hormone (2,74 mIU/L), there were no complaints of headache, no signs of space-occupying lesion in his brain. Gonadotrophin releasing hormone stimulation test didn't reveal the hypogonadotropic hypogonadism (LH peak 12,8 U/l, FSH peak 8,2 U/l) The diagnosis of KS was confirmed by karyotype (47XXY, [100]) and fluorescence in situ hybridization method (47,XXY nuc ish (DXZ1x2,DYZ3x1, SRYx1)[100]). Testosterone therapy was initiated with the starting dose of 50 mg 1 time per 4 weeks with further increase to 250 mg 1 time per 4 weeks. After a year of treatment levels of LH (0.9 U/l) and FSH (3.6 U/l) stayed low, testosterone was 9.0 U/l, inhibin B was 51.1 pg/ml, AMH was 75.9 ng/ml.

Conclusion: There are very few cases of KS without hypergonadotropic hypogonadism described today. Low gonadotropin levels could be explained by significant variability of manifestations of KS even with classical karyotype.

P3-P333

Young Male Adolescent with Gender Dysphoria (GD) / Gender Incongruence - A Case Presentation

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Background: Children and adolescents who have a gender identity that does not correlate with their assigned gender (based upon genital anatomy and chromosomes) are described as Gender-Dysphoric/Gender-Incongruent Persons (GD / gender incongruence) based on the ICD-11 classification of the World Health Organization.

Objective: The case of a young teenager with Gender Dysphoria Disorder

Case presentation: A boy, aged 13 and 4/12 years, was admitted because of marked discomfort with his primary and secondary sex characteristics and a strong feeling that he belongs to the female gender. The patient used to dress up with female clothes since childhood and he was constantly seeking information on the website about medical and surgical treatments for gender congruent boys. Medical history was remarkable for a long-lasting and intense pattern of gender non-conformity, starting at the age of 6-8 years. On physical examination, he was in early puberty, as evidenced by pubic hair Tanner II and testicular volume of 4 mL. Initial laboratory examination was compatible with pubertal initiation, while karyotype was 46, XY. He was followed by a pediatric psychiatrist who confirmed that the adolescent's gender dysphoria worsened following the onset of puberty and that the adolescent's situation and functioning were stable enough to start treatment. His parents were informed of the effects and side effects of treatment and they gave informed consent to start treatment with GnRH analogues in order to suppress pubertal hormones and he gave assent.

Results: The patient today is 14 and 9/12 years old. He is regularly monitored by both specialists, Pediatric Psychiatrist and Endocrinologist and he continues therapy with GnRH analogues, in order to have time to confirm the persistence of gender dysphoria and for the adolescent to have adequate mental capacity to give informed consent for treatment with estrogens. His feelings have not changed, he has persistent gender dysphoria and he persistently demands initiation of subsequent sex hormone treatment, being quite angry and emotional dealing with the delay of treatment that the medical team had advised.

Conclusion: Children and adolescents with gender identity disorders should be treated only by trained group of physicians, mental health and endocrinology professionals, who meet the criteria according to International Guidelines, in order to help them make a thorough and informed decision about permanent physical changes.

P3-P334

Effect of Gonadotropin-Releasing Hormone Agonist Treatment in Boys with Central Precocious Puberty and Early Puberty

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Purpose: Central precocious puberty (CPP) is less common in boys than girls; very little data is reported on effect of gonadotropin-releasing hormone analog (GnRHa) treatment in boys with CPP. The aim of the study was to evaluate growth changes in boys with CPP and early puberty (EP) treated with GnRHa therapy for 1 year.

Subjects and Methods: In 60 (39 CPP and 21 EP) boys with confirmed diagnosis of CPP and EP, auxological [height, height standard deviation score (HtSDS), bone age (BA), Ht prediction) and endocrinological parameters were obtained at baseline, at 6 months, and at 1 year after GnRHa treatment in boys with CPP and EP. Pubertal progression ceased in all patients.

Results: During the treatment a decline in Ht SDS and growth velocity, LH, FSH and testosterone levels were observed ($p<0.01$); and a deceleration in the maturation of bones after 1year GnRHa treatment was observed ($p=0.000$). Predicted adult height (PAH) SDS was increased during treatment with GnRHa ($p<0.01$). There was no difference in the auxological and endocrinological parameters after 1 year treatment between CPP and EP. There was significant difference in PAH SDS between organic CPP and non-organic CPP ($p<0.05$).

Conclusion: The present data indicate that GnRHa therapy significantly improves growth prognosis in boys with CPP and EP. Boys with organic forms might have poorer height prognosis.

P3-P335

DSD in Ukraine: Our Experience

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Background: The term "disorder of sex development" (DSD) includes congenital conditions in which development of chromosomal, gonadal or anatomic sex is atypical.

Materials and methods: A retrospective analysis of the 75 medical cards of patients with DSD since 2000 up to 2017 year was done. The criterion for including patients to the database was ambiguous genitalia and/or a discrepancy between the chromosomal and gonadal/genital sex. At the time of examination the number of patients aged < 1 month was 17%, 1month-<1 y.o. - 25%, 1-12 y.o. - 37%, > 12 y.o. - 21%. The results of clinical data, laboratory

Table 1. (for Abstract no P3-P335)

Androgen insufficiency syndrome (CAIS/PAIS)	3/18
Complete gonadal dysgenesis	6
Bilateral anorchism	5
Perineal hypospadias	7
Androgen biosynthesis defect	4
Ovotesticular DSD	2
Partial Gonadal dysgenesis	3

tests and instrumental examination were analyzed. All patients (from birth to 18 y.o.) carried out a cytogenetic test, and, if necessary, fluorescence in situ hybridization (FISH). Molecular genetic testing was done in selected group of patients with 46,XY DSD in Ukraine (n=2) and in Institute Pasteur, France (n=13), using exome sequencing.

Results and discussion: Sex chromosome DSD was diagnosed in 21,3% (n=16), 46,XY DSD- in 64% (n=48), 46,XX DSD - in 14,7% cases (n=11). The most frequent variant of the karyotype among the first group was 45,X/46,XY (n=5; 31.2%). In a group of patients with 46,XX DSD we diagnosed: testicular 46,XX DSD (n=5), 21-hydroxylase deficiency with virilization IV-V degree by Prader (n=4), 46,XX gonadal dysgenesis (n=1) and DSD in VACTER-association (n=1).

In a group of patients with 46,XY DSD at first visit we suspected following clinical diagnoses:

Genetic testing in 46,XY DSD group was done in 15 (31%) cases. In 7 patients (47%) we found such genes are known to be involved in DSD as *DAX-1, WT1, SRD5A2, NR5A1, HSD17B3* and *AR (n=2).* In 4 patients (27%) genes we found were not consistent with phenotype and their causality should be proven in further studies.

In the entire cohort in 6/75 (8%) cases the gender registration of the civil sex was changed during the first 2 years of life.

A multi-disciplinary team has been created for gender assignment in DSD newborns and to improve the tactics of further management, including the time of gonadectomy.

Conclusions: Further studies to identify novel genes causing DSD are required.

P3-P336

A Turkish Family with 46,XY Disorder of Sex Development Due to 17b-Hydroxysteroid Dehydrogenase Type 3 Deficiency

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17β-Hydroxysteroid dehydrogenase type 3 (17β-HSD3) is expressed mostly in the testes and converts the inactive Δ4-androstenedione (A) to testosterone (T). 17β-HSD3 deficiency is a rare autosomal recessive disorder and the most common testosterone biosynthesis defect leading to 46,XY Disorders of Sex Development (DSD). To date, more than 40 mutations of HSD17B3 have been reported. 46,XY patients with 17β-HSD3 deficiency would present with wide variable external genitalia (Sinnecker Type 5 → Tip 2, but mostly Sinnecker Type 4,5.

The patient was referred to our practise at the age of one year due to atypical external genitalia. Patients' parents were first-degree cousins. On physical examination displayed nearly complete female external genitalia and bilateral mass in her groin (Prader stage 2 & Sinnecker Type 4). Chromosomal analysis revealed a 46,XY karyotype, therefore patient diagnosed 46, XY DSD. In laboratory, T/A ratio was less than 0.8. When the patient was seven years old, his newborn twin sisters referred to us due to the same clinical condition, external genitalia and laboratory parameters. Their chromosomal analysis revealed a 46,XY karyotype too. We detected a de novo homozygous c.577C>T (p.P193S) mutation in HSD17B3 gene in three siblings. Parents and one brother were heterozygous for this mutation. Furthermore, same homozygous mutation was detected in a sister with 46, XX chromosomes without any complaint. In slico variant analysis, DANN Score was 0.9989 (Disease causing).

We reported 3 siblings patients with 17β-HSD3 deficiency. Ambiguous genital phenotype, 46,XY male karyotype and the ratio of testosterone versus androstenedione less than 0.8 could suggest the diagnosis.

P3-P337

Normal External Genitalia in a Female with Classic, Salt-Wasting 21-Hydroxylase Deficiency

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Background: 21-hydroxylase deficiency is the most common cause of congenital adrenal hyperplasia, a family of autosomal recessive disorders involving impaired synthesis of cortisol by the adrenal cortex. Females with severe, classic 21-hydroxylase deficiency are exposed to excess androgens prenatally and are born with virilized external genitalia. This form is further divided into the simple virilizing form and the salt-wasting form, in which aldosterone production is inadequate which predispose to life-threatening salt-wasting crises.

Clinical case: Our patient is a female presented at the age of 14 days with fever, poor feeding, and lethargy. She was born full term, normal vaginal delivery without complication. Mother was healthy with regular prenatal care. She didn't have hirsutism and was not taking any medications. Parents are related with no history of neonatal deaths or infertility in the family. Patient presented febrile, lethargic with signs of severe dehydration with normal blood pressure. Skin was hyper-pigmented. External genitalia were normal with 2 labial folds and two opening (urethral/vaginal) without palpable gonads. It was hyper-pigmented with mild cliteromegaly. Investigations showed high anion gap metabolic acidosis. Electrolytes showed sodium of 114mEq/L(reference range 135-145,mEq/L), potassium of 7.3mEq/L(reference range 3.5-5.0,mEq/L). Ammonia and lactic acid were normal. Hyponatremia was corrected gradually and she was started on hydrocortisone as stress dose then maintenance.

17-hydroxyprogesterone level was 2541ng/dl and 2946ng/dl pre and post ACTH stimulation respectively(reference range

<630ng/dl). Androstenedione level was 5.44 ng/ml(reference range o.18-0.80,ng/mL). 11-deoxycortisol level was 0.34ug/dl (reference range <1 ug/dl). Testosterone level was 11.4nmol/L(reference range 0.42-0.72,nmol/L). Aldosterone was <22ng/dL(reference range 4-16,ng/dl). Renin level was >550. ACTH level was 196pmol/L (reference range 1.6-13.9, pmol/L). DHEAS level was 27mcmol/L (reference range 0.86-11.7,mcmol/L). Estradiol level was 182pmol/L(reference range 22-139, pmol/L). Chromosomal analysis showed 46XX. Pelvic ultrasound showed normal uterus and ovaries. Patient was diagnosed with classic 21-hydroxylase deficiency and was started on oral hydrocortisone and fludrocortisone.

Conclusion: A cardinal feature for females with classic 21-hydroxylase deficiency is genital ambiguity and salt wasting. Like our patient we can consider classic 21 hydroxylase deficiency in females with normal external genitalia and hyper-pigmented skin presenting with salt loosing crisis. If the disorder isn't recognized and treated patient may suffer from fatal hypovolemia and shock.

P3-P338

Ovarian Leydig Cell Tumor in an 8 Years Old Girl Misdiagnosed as Congenital Adrenal Hyperplasia Due to Elevated 17-Hydroxi-Progesterone

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Introduction: Non-classical congenital adrenal hyperplasia is the most common pathological cause of early pubarche in prepubertal patients. However, this may also be the first manifestation of central precocious puberty or an androgen producing suprarrenal or ovarian tumor.

Objective: To present a clinical case initially misdiagnosed as Congenital Adrenal Hyperplasia that turned out to be an Ovarian Tumor of Leydig Cells.

Clinical Case: An 8-year-old girl is presented with early pubarche and hirsutism, referred for further evaluation. Her height was in percentile 75 (target height: 25th percentile), her BMI in percentile 90, and blood pressure was normal. She presented hirsutism (Ferriman score 8), breast Tanner 1, pubic hair Tanner 3 and a normal clitoris. Laboratory study showed elevated androgens levels: testosterone of 47.2 ng/dL, androstenedione of 5.1 ng/mL, basal 17-hydroxi-progesterone (17OHP) of 15 ng/dL, and normal DHEAS (0.26 ug/mL) as well as Plasma Renin Activity (0.22 ng/mL/hr). Initial imaging study showed an advanced bone age (11 years for a chronological age of 8 years 4 months) and a normal abdominal and pelvic ultrasonography. No pathogenic variants in the *CYP21A2* gene were found. Since she could have congenital adrenal hyperplasiaanother with a defct in another gene, she was treated with hydrocortisone (12 mg/m^2). Pubertal development started at 8.7 years; then analogues of LHRH were initiated. Despite both treatments, signs of virilization accentuated progressively along with elevation of androgens (testosterone as high as 120 ng/mL). Although different therapeutic schemes with hydrocortisone, prednisone and dexamethasone were tried, it was not possible to reduce testosterone levels. Then abdomen and pelvis MRI was performed, showing a solid nodular image of 2.1x1.6 cm in the right ovary. Biopsy analysis after laparoscopic oophorectomy demonstrated a Leydig cell tumor. One month after surgery, the patient normalized all androgenic levels and gradual suspension of corticosteroids was started.

Conclusions: In the presence of early pubarche, hirsutism and high 17OHP levels, Non-Classical Congenital Adrenal Hyperplasia should be suspected. But when no pathogenic variants in the *CYP21A2* gene are present and it is associated with progressive clinical and biochemical hyperandrogenism despite an adequate treatment, MRI should be performed to ruled out androgen producing tumors.

P3-P339

Analysis of Genetic Mutations in a Chinese Pedigree Affected with Idiopathic Hypogonadotropic Hypogonadism Syndrome

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Objective: The aim of this study was to detect potential gene mutation of idiopathic hypogonadotropic hypogonadism Syndrome (IHH) in a Chinese family.

Methods: Patient with clinical diagnosis and parents were analyzed in this study. The analysis included medical histories, clinical analysis, and genetic tests. A Disorder of Sexual Development (DSD) gene panel was applied to identify the pathogenic mutation responsible for the DSD and verified by Sanger.

Results: A novel mutation c.533G>C (p.W178S) of the PROKR2 gene was found in the patient and his father. The same mutations were not found among 100 healthy controls.

Conclusion: A novel mutation c.533G>C (p.W178S) of the PROKR2 gene mutation can be a cause of IHH in Chinese. We think that genetic studies to may assist in making IHH diagnosis and providing the consultant for their families.The novel mutations have enriched the mutation spectrum of the IHH gene.

P3-P340

Cytogenetic spectrum of Ovotesticular Disorder of sex development in Egyptian DSD patients

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Ovotesticular disorder of sex development (OT-DSD) is a rare disorder of sexual differentiation characterized by the presence of both testicular and ovarian tissues in the gonads of the same individual. Patients usually present at birth with ambiguous genitalia, and the majority showed a 46,XX karyotype, with absence of the *SRY* sequence. In this study we reported on nine patients with OT-DSD, who were referred to the Human Genetics and endocrinology Clinics, division of Human Genetics and Genome Research, National Research Centre (NRC), Cairo, Egypt. The patients were selected from 540 DSD patients studied over a period of 5 years (2013-2018) Eight patients presented with ambiguous genitalia and one male patient presented with gynecomastia The patients constituted 6.4% of the patients presenting with ambiguous genitalia The patients underwent conventional cytogenetic and FISH analysis, ultrasonographic and laparoscopic assessment with gonadal histopathological examination. FISH on gonadal tissue biopsies were also performed in three patients. Five patients had 46,XX karyotype, one patient had a chimeric 46,XX/46,XY karyotype and three patients had unusual structural sex chromosomal abnormalities. This study extends the cytogenetic spectrum of OT-DSD patients and indicates the necessity of comprehensive studies for the accurate diagnosis of DSD patients. Reaching a definitive diagnosis is important for proper sex assignment and for medical, surgical and psychological intervention.

P3-P341

Cytogenetic Spectrum of Ovotesticular Disorder of Sex Development in Egyptian DSD Patients

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P3-P342

Characterization of Genotype-Phenotype in Inter-Familial and Intra-Familial Patients with Same Mutation of *SRD5A2* Gene

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Background: Deficiency of microsomal membrane enzyme 5α reductase 2 impairs the DHT production and differentiation of external genitalia, seminal vesicles and prostate in males. The present study describes the Genotype-Phenotype in inter-familial and intra-familial patients with same mutation of *SRD5A2* gene.

Methods: All patients underwent detailed clinical evaluation, hormonal profile, karyotyping and molecular analysis of *SRD5A2* gene.

Results: *Inter-familial:* Six patients from 3 families had a common p.R246Q mutation. Four patients had female sex of rearing and all of them had under gone male gender re-assignment. Two patients were reared as males. Another common combined mutation of p.V89L and IVS(1-2)T>C was present in 6 unrelated patients. Four patients had female sex of rearing and all of them under went male gender re-assignment. Two patients were reared as male.

Two unrelated patients with 5αRD2 had a novel insertion of TA nucleotides in the exon 1 (188-189) of *SRD5A2* gene that lead to premature termination of protein and synthesis of truncated non-functional enzyme.

Intra-familial: One family had all four children affected and the other family had two affected children. Family 1: Sequence analysis of *SRD5A2* gene showed p.R246Q homozygous mutation (exon 5) in all the four siblings. Family 2: This family had two affected sibling. Sequence analysis of *SRD5A2* gene showed a combined mutation of homozygous p.R246Q (exon 5) and heterozygous p.A12T (exon 1) in both the siblings.

Conclusion: The phenotype and sex of rearing was not identical in children from one family with same genotype or family environment. Though a specific genotype- phenotype correlation could not be established in our patient but confirming the diagnosis of 5αRD2 with assessment of *SRD5A2* gene may help in appropriate gender assignment.

P3-P343

Genital Abnormalities and Management Outcomes as Seen in the University of Port Harcourt Teaching Hospital

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Background: Genital abnormalities are a source of concern and anxiety to parents and patients and in some cases, for the physicians who may have difficulty making pathological and eventually genetic diagnosis. They range from simple small penis and labial adhesions to the complex genital ambiguity and disorders of sex development.

Hypothesis: To determine the genital abnormalities presenting in the Paediatric endocrinology unit of the University of Port Harcourt Teaching Hospital.

Patients and methods: A retrospective cohort review of all children presenting to the Endocrinology unit of the Department of Paediatrics, UPTH with genital abnormalities was undertaken from 1st of January 2013 to 31st of December 2017. The evaluation of the children include detailed history, physical examination, place of birth, age and sex of rearing at presentation, clinical presentation, investigations, management and outcome of treatment /follow up.

Results: There were 31 children presenting with genital abnormalities of various kinds. Sex assigned to these children was 8 females and 23 males irrespective of complete pathological diagnosis. The median age of presentation was 13 months with a range of 0.1 – 168 months. The commonest diagnosis was micropenis (32.2%) with various forms of DSD being the second commonest (29%) and most females had labial fusion (16.1%). Females with labial fusion had complete resolution following oestrogen cream application, and 4 of the 7 children with DSD died.

Conclusion: Making diagnosis and managing complex genital abnormalities like DSD in UPTH remain challenging because of lack of diagnostic equipment and drugs but simpler conditions have better and long term outcome.

P3-P344

A Case Report: A Girl with 46,XY Karyotype and Disorder of Androgen Synthesis

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Background: Disorders of androgen synthesis are rare causes of 46,XY disorder of sex development (DSD) that present with undervirilization or sex reversal.

Objective: A history of a female adolescent with 46,XY DSD, initially suspected to have complete androgen insensitivity is presented.

Methods: Patient history was obtained from the medical records. Urinary steroid profile was preformed using gas chromatography/mass spectrometry. The genetic analysis was performed by TruSight One sequencing panel using MiSeq desktop sequencer.

Results: The patient with prenatal karyotype 46,XY, born with female genital appearance, was first evaluated 3 days postnatally. She was found not to have Mullerian structures; the gonads were located in inguinal regions, with the ultrasound appearance of testes, and were left in situ. Testosterone (T) and dihydrotestosterone (DHT) were detected by immunoassay (T 0,6 nmol/L, DHT 1,1 nmol/L), and complete androgen insensitivity was suspected. No mutations or deletions in *AR* and *SRD5A2* genes were identified. At presentation she was 12 years old and had no clinical signs of puberty or virilisation, but gonadotropins were in pubertal range (basal luteinizing hormone (LH) 5 kIU/L, peak 43,3 kIU/L). Adrenal androgen levels were very low basally and with adrenocorticotropin stimulation (T <0,1 nmol/L, dehydroepiandrosterone sulfate 0.5 μmol/L, androstenedione 0.2 nmol/L). There were no signs of gonadal failure (basal follicle-stimulating hormone (FSH) 2,3 kIU/L, peak FSH 4,5 kIU/L, Inhibin B 361 ng/L), salt loosing, salt retention or hypocorticism. The level of 17-OH progesterone was borderline elevated. No suspicious changes in the gonads were detected by ultrasound during regular follow-up. Urinary steroid metabolome analysis by gas chromatography-mass spectrometry (GC-MS) showed increased 17- deoxygenated steroids, normal glucocorticoids and subnormal sex hormones pointing to a general weakness of the 17-hydroxylase/17,20- lyase system with strongly impaired lyase function. This constellation was highly suspicious of "isolated" 17,20-lyase deficiency. Targeted genetic analysis showed that the patient is compound heterozygote for CYP17A1 gene (NM_000102: c.1040G>A (p.R347H; rs61754278) in exon 6 and NM_000102: c.1247G>A (p.R416H; rs104894155) in exon 8). Both variants are classified as pathogenic in ClinVar database.

Conclusion: A disorder of androgen synthesis due to isolated 17,20-lyase deficiency was identified in a patient with complete sex reversal. Unlike immunoassays,GC-MS urinary steroid metabolome analysis is independent of cross reactivity and also due to its high differential diagnostic potential is extremely helpful in the delineation of DSD.

P3-P345

The Positive Effect of the Low-dose Contraceptive on the Course of Cystic Fibrosis in the Adolescent Female

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Backround: In female patients with cystic fibrosis (CF), female sex predisposes to the progression and worsening of lung function, which increases the incidence of acute exacerbations, and leads to the earlier bacterial colonization of Pseudomonas aeruginosa. The

negative effect of estrogens on the clinical course of CF in girls begins to manifest with the onset of puberty and the appearance of secondary sexual characteristics. On the cellular-level estrogens affect: 1.) immune and anti-inflammatory processes (reduced lactoferrin production, decreased response of IL-8), 2.) microbial spectrum - the early colonization of Ps. aeruginosa and its faster conversion to the mucous strain; and 3.) mucociliary clearance - estrogens lead to dehydration of the mucus layer by increasing the sodium channels expression and by reducing the activity of the calcium-activated chloride channels. During the phase of the menstrual cycle with the highest concentration of estrogens, the mucociliary transport is impaired, and thus airway cleansing, which predisposes to acute exacerbation of the pulmonary infection. Adult women with CF receiving hormonal contraceptives have shown significantly lower estradiol concentrations associated with reduced incidence of acute exacerbations and decreased consumption of antibiotics.

Case report: Authors present a case study of a 15-year-old patient with CF diagnosed in the neonatal period with a relatively favorable course of the disease. With the onset of menarche, there have been repeated acute exacerbations of pulmonary infection with altered clinical status. After the fifth bronchopneumonia, a low-dose hormonal contraceptive was given, which significantly reduced the incidence of exacerbations of pulmonary infection. We have not experienced any undesirable effects during continuous hormonal contraception.

Conclusion: The use of hormonal contraceptives in the light of the latest findings has been shown to be a promising way to influence the incidence of exacerbations of lung infections and to improve the prognosis of patients with CF.

P3-P346

Ovotesticular Disorder of Sexual Development: 31 Cases Followed-up in a Single-Center in Brazil

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The Ovotesticular Disorder of Sexual Development (OT DSD) is a rare condition characterized by histologic demonstration of both ovarian and testicular tissue in the same individual. Descriptions in literature usually have small samples and do not include patient evolution data. The aim of this study is to describe clinical, biochemical and histological findings, as well as long-term outcomes (including onset and progression of puberty) in patients with OT DSD, accompanied between 1978 and 2018, at the Instituto da Criança do Hospital das Clínicas da FMUSP, São Paulo-Brazil. It is a retrospective non-interventional unicentric study in which thirty-one patients were included.

The mean age of the first visit was 32.1 months; the majority of the patients had initial male sex (54.8%) and the majority had final female sex (54.8%). The mean phallus size was 2.5 cm, there were palpable gonads in 67.7% and the urethra was perineal in 74.2% of the patients. The mean testosterone value was 245.4 ng/dL. The number of surgeries was 2.76 per patient. The most frequent karyotype was 46,XX (58.1%), followed by mosaics (25.8%). Mullerian structures were present in 74.2% of the patients. The most frequent gonad was ovotestis (48.4%) and the most common combination was ovotestis + ovary (38.7%). It was possible to evaluate puberty in 19 (61.3%) of the 31 patients. Of these, 12 went on spontaneous puberty. The mean age of pubertal onset was 12 years. This is a significant sample of OT DSD patients, with phenotypic and genotypic data compatible with literature. OT DSD remains a challenge for clinicians and the evolution of these patients in terms of puberty is still not properly explored in current literature.

P3-P347

Genital Swelling and Ovarian Stimulation Syndrome in an Extremely Preterm Infant

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Introduction: Ovarian stimulation syndrome (OSS) in an infrequent disorder, in preterm infants under 30 weeks gestation. The are very few cases described in the literature. The immaturity, lack of gonadal axis feed-back or mutations in the FSH receptor genes, may explain its physiopathology. We present the case of a 26-week neonate with this syndrome.

Case summary: 26-week newborn with extremely low weight (460g) born by emergency cesarean section due to severe maternal preeclampsia with loss of fetal wellbeing. She had an Apgar 4/6. She needed to be admitted to NICU for 3 months, where she was hemodinamically stable and presented pathologies due to her immaturity, such as: bronchopulmonary dysplasia, necrotizing enterocolitis grade 1, and cerebral haemorrhage grade IV. At 2 months of age genital swelling began to appeared, including clitoris, minor and major labia, reaching upper part of inferior extremities and hypogastrium. An ultrasound was performed to rule out vascular and lymphatic pathology. Some investigations were performed: kidney and liver function, electrolytes and proteins, and all of them were normal. Hormonal investigations shown elevated serum oestradiol levels (232pg/mL), LH (14UI/L), and FSH (25,2UI/L), 17.OH-progesterone levels were normal. An ovarian ultrasound was performed finding a normal uterus size and morphology (20x10x10mm), normal right ovary and a simple cyst (18mm) in the left ovary. We decided to maintain an expectant attitude. When she was discharged the edema was limited to genital area. She had monthly follow-up observing a progressive disappearance of the edema.

Conclusions: A pathognomonic sign characterizes OSS, which is edema. Ovarian cysts are observed in most of the cases described in the literature. It is convenient to identify this disorder by clinical signs to avoid both performing useless investigations and misdiagnosis. It is also important to know that it does not need treatment.

P3-P348

Significant Penile Growth with Local DHT-gel in an Infant with 17-Beta HSD-Deficiency

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We demonstrate significant penile growth in an infant with 17 beta HSD-deficiency treated with DHT-gel.

Background: The child was born with ambiguous genitalia at full term. Investigations revealed 46,XY karyotype, testosterone and DHT levels were 2,5 nmol/L and <0.1 nmol/L respectively. No female internal genitalia were found. hCG stimulation did not result in an increase in testosterone, but a clinically obvious increase in phallus size. Subsequent genetic analysis confirmed a 17-beta HSD-deficiency. The child was assigned male sex.

Methods: The penis measured 12 mm at 5 days of age. Local treatment with 2,5% DHT-gel, 0,2 ml daily was started and continued for 8 weeks all together, until the age of 4 months.

Results: After 2 months of therapy, the penis had grown to a length of 35 mm and a width of 12 mm.

Conclusions: We conclude that early treatment with locally applied DHT may have a significant effect on penile growth in 17-beta HSD deficiency.

P3-P349

Mother and Baby Diagnosed Noonan Syndrome with Dysmorphic Findings

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Objective: Noonan syndrome; is an autosomal dominant genetic disorder characterized by short stature, low hair line, webbed neck, cubitus valgus, chest wall deformities and congenital heart defects. Here; the patient was admitted to hospital by parents due to undescended testis and finally infant and mother were diagnosed Noonan syndrome.

Case: A 14-month-old male patient was admitted to hospital because of bilateral undescended testis. On physical examination there was growth failure. Body weight 7.5 kg (<3p), height 69 cm (<3p). There were also dysmorphic face, hypertelorism, ptosis, bilateral undescended testis. Cytogenetic chromosome analysis of the case was 46 XY. Ultrasonography and echocardiography were normal. Genetic mutation was reported as Noonan syndrome. The genetic test also sent from the mother on observing similar dysmorphic findings. The diagnosis was again Noonan's syndrome. Orchiopexy-applied case was followed because of growth retardation.

Conclusion: In this study; we showed that dysmorphic findings and undescended testis may be stimulant for the diagnosis of Noonan syndrome in the early period. The mother of the case also was diagnosed as Noonan syndrome interestingly by showing the dominant transition effect.

P3-P350

5-Alpha Reductase Type 2 Deficiency Among Iranian Patients with Ambiguous Genitalia

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5-alpha reductase converts testosterone to dihydrotestostrone. SRD5A2 mutation leading to deficiency of 5-alpha reductase causes a disorder of 46,XY sex development named 5-alpha reductase type 2 deficiency. Due to deficit of this enzyme, female external genitalia is common sign of disease in 46,XY individuals. SRD5A2 mutations have been reported in different ethnicities. Here, mutations of this gene are reported in Iranian subjects.

Affected individuals were subjected to study in this survey. Clinical data were documented. Genetic analyses including karyotype and direct DNA sequencing of the exons and flanking regions of SRD5A2 were performed for the patients. Bioinformatics analyses were also done for unknown variants.

Ambiguous genitalia was confirmed by pediatric endocrinologist. Three known pathogenic variants, c.145G>A, c.271T>C and c.476T>G and one novel variant, c.272A>G, were found to cause disorder. In silico analysis predicted pathogenicity of the variants.

SRD5A2 may be a common cause of ambiguous genitalia in our country. Bioinformatics tools could provide more information about pathogenicity of SRD5A2 mutations.

P3-P351

A Case Report of Spironolactone Treatment for Becker's Nevus Associated Ipsilateral Breast Hypoplasia

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Introduction: Becker's nevus (BN) is an epidermal cutaneous hamartoma and can be the presenting feature of a larger syndrome that includes muscle, dermatological, and skeletal findings. Although Becker's nevi are more common among adolescent males, one specific, but rare, association in females is ispilateral breast hypoplasia hypothesized to be secondary to increased concentration of androgen receptors within the nevus.

Case Report: Patient is an 11 year-old female with a history of precocious puberty (menarche at age 9 9/12, thelarche approximately at age 8), who presented with left ipsilateral breast hypoplasia and overlying BN. Physical examination showed a moderately hyperpigmented patch without hypertrichosis or acne encompassing the lower half of the left breast. Right breast was 11 cm, glandular breast tissue while left breast was 8 cm and primarily underlying muscles. Normal female external genitalia were present (Tanner 4). Breast ultrasound showed no left breast tissue, but intact chest wall musculature. Patient was started on spironolactone 50 mg daily, dose was increased to 100 mg daily 3 months later. Breasts size after 3 months measured 13 cm on the right and 9 cm on the left. Unfortunately, 4 months post-treatment she developed spironolactone induced hypermenorrhea, thus the dose was gradually reduced to 75 mg and finally 50 mg daily by 6 months with resolution of hypermenorrhea. At 6 months post treatment, breasts re-measured 16 cm on the right and 12 cm on the left. A repeat ultrasound 10 months post-treatment confirmed interval development of left breast tissue, albeit minor.

Discussion: Recently, the relationship between androgen receptors within the BN and its association with ipsilateral breast hypoplasia has gained substantial attention given the role for medical management. The presence of androgen receptors was first reported in 1984 where a punch biopsy from a BN in the right pectoral region showed androgen receptor levels comparable to those in genital skin. More recently, staining with androgen receptor antibodies showed specificity for dermal fibroblasts within the BN. Thus, spironolactone, due to its anti-androgenic properties, can be tried in the management of BN associated ipsilateral breast hypoplasia. Our literature search yielded two similar reports of pubertal females (ages 11 and 17 years-old) who were treated with spironolactone. We also report the confirmatory post treatment imaging findings.

Conclusion: Clinicians should be aware that spironolactone presents a novel use in the treatment and de novo growth of hypoplastic breast tissue secondary to Becker's nevus.

P3-P352

New Mutation in 5-Alpha-Redoctase:a Five-month-Old Infant with a Karyotype of 46 XY

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5-alpha-reductase is an enzyme for converting testosterone to dehydrotestestrone (DHT). A five-month-old infant with a karyotype of 46 xy and female genitalia referred to endocrinology clinic. Regarding the presence of Down syndrome in the family medical history, her mother had amniocentesis during pregnancy. The amniocentesis mentioned xy karyotype. However, repeated ultrasounds mentioned female genitalia. After birth, at 5 months, a first ultrasound mentioned no testis but second ultrasound confirmed the existence of testis

No ovary and uterine was noted and there was a pseudovagina. Regarding the lack of electrolyte imbalance and definite female genitalia during first 5 months, less probably it seemed that patient had congenital adrenal hyperplasia. Therefore, based on function and receptor of testosterone, 46 xy DSD was noted for this patient. To assess the androgen insensitivity by 17 ketosteroidase and 5 alfa redoctase, Hcg test with three dosages was performed. Then, to confirm the result, a genetic and molecular study was performed and to the best of our knowledge, results showed a new mutation in PLLE159 ARG variant in the SRD5A2 gene which has ot been published in our knowledge. in silica analysis predicts the variant in disease causingthe protein structure/ function.

P3-P353

A Novel Compound Heterozygous Mutation in *CYP19A1* Resulting in Aromatase Deficiency with Normal Gonadotropin Levels and Ovarian Tissue

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Introduction: Aromatase deficiency leading to virilization in mother and female fetuses during pregnancy is a rare disease. It is characterized by impaired estrogen production, increased go-

Table 1. (for Abstract no P3-P353)

	16. days	4. months	6. months	8. months	11. months	17. months
FSH (mIU/mL)	6.4	7.02	36.3	18.7	27.9	75.1
LH (mIU/mL)	0.53	0.97	4.36	1.27	0.77	15.64
Estradiol (pg/mL)	5.0	<20	<20	<20	<20	<20
Total testosterone (ng/dL)	78	<10	<10	-	-	-

nadotropins, and ovarian cysts. Herein, we report a clinical phenotype of the virilized female due to a novel compound heterozygous mutation in *CYP19A1*.

Case report: A 4-month-old girl was referred due to cliteromegaly. Her mother had developed acne, hair loss, voice change, and hirsutism during pregnancy. She was born with a birthweight of 2710 gr at the 35th week of gestation. Her clitoris size had regressed after birth. The parents were no relatives. The physical examination revealed that her weight was 6.8 kg (0.36 SDS), length was 64 cm (0.48 SDS), a clitoral length of 1 cm, and posteriorly fused labia minora. Initial evaluations excluded congenital adrenal hyperplasia. Ultrasonography revealed a normal uterus and but no ovarian tissue. Gonadotropin levels were normal at the time of admission but increased by the age of 6 months (Table 1). Karyotype was identified as 46, XX and SRY was negative. The laparoscopic evaluation showed normal uterus and ovaries. The biopsy specimens from both gonads were histologically consistent with ovarian tissue and the karyotype analysis of this specimens revealed 46,XX. The diagnosis of aromatase deficiency was suspected and a previously unidentified compound heterozygote mutation in *CYP19A1* [IVS10 + 1 G> A; p.R115Q (c.344 G> A)] was found. The parents were carriers. The *in silico* analyzes categorized the variant to be pathogenic. During the follow-up, the fusion at the posterior of the labium minus was surgically corrected and no ovarian cyst was observed with pelvic ultrasonography until now.

Conclusions: Aromatase deficiency should also be considered even if the initial FSH and LH levels are normal and ovarian cysts are lacking.

P3-P354

Emblematic Case CAH, Obliges to Consider an Adequate Civil Gonadal Recognition – REGOCI, and Neonatal Screening

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Introduction: The National Registry of Civil Status through circular 33 of February 24, 2015 instructed the guidelines for the allocation of a sex through an inscription on the Civil Registry of Birth for intersexual minors.

Objective: To create clinical and medical awareness on the importance of making an accurate diagnosis of Congenital Adrenal Hyperplasia CAH in order to avoid adverse effects due the omission of the due diligence by violating of the pro-childhood rule.

Methodology: If there is any clinical suspicion on patients with congenital adrenal hyperplasia, it is important to take into account the neonatal screening for 17 hydroxyprogesterone accompanied by an adequate recognition of genital configuration on the newborn. This ensures compliance with the provisions of the aforementioned circular.

Analysis: The absence of an adequate civil gonadal recognition generated the sanction of Circular 33 of February 24, 2015. This demonstrates that CAH demands and active, objective and a solidarity responsibility from the entire medical community.

Results: The State authorized an additional intersexual inscription to the masculine or feminine gender for patients with CAH or similar.

Conclusions: Socialize the importance of teaching the clinical diagnosis in order to perform adequate gonadal recognition as well as the urgent need to legislate the neonatal screening for 17 hydroxyprogesterone in cases related with CAH.

Avoid adverse effects such as death, low stature, precocious puberty, mental deterioration and gender dysphoria in CAH cases where the patients are annotated in the sex not corresponding to their karyotype.

References

R., A., Igancio, J., C., M., E.,. . . E. (2017, August 01). Recomendaciones para el diagnóstico y tratamiento de pacientes con formas clásicas de hiperplasia suprarrenal congénita por déficit de 21-hidroxilasa. Retrieved March, 2018, from http://www.analesdepediatria.org/en/recomendaciones-el-diagnostico-tratamiento-pacientes/articulo/S1695403316303393/(n.d.). Retrieved March, 2018, from https://www.infobioquimica.com/wrapper/CDInterpretacion/te/bc/004.htm

Colombia, normas. Circular 33 de 24 de febrero de 2015 expedida por Director Nacional de Registro Civil de la Registraduría del Estado Civil de Colombia.

P3-P355

The Republic of Colombia Has a Constitutional Jurisprudential Precedent Identified as T622 of 2014, This Sentence Reaffirms the Importance of the Accurate Diagnosis of *Intersexual* Patients and Updates How the State Looks at Them

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Summary: The Republic of Colombia has a constitutional jurisprudential precedent identified as T622 of 2014 [1], this sentence reaffirms the importance of the *accurate diagnosis of INTERSEXUAL patients* and updates how the state looks at them [2-4].

Cause: The Colombian Society of Urology published in May 1993; *A Modern Approach to Sexual Ambiguity Syndromes* which discuses sexual differentiation and sexual disorders associated with sexual development to determine a binary gender with surgical reconstruction.

Objective: Gather the members of ACEP (Colombian Association for Pediatric Endocrinology) to clarify, update and create an approach of human sexuality from a *biosociocultural* perspective on genito-urinary normoconficuration and expose genotypic effects from the sexual differentiation process of conception, gestation and embryo inside the uterus. However, it only starts to exist in the legal system once its separated from the umbilical cord and takes it first breath with complete *autonomy*. All of this in regard to the civil legislation of the Republic of Colombia.

Materials: T-622 of 2014 constitutional court of colombia.

Conclusions: *RECOGNIZE* the safeguarding of all the fundamental rights affecting the patients' sexual identity, noble life, health, human diagnostics, sexual and reproductive rights in favor of the pro-child rule (*Pro-infancia*). *PROTEC* the right to privacy. *DEMAND* to both public and private health insurance institutions to inform, educate and raise awareness of all consequences regarding genital readjustment surgery and sex allocation treatments. All with informed consent of the patient and his parents about the final decision with an interdisciplinary team present for any assistance. *RESTRUCTURE* the official protocols for the management in health institutions regarding patients' that desire sexual readaptation with a leading medical crew from ACEP.

References

1 http://www.corteconstitucional.gov.co/relatoria/2014/t-622-14.htm
2 http://revistas.urosario.edu.co/index.php/sociojuridicos/article/view/1515
3 S. Chahín; Paediatric Endocrinologist; Bogotá, Colombia
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P3-P356

Paediatric Doctors' Experience and Knowledge of the Initial Management of Neonatal Ambiguous Genitalia

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Introduction: Neonatal ambiguous genitalia can herald sensitive, time-critical, and life-threatening diagnoses and thus paediatric doctors must be competent in their management. However, ambiguous genitalia are rare, limiting clinical exposure. We assessed paediatric doctors' experience of, knowledge of, and confidence in managing this condition.

Methods: A questionnaire was circulated to paediatric doctors at two tertiary and four secondary level paediatric teaching hospitals. It established doctors' clinical experience of ambiguous genitalia and used a Likert scale to assess doctors' confidence in their management (1=I am very unconfident, 3=I am reasonably confident, 5=I am very confident). A clinical vignette followed by multiple choice questions (MCQ) assessed knowledge of initial diagnostic tests and differential diagnoses. A response was deemed correct if a right answer was selected or if a wrong answer was not selected. An educational module was then designed.

Results: Response rate was 100% (n=42; 26.2% male; 71.4% (n=30) junior trainees, 14.3% (n=6) senior, 14.3% (n=6) consultants). 61.9% (n=26) worked in tertiary centres. 42.9% (n=18) had never seen ambiguous genitalia. Junior trainees had seen fewer cases (M=0.9, SD 1.4) than senior (M=2.4, SD=2.2), (t(14.7)=-2.2,p=0.04). 33.3% (n=14) had helped manage a case. 21.4% (n=9) had been the first to review an infant with ambiguous genitalia, and 11.9% (n=5) the first to inform parents of the finding. 16.7% (n=7) had ordered initial investigations. On 1-5 Likert scoring, doctors were not confident in the overall management of ambiguous genitalia (M=2.5), in discussing findings with parents (M=2.9), in examining ambiguous genitalia (M=2.9), or in employing the Prader (M=1.5) or External Masculinisation Scores (M=1.4). Seniority, number of cases seen, and tertiary experience did not significantly influence mean confidence levels. MCQ responses were correct a mean of 64.0% of the time. While correct initial diagnostic tests were identified a mean of 85.2% of the time, 90.5% of participants also selected at least one incorrect response. While correct differential diagnoses were identified a mean of 70.8% of the time, 62.0% of participants selected incorrect responses. Seniority, number of cases seen, and tertiary experience did not significantly influence performance.

Discussion: Paediatric doctors, regardless of seniority, have insufficient knowledge and confidence to manage neonatal ambiguous genitalia. This reflects limited clinical exposure. As we cannot rely on experiential learning, paediatric doctors must receive targeted educational sessions on the management of ambiguous genitalia. We have designed an educational module in our centre, and will re-administer our questionnaire on its completion.

P3-P357

A Case of Transverse Testicular Ectopia with Persistant Müllerian Duct Syndrome:a Novel *Amh* Gene Mutation

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Background: The concurrence of transverse testicular ectopia (TTE) with persistent müllerian duct syndrome (PMDS) is extremely rare. Here, we report a case of TTE with PMDS in a 7-month-old male infant presenting with inguinal hernia and a novel homozygous mutation in the *AMH* gene.

Case Report: A 7-month-old male infant presented to pediatric surgery department with an inguinal hernia on the left side and bilateral undescended testis. During left herniotomy, tissues suggestive of a rudimentary uterus with fallopian tubes and testes like structures on both sides of uterus were observed. A biopsy of the gonads and structure located midline to the gonads was performed and the patient was referred to pediatric endocrinology department. At physical examination, the testes were not palpable and the phallus was 4x1.2 cm in length. Parents were first-degree relatives. The laboratory examination revealed normal gonadotropin levels for his age (FSH: 0.92 IU/ L, LH: 1.17 IU/L, total testosteron 0.025 ng/mL). Serum anti-müllerian hormone level was <0.02 ng/mL (N: 24.2-275.4 ng/mL). Karyotype was XY. *AMH* gene sequence analysis performed with a preliminary diagnosis of *AMH* gene mutation revealed a previously undescribed homozygous IVS2-3C>G (c.556-3C>G) mutation.

Conclusion: If patients had a unilateral inguinal hernia and contralateral cryptorchidism, TTE with PMDS should be considered. The mutation detected in the *AMH* gene is associated with PMDS and its phenotype is variable.

P3-P358

Argentinean First Experience with Transgender Children and Youths

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Introduction: During last years there is an increasing number of referrals because of gender incongruence worldwide. In Argentina, in 2012, a gender identity law was sanctioned, stablishing the right of gender reassignment during childhood, adolescence, youth and adulthood, without the need of previous medical and/or mental health evaluation. This was followed by a great number of referrals. There is scarce literature regarding longterm outcome in transgender persons who started treatment at early Tanner stages (2-3)

Objective: To describe clinical, biochemical and epidemiological features of the first pediatric transgender cohort in a pediatric hospital of Argentina.

Methods: Epidemiological characteristics, such as number of referrals/year, age, desired gender, age at first manifestations; anthropometric data (height, weight, target height, BMI); biochemistry (gonadal and adrenal function, metabolic and bone profile); age at menarchy in transgender boys and the presence of comorbidities was evaluated.

Results: 21 patients were evaluated (6 transgender girls and 15 transgender boys), with a ratio M:F 2,5 to 1. The number of referrals/year was: 2014:1/2015:2/2016:7 and 2017:11. Median age at referral was 14,23 ± 2,16, without differences between sex (range 9,25-16,91). First manifestations were detected during infancy in 10 patients and during puberty in 9 patients (in 2 patients it was not possible to determine age at first manifestation because of mental retardation). There were no differences regarding height, target height or final height in SDS, nor differences regarding biochemical study of gonadal and/or adrenal function. Median age of GnRH analog treatment initiation was 13,7 years and only one patient started gender reinforcement treatment with testosterone at 17,8 years of age. Regarding comorbidities 4 patients have obesity (2 with hyperinsulinism), 1 has type 1 diabetes, 2 have personality disorder and mental retardation, 1 central precocious puberty, 1 celiac disease, 1 minor thalassemia, 1 tricho-rhino-phalangeal syndrome with chronic renal failure, 1 acute myeloblastic leukemia and 1 patient presented urticarial after first triptorelin dose.

Conclusion: During 3 years, 21 transgender children and adolescence were evaluated, and no significant alterations were seen regarding height, weight, gonadal and adrenal function and metabolic profile. Transgender in pediatric endocrinology is seen every year with more frequency, so it is necessary to keep studying this growing population, specially those who start puberty suppression treatment at early Tanner stage (2-3). More studies are needed with focus in the impact of treatment in quality of life.

P3-P359

Long-term Follow-up in a Chinese Child with Lipoid Congenital Adrenal Hyperplasia Due to STAR Mutation

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Congenital lipoid adrenal hyperplasia (CLAH) is the most severe and extremely rare form of congenital adrenal hyperplasia (CAH). The typical features include 46, XY disorder of sex development (DSD), early-onset adrenal crisis and enlarged adrenal with fatty accumulation. We reported a case of congenital lipoid adrenal hyperplasia (CLAH) caused by steroidogenic acute regulatory protein (STAR) gene mutation. The patient had typical early-onset adrenal crisis at the age of 2 months. She had normal-appearing female genitalia with karyotype of 46, XY. Her serum cortisol and adrenal steroids levels were always nearly undetectable along with extremely high ACTH. Genetic analysis revealed compound heterozygous mutations for c. 229C>T in exon 3 and c. 722C>T in exon 7 of the STAR gene. The former one was previously only detected in two other Chinese patients of CLAH. It changed glutamine 258 to terminator codon and the synthesis of STAR protein is terminated much earlier on the crucial carboxyl-terminal. This seemed to be a classical case of CLAH except that the patient's adrenal glands were very small on CT scanning. It should be so far the second reported case of CLAH with small adrenals. This patient had been followed up for 15 years from the 2nd month after birth. We showed the first growth curve of this kind of patient. Her height was around female average before the age of 10 years and fallen to -1SD thereafter. Her bone age was similar to her chronological age from the age of 4 years to 15 years. In conclusion, this was a classical case of CLAH but with exceptional small adrenals. After a 15-year follow-up, we presented the first growth curve of this kind of patient.

P3-P360

46, XY Gonadal Dysgenesis Accompanied by Neuropathy Caused by a *DHH* Mutation

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Objectives: To summarize the clinical manifestations of a patient of 46,XY partial gonadal dysgenesis (PGD) accompanied by neuropathy. This is the first reported case of DHH mutation from China.

Methods: We retrospectively reviewed the case and summarized the clinical history, physical examinations, laboratory and genetics tests, electromyography, ultrasound, surgical exploration and histopathology results.

Results: The 14.3-year-old child raised as female came to our hospital because ultrasound examination revealed the absence of ovaries and uterus 2 years ago. She also complained of muscle cramps of the feet and hands. The karyotype result was 46, XY. SRY gene was positive. Bilateral gonads located in the abdominal cavity detected by ultrasound. Vaginoscopy revealed a blind-ending vagina. Laparoscopy detected no uterine. Pathology of bilateral gonads revealed dysgenetic testes which was consistent with PGD. The gonads confirmed by negative reaction with OCT3/4. Electrophysiology of peripheral nerves showed that the motor and sensory nerve conduction velocities were slightly slowed down. The genetic examination revealed a homozygous mutation (p. Cys343Arg) in exon 3 of *DHH* gene in the child. The same heterozygous mutations were found in the patient's parents.

Conclusions: This is the first reported case of 46, XY partial gonadal dysgenesis accompanied by neuropathy caused by a *DHH* homozygous missense mutation [c.1027T>C (p. Cys343Arg>] from China. And literatures were reviewed.

P3-P400

Clinical and Molecular Characterization of One *NR5A1* Gene Mutation Found in a Patient with 46, XY DSD

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Introduction: Steroidogenic factor-1 (SF1), encoded by the *NR5A1* gene, regulates several genes involved in male sexual determination, such as *SOX9* and *AMH*, cholesterol mobilization and synthesis of a number of steroidogenic enzymes, like 3βHSD, and androgen biosynthesis, like *INSL3*. Mutations in *NR5A1* have been associated to a broad phenotypic spectrum in 46, XY subjects, including pure gonadal dysgenesis, infertility, anorchia or hypospadias, often in conjunction with normal adrenal function

In the present study, we describe a patient with extreme hypospadias, micropenis and bifid scrotum.

Patients and Methods: Male patient with 46, XY karyotype presenting at birth scrotal hypospadias, micropenis, undescended testes and bifid scrotum. Biochemical analysis revealed LH: 2,5 mU/ml, FSH: 3,7 mU/ml, Testosterone: 67,5 ng/ml, DHT: 1,7 ng/ml, DHEA-S: 400 ng/ml and Cortisol: 10,4 mcg/dl. Abdominal ultrasound without findings. Good response of the penis to treatment with testosterone.

Maternal uncle presented with scrotal hypospadias at birth. Apparently there is no additional family background of interest.

Genomic DNA was isolated from peripheral blood leukocytes and genetic characterization was performed using a targeted gene panel by NGS. PCR and Sanger sequencing was used for variant confirmation and to test parents and affected family members to establish the mode of inheritance.

Results: DSD targeted gene panel sequencing identified the heterozygous *NR5A1* c.250C>T; p. Arg84Cys mutation. This mutation has been previously reported and associated with gonadal dysgenesis by Reuter Al et al (2007). Functional studies demon-

strated that p. Arg84Cys diminishes DNA binding site affinity and transcriptional activity.

Mother presenting with precocious puberty, maternal aunt with menstrual disorders and uncle with scrotal hypospadias presented the variation in heterozygosis, as well as the healthy grandfather.

Conclussions: Our results agree with previous studies in which the complex penetrance, expressivity and inheritance of the alterations found in the *NR5A1* gene, give rise depending on the mutation to phenotypes in 46 XY patients that encompass from pure gonadal dysgenesis to completely asymptomatic carriers, whereas in 46 XX patients lead to mild forms such as primary ovarian failure.

P3-P408

Genetic Testing by SNP Array Analysis in a Group of Romanian Patients with Disorders of Sexual Development

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Context: Disorders of sexual development (DSD) are those medical conditions with abnormalities of sex chromosomes, gonads, internal ducts or external genitalia. Sex determination and differentiation is a process under genetic control, only partially explained. Genetic testing and identification of a cause in DSD is essential for a precise diagnosis and correct management and also has an important psychosocial motivation.

Aim: To make a genomic analyse, using SNP array technology, of a group of Romanian patients with DSD, with the aim to identify the CNV (*copy number variants*).

Material and method: We analysed 17 patients diagnosed in Clinical Emergency Hospital for Children, Cluj-Napoca, for each of them being made the clinical exam, hormonal/biochemical investigations, anatomic evaluation, by ultrasounds, genitography, IRM or biopsy, caryotype and SRY, analysis of CYP21A2 gene by stripassay (if elevated 17OH-progesterone) or other individualised analysis depending on clinical picture. For those patients without an obvious cause for DSD at clinical or paraclinical exam was done SNP array analysis using Infinium OmniExpress-24 BeadChip array (Illumina), the image acquisition being made by iScan System (Illumina). The data analysis was made using Genome Studio 3.0 and the CNV interpretation was made using: UCSC, DGV, Decipher, and OMIM databases.

Results and discussions: We identified 4/17 patients (23%) with pathogenic CNV or VOUS (variants of unknown significance). These CNV were: 10q26.3 duplication (121kb) in 2 patients, 16p11.2 duplication (597kb) and 6p21.33 homozygous deletion (1kb). Two CNV were considered pathogenic and two CNV were considered VOUS. Three patients presented a syndromic DSD and one an isolated DSD. In our country is the first group of DSD patients for whom we tried to go further with genetic testing, using a genomic approach. This genetic test permit to clarify the diagnosis in some cases and we hope to go further for unsolved cases, using the massively parallel sequencing. However, SNP array could be an analysis which can be useful in etiological diagnosis, especially in syndromic DSD.

P3-P409

A Novel Gene Mutation and Atypical Clinical Phenotype of Kallmann Syndrome

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Case: The case is a 19-year-old woman. Her chief complaint is primary amenorrhea.

She was born at 40 weeks of gestational age. Birth weight was 2456 g and birth height was 47 cm and she was admitted to the hospital due to abnormality of facial formation, post-nasal cavity closure and respiratory disorders. Her motor development was delayed (standing at 3 years old, walking at 5 years old) and she underwent plastic surgery for 6 times. On admission her height was 151.6 cm (-1.2 SD), her weight was 36.9 kg, and her Body Mass Index (BMI) was 16.1. She had no sense of smell, had left and right facial differences, mild hirsutism, mild valgus elbow and high arched palate. Tanner stage was Breasts 1, Pubic hair 1. LH, FSH and LHRH stimulation tests showed pre-pubertal states. Karyotype was 46,XX. Abdominal ultrasonography showed small uterus but no ovaries. There was a renal cyst about 20 mm in the left lower Kidney. The bone mineral density of the lumbar was as low as 0.488 g/cm2 and her bone age was 11 years old. Head MRI showed pituitary gland hypoplasia, and the bone defect of the Turkish saddle. We also found hypoplasia of hard palate and nasal septum. Olfactory testing showed no sense of smell. Genetic testing showed missense mutation of c.1979 G> A, p.Arg 660 Gln (chr 3: 57131752 C> T) heterozygous in exon 12, IL17RD. The same mutation was found in her father.

Discussion: The gene mutation in this case is a novel mutation. According to the previous reports IL17RD mutation is a autosomal dominant mutation with low or no sense of smell, partial deafness, tooth abnormality and decreased bone mineral density. Many of the patients first aware the delay of puberty with gonadotropic hypogonadism. In this case, not only the teeth but also the facial dysplasia was recognized, as well as renal cysts and hypoplasia of the pituitary. Since her father showed no symptoms, this could be explained by phenotypic variation and we need to investigate further.

Thyroid P1

P1-P248

Early Determinants of Thyroid Function Outcome in Children with Congenital Hypothyroidism and a Normally Located Thyroid Gland: A Regional Cohort Study

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Background: An increase in the incidence of congenital hypothyroidism (CH) with a normally located gland has been reported worldwide. Affected individuals display transient or permanent CH during follow-up in childhood. We aimed to determine the prevalence of transient CH and to assess the possibility of distinguishing between transient and permanent CH in early infancy.

Methods: This observational cohort study included all patients identified by systematic neonatal screening for CH in the northern Parisian region between 2002 and 2012 and treated for CH with a normally sited gland. A standardized data collection form was completed prospectively at diagnosis. Patients were classified, during the follow-up, as having transient or permanent CH.

Results: Of the 92 patients initially treated for CH with a normally located gland during the neonatal period, 49 (54%) had a transient form of CH after the cessation of levothyroxine treatment at 1.5 (0.6 - 3.2) years of age. Multivariate analysis revealed that transient CH was associated with a lower likelihood of having a family history of CH ($p = 0.03$) and a lower levothyroxine dose at six months of age ($p = 0.03$) than permanent CH. Sex, ethnicity, neonatal problems, such as prematurity, being small for gestational age and/or neonatal distress, iodine status, coexisting malformations, initial CH severity and thyroid morphology at diagnosis had no effect. Receiver operating characteristics curve analysis showed that a cutoff of 3.2 µg/kg/d for levothyroxine dose requirement at six months of age had a sensitivity of 71% and a specificity of 79% for predicting transient CH, with values below this threshold considered predictive of transient CH.

Conclusion: In patients with CH and a normally sited gland, these findings highlight the need to evaluate levothyroxine dose requirement early, at six months of age, particularly in patients with no family history of CH, for early identification of the approximately 50% of patients for whom treatment should be stopped. Parents should be made aware, when they are informed of their child's diagnosis during the neonatal period, that subsequent reinvestigation will be necessary to determine whether the CH is persistent during childhood. However, the natural course of thyroid function of patients with transient CH during early childhood remains to be determined, and it is unknown whether these patients need to resume L-T4 treatment later in life during times of increased thyroxine need due to increases in metabolism, such as puberty and pregnancy.

P1-P249

Neonatal Screening for Congenital Hypothyroidism: Age-dependent Reference Intervals for Dried Blood Spot TSH in the Neonatal Period

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Background: National and international guidelines recommend thyrotropin (TSH) determination as the most sensitive test for detecting primary congenital hypothyroidism (CH) in newborn screening programs. A strategy of a second screening at 2 weeks of age, or 2 weeks after the first screening was carried out, is also recommended in preterm, LBW and VLBW neonates, twins, neonates admitted in NICU, and babies with specimen collection within the first 24 hours of life [1-3]. However specific recommendations on the TSH cut off at 2 weeks of age are lacking, as well as specific reference intervals for TSH at this age. The aim of this study was to determine TSH reference intervals at 2-4 and 14-16 days of age in healthy term newborns.

Methods: Dried blood spot (DBS) samples were obtained from 70,962 healthy term newborns ($\geq$37 week Gestational Age) residing in Lombardia region and screened in 2015 at the Lombardia region Reference Laboratory for Neonatal Screening. A time resolved-fluoroimmunoassay (TR-FIA) method was used to detect TSH on DBS at the first (2-4 days) and second screening (14-16 days). STATA 11.0 was used to analyze 2.5th, 50.0th, 97.5th, 99.0th, 99.5th percentiles for DBS-TSH.

Results: No significant difference was found between the 2.5th percentile of DBS-TSH at 2-4 days (0.59 mU/L; 95% CI: 0.59-0.60) and the same percentile at 14-16 days (0.58 mU/L; 95% CI: 0.56-0.59); whereas the 50.0th percentile was significantly higher at 2-4 days (2.06 mU/L; 95% CI: 2.05-2.07) than at 14-16 days of life (1.52 mU/L; 95% CI: 1.51-1.54), as well as the 97.5th percentile (6.24 mU/L; 95% CI: 6.19-6.29 *vs* 4.04 mU/L; 95% CI: 3.91-4.21), the 99.0th percentile (7.60 mU/L; 95% CI:7.49-7.73 *vs* 5.10 mU/L; 95% CI: 4.80-5.64), and the 99.5th percentile (8.80 mU/L; 95% CI: 8.65-9.00 *vs* 6.64 mU/L; 95% CI: 6.11-7.55).

Conclusions: Our data showed that marked changes occur in concentrations of TSH during the first 2 weeks of life with DBS-

TSH concentrations significantly higher at 2-4 days than at 14-16 days of life. These results have implications for selection of age-related cut off values of DBS-TSH at screening (2-4 days) and re-screening (14-16 days) to correctly identify newborns at risk for CH.

References

1. Leger J et al. J Clin Endocrinol Metab 2014, 99:363-384
2. Cassio A et al J Endocrinol Invest 2013, 36: 195-203
3. CLSI document I/LA31-A, Clinical and Laboratory Standards Institute; 2009

P1-P250

Thyroid Scintigraphy in the Diagnosis of Congenital Hypothyroidism

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Background: Identification of Congenital Hypothyroidism (CH) is an essential part of Newborn Bloodspot Screening (NBS) in the UK. NBS for CH relies on Blood Spot (BS) Thyroid Stimulating Hormone (TSH) measurement in newborns on day 5 of life. Diagnostic confirmation of a screen positive result requires measurement of plasma/serum free thyroxine (fT4) and TSH but technetium thyroid scanning is not mandatory. Technetium-99m scintigraphy can be used to define size and location of the thyroid gland but is not available in all screening centres. We aimed to investigate the utility of scintigraphy to establish the cause of CH and impact on clinical management.

Methods: Scintigraphy outcomes of newborns referred to a regional NBS centre between 2007-2017 on the basis of initial screening BS TSH>20 mU/L or >8 mU/L in the second/subsequent sample following a borderline result were retrospectively reviewed in the following categories –normal/large gland (dyshormonogenesis), small/absent (dysplasia) and abnormal position (ectopia). Scintigraphy was tested for correlation with BS TSH screening level and venous plasma TSH and free thyroxine (fT4) levels ascertained during diagnostic workup.

Results: 418 newborns were referred for possible CH from 534,783 newborns screened by NBS, of whom 342 were treated with levothyroxine. Based on scintigraphy appearances (n=293) the largest diagnostic CH group was dyshormonogenesis (n=134, 45.7%) followed by ectopia (n=80, 27.3%) and dysplasia (n=79, 27.0%). Median (interquartile range) BS TSH (mU/L) was lower in dyshormonogenesis [23.5(28.0)] than in ectopia [106.0(147.0)] and dysplasia [172.0(183.0)] [p<0.001 for difference between groups] but was non-discriminatory between dysplasia and ectopia [p=0.12]. Plasma TSH showed similar differences. Conversely, fT4 levels (pmol/L) were higher in dyshormonogenesis [12.0(9.5)] than in ectopia [9.6(8.9)] and dysplasia [4.0(11.1)] [p<0.001]. Corresponding initial levothyroxine treatment doses (micrograms/day) were 25.0(12.5), 37.5(12.5) and 37.5(25.0) [p<0.001] respectively, consistent with the severity of thyroid dysfunction in each group. Levothyroxine dose correlated independently with fT4 levels in analysis of covariance for either dyshormonogenesis or ectopia [p=0.009, R^2=0.40 for model], but not for dysplasia or ectopia [p=0.22, R^2=0.38] suggesting diagnosis-specific influence of scintigraphy on initial treatment dose.

Conclusions: Thyroid scintigraphy demonstrates dyshormonogenesis as the most frequent form of CH. Scintigraphy identifies and locates ectopia which might otherwise be incorrectly classified as dysplasia. Accurate CH classification is crucial for initial levothyroxine dosage. The diagnoses of dyshormonogenesis and ectopia are likely to influence long-term clinical management of CH.

P1-P251

Congenital Hypothyroidism (CH) with Delayed TSH Elevation: The Importance of the Second-screening Strategy and the Evolution of CH in Preterm Infants

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Objectives: Preterm infants often present CH characterized by delayed TSH elevation. We describe the clinical and biochemical features and the evolution of CH in preterm infants with delayed TSH elevation, detected by the second screening for CH.

Material and Methods: All preterm infants born between 2007-2014 negative to the first screening (b-TSH<10mcU/ml) at 2-5days of life and positive to the second screening at 12-33days (b-TSH≥5mcU/ml), diagnosed with CH and followed-up in a single tertiary Centre of paediatric endocrinology were included. At 2-3years, patients with gland in situ (GIS) underwent a clinical re-evaluation including thyroid function testing (TFT) after LT4 therapy withdrawal. According to the result of the TFT after the withdrawal of therapy, patients were divided into 3 groups: permanent CH (TSH persistently>10mcU/ml), persistent hyperthyrotropinemia (HT) (TSH 5-10mcU/ml) and transient CH (TSH<5mcU/ml).

Results: 46 preterm patients were included in the study (26 males, 20 females). Four patients were extremely preterm (<28weeks), 9 patients were very preterm (28-31weeks), 33 were moderate-to-late preterm (32-36weeks). The sample included 14 twins, 7 patients who were born small for gestational age, 10 cases of syndromes/malformations, 7 cases born after assisted reproduction techniques. Four patients underwent surgery in the neonatal period. At diagnosis, serum TSH was between 10-20mcU/ml in 25 cases, 20-40mcU/ml in 7 cases, 40-100mcU/ml in 6 cases, and >100 mcU/ml in 8 cases (7/8 with very low FT4, range 0,1-0,44ng/dl). At diagnosis, the neck ultrasound showed 1 ectopy, 1 hemiagenesis,

and 44 cases of GIS. Treatment was started at an average age of 40 days (median 32, range 15-89). 37/44 patients with GIS were reevaluated. At reevaluation, 4 patients had permanent CH (TSH after withdrawal of therapy: range 17,89-24,07mcU/ml) requiring the reintroduction of LT4 (10,8%), 10 had HT (27%), 23 had transient CH (62,2%). The 4 permanent cases with GIS were moderate-to-late preterm, 2/4 were twins and in both cases the other twin (not included in the study) had HT. Moreover, they showed only mild TSH elevation at diagnosis (TSH 14,40-19,77mcU/ml).

Conclusions: We confirmed the usefulness of the second-screening strategy for CH to detect preterm infants who otherwise would not be identified at the first screening. Although preterm infants very often have transient CH, many of them may have severe CH at diagnosis, which requires prompt treatment, and some others may have permanent CH (including thyroid dysgenesis), despite mild TSH elevation at diagnosis.

P1-P252

Morning versus Bedtime Levothyroxine Administration: What Is the Choice of Children?

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Aim: The present study compared the administration of levothyroxine (LT4) before breakfast and bedtime in school children diagnosed with hypothyroidism and analyzed the effects of timing on thyroid functioning and patient satisfaction.

Methods: A total of 163 children with hypothyroidism (125 females and 38 males) between 8 and 18 years of age and taking LT4 for at least three months were enrolled in the study. The timing of administration of the drug of all subjects was shifted to bedtime. The levels of thyroid hormone and blood lipid, anthropometric measurements, Pediatric Quality of Life Inventory, Morisky Medication Adherence Scale, and Hypothyroidism Symptoms scores were analyzed and compared at the beginning of the study and three months later after the shift in the timing of drug administration.

Results: There was no difference between the bedtime and morning regimens of LT4 with respect to thyroid hormone levels, quality of life, drug adherence, and symptoms of hypothyroidism. At the end of the study, 45 of 70 new-onset treated subjects preferred the bedtime regimen. Also, drug adherence was found to be better in these patients.

Conclusion: We found no difference between the bedtime and morning regimens in both new-onset and long-standing treated patients. In naive patients, consideration of patient's preference for timing of drug administration may increase their adherence to medication. Therefore, we suggest that choice of drug administration timing should be based on the preference of patients.

P1-P253

Long Term Comparison Between Liquid and Tablet Formulations of L-Thyroxine (L-T4) in the Treatment of Congenital Hypothyroidism (CH)

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Introduction: Few studies have been published comparing the liquid and tablet formulations of L-T4 in pediatric patients, with a short follow-up period. Both formulations seemed to produce a rapid normalization of thyroid fuction with a tendency of a greater TSH inhibition in children taking the L-T4 liquid drops. The aim of our study is to compare the long-term effectiveness and saftey of both liquid and tablet L-T4 therapy in CH patients up to 3 years old via a multicenter study.

Methods: 276 children affected with CH identified by neonatal screening were included in this study: 129 treated with liquid formulation (Group A) and 147 treated with tablets (Group B). Birth data, TSH and FT4 values and L-T4 dose were collected at 15 days, 1-3-6-12-24-36 months. The liquid formulation contains ethanol as an excipient: to further evaluate its influence on childrens' cognitive development, we evaluated the patients' Developmental Quotient (DQ) at 1 and 3 years of age.

Results: There was no significant difference in birth weight and length, gestational age, TSH and FT4 at diagnosis, and etiology of CH between groups A and B. Group A began therapy with a median dose of 11.02 mcg/kg/die (range 3.5 – 15.67) and group B with 11.13 mcg/kg/die (range 4.6 – 15) ($p=0.052$; $\alpha=0.006$). There was no significant difference between L-T4 dose, TSH and FT4 serum levels at 15 days, 1-3-6-12-24-36 months.

The median DQ at 1 and 3 years of age was 101 (range 50 - 135) and 104 (range 88 - 133) in group A, and 108.5 (range 74 - 127) and 110 (range 72 - 125) in group B, without a significant difference between the two groups ($p=0.045$ at 1 year; $p=0.19$ at 3 years; $\alpha=0.025$).

Conclusions: These data confirm that both liquid and tablet formulations are efficient in treating CH and TSH inhibition never occurred when using the liquid formulation.

No negative effects in cognitive development were observed in the patients treated with liquid drops.

P1-P254

Isolated Congenital Central Hypothyroidism due to a Novel Mutation in TSH Beta Subunit Gene

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Objective: Congenital isolated thyrotropin (TSH) deficiency is a rare condition due to autosomal recessive defects in *TSHβ, TBL1X, IGSF1, TRHR* genes. There are a few patients described with *TSHβ* mutations to date. These patients display the typical manifestations of severe untreated congenital hypothyroidism. Most patients are unrecognized, even in newborns screening settings due to unelevated TSH levels, which results in severe growth failure and intellectual disability. We describe a baby boy with isolated congenital central hypothyroidism (ICCH) due to a novel homozygous *TSHβ* gene mutation.

Case: A 53-day-old male was admitted for investigation of severe hypotonia, prolonged jaundice, and constipation which began around 4 weeks of age. Parents were third degree cousins. Following a normal delivery with birth weight of 4230 g (+3.4 SDS), he had been hospitalized for 8 days in a neonatal care unit for hypotonia and transient tachypnea of the newborn. There was no jaundice, umbilical hernia or macroglossia noted in the newborn period. At referral to our clinic, he was 5940 g in weight (+0.9 SDS), 60.5 cm in height (+1.29 SDS), and 40,5 cm (+0,89 SDS) in head circumference. He had severe hypotonia, jaundice, dry skin with, macroglossia, and coarse facial features. Anterior fontanelle was 2x2 cm, and posterior fontanelle was closed. His physical examination was otherwise unremarkable. On laboratory testing, free T4 was < 0.25 (normal range, 0,61-1,12 ng/dl); TSH was, 0.06 μIU/ml (0.34–5.6 μIU/ml).To rule out multiple pituitary hormone deficiencies, additional hormone tests were performed which revealed a spot GH level of 5.8 ng/dl (0-1 ng/ml), IGF-1 33.1 ng/ml (15-189 ng/ml), IGFBP-3 1.53 μg/ml (0.7-3.6 μg/ml), FSH: 2.65 mIU/ml, LH 1.75mIU/ml, total testosterone 0.93 ng/ml and PRL 26 ng/ml. Sufficient cortisol response detected in the low-dose ACTH stimulation test. An MRI of the head and pituitary was unremarkable. He was started on levothyroxine replacement. After 4 weeks of treatment, he was much more alert, active, and feeding better.

Conclusion: We identified a novel homozygous mutation c.217 A>C (p.T73P) of the *TSHβ* gene responsible for a severe isolated TSH deficiency in male infant missed from neonatal screening. Its should be remembered that clinical features of hypothyroidism related to *TSHβ* mutations can be as severe as in cases with primary hypothyroidism.

P1-P255

Patterns of Thyroglobulin Levels in Infants Referred with High TSH on Newborn Screening, Compared with Iodine-Sufficient Healthy Controls

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Background: Thyroglobulin (Tg) is exclusively synthesised by thyroid tissue and a potentially useful aid to diagnosis in congenital hypothyroidism (CH). However, its role has yet to be fully evaluated.

Objective: To examine the sensitivity and specificity of Tg in helping define the etiology of CH.

Patients and methods: Tg was measured in a single laboratory by Immulite 2000 chemiluminescent immunometric assay (CVs 9.8, 5.7 and 5.7% at 1.6, 8.5 and 55 μg/l) in 29 healthy iodine-sufficient babies from Czech Republic (2008-2012), and 80 infants (51 female) referred with TSH elevation on the Scottish screening program (2004-2013). Tg was measured on day 3 for controls, usually days 10-20 for patients.

Results: Median (interquartile range) Tg in normal infants was 123(91-148) μg/L. Equivalent values were 168(2-3977) μg/L for thyroid ectopia [n=31] (<90μg/L in 8 and >150μg/L in 17); 34(3-173) μg/L for apparent athyreosis [n=13] (<90μg/L in 11), undetectable (<2μg/L) in true athyreosis [n=2]; and 63(32-219)μg/L in thyroid hypoplasia [n=5] (<90μg/L in 2). Tg was < 20μg/L in 4 patients with dyshormonogenesis due to Tg mutation; and mean/median (range) 1198/1141 (300-2301)μg/L in 8 patients (3 transient) with other dyshormonogenesis (300-359 μg/L [n=3], 705 μg/L [n=1] and >1000μg/L [n=4]). Tg varied widely (8-4995μg/L) in 18 patients with transient hypothyroidism related to dyshormonogenesis (n=3), TSH receptor mutation (n=3), maternal blocking antibodies (n=1) and other causes (n=11). High levels (>1000μg/L) of Tg were seen in 2 patients with transient hypothyroidism (cause unknown), one with thyroid ectopia, and one with permanent CH of unknown etiology as well as the 4 with dyshormonogenesis. Tg was significantly lower in patients with athyreosis (p<0.001). Analysis failed to show an overall correlation between serum Tg and TSH levels for the patient group.

Conclusion: Serum Tg shows low specificity for different forms of CH, with considerable overlap. However, levels are unrecordable in true athyreosis, very low in dyshormonogenesis due to Tg mutation; low in apparent athyreosis and thyroid hypoplasia; variable but usually elevated in thyroid ectopia and often high in other forms of dyshormonogenesis. Tg is a useful adjunct to diagnosis in CH but should be interpreted together with thyroid function and imaging. Further work is required to determine whether Tg, in combination with fT4, is useful in predicting thyroxine dose requirement for CH.

P1-P256

Mutation Screening in 60 Chinese Patients with Congenital Hypothyroidism

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Objectives: Congenital hypothyroidism (CH) is the most common neonatal endocrine disorder in infancy. The aim of this study was to screen for reported gene mutations among CH patients in our hospital and to illustrate a genetic mutation spectrum of CH in China.

Methods: We designed a gene panel consisting of more than 20 relevant genes including TSHR and DUOX2. Blood samples were collected from 60 CH patients and their parents in Children's Hospital of Fudan University, China. Genomic DNA was extracted from peripheral blood leukocytes. All exons of the gene were screened by next-generation sequencing (NGS) and Sanger sequencing was performed to detect the gene mutations.

Results: 27(45%) of 60 CH patients revealed clear gene mutations of DUOX2, TSHR, DUOXA2, GNAS and TG. Of them, 16 (59.3%)patients had mutations in DUOX2 gene, 6(22.2%) patients had mutations in TSHR gene, 2(7.4%) patients had mutations in GNAS gene, 2(7.4%) patient had mutations in DUOXA2 gene, 1 (3.7%) patient had mutations in TG gene. The other 33 CH patients were not found clear mutations so far.

Conclusions: Our study indicated that with our own designed CH gene panel, we screened out 45% CH patients and in our cohort of CH, DUOX2 and TSHR gene mutations were the most common genetic causes of CH.

P1-P257

Results of the hTPO Mutational Screening in Bulgarian Patients with Congenital Hypothyroidism (CH)

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Congenital hypothyroidism (CH) is a partial or complete loss of function of the thyroid gland resulting in absent or decreased synthesis and secretion of thyroid hormones affecting infants since birth. Mutations of the hTPO gene are associated with autosomal recessive forms of CH.

Based on our TSH screening results, the number of children with eutopic primary CH is increasing. Molecular biology techniques can identify the CH genetic cause after selection based on family history, thyroid morphology and baseline hormonal data. The identification of Tg or TPO mutation suggests a risk of thyroid cancer within the goiter in adulthood. It is unclear whether the thyroid cancer is gene-specific event or related to goiter development. TPO is mediating two central steps of thyroid hormone synthesis: 1. Organification of iodide to iodinated tyrosyl residues and 2. Coupling of MIT and DIT to T3 and T4. Aim: To set up a multistep mutational screening strategy in CH patients with eutopic thyroids, starting by the analysis of the hTPO gene. Material and Methods: Using the candidate gene approach (permanent CH, eutopic thyroid, elevated Tg) selection of patients suitable for hTPO molecular analysis was performed. Thirty nine patients from 32 families were included. Molecular analysis on genomic DNA was done by Sanger sequencing and MLPA. Results: Seven different mutations were found by Sanger sequencing-c.31_50dup, p.(Glu17AspfsTer77),in exon 2; c.819+4A>C (2.6%), and c.621_622delGG,: p.(Glu207AspfsTer11) (1.3%) – both in exon 7, the second one is novel; c.1430_1450del,p.(Ala477Asn-483del), in exon 9 (1.3%), and one whole gene deletion detected by MLPA analysis. In 8 of the 39 patients (20.5%) the phenotype could be explained by the genotype: 3 of all patients showed homozygous mutations - rs76366277:c.2422delT p.(Cys808AlafsTer24), exon 14 (6.4%); rs17855780, c.208C>G, p.(Pro70Ala), exon 4 (5.1%), and a novel one c.1268G>A, p.Gly393ARG in 8 exon (2.6%), 3 were compound heterozygous carriers. 2 of the patients (2.6%) were carriers of heterozygous deletions of all exons included in the MLPA kit. Conclusions: There is considerable heterogeneity among the hTPO gene mutations in the screened population and novel mutations were found. Some patients with large eutopic glands, high Tg and severe CH were negative in the present mutational screen, therefore NGS is the next step of analysis that could establish the genetic causes of CH in Bulgarian patients.

P1-P258

Thyroid Hormone Resistance Beta: Eighteen Pediatric Patient Experience

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Resistance to thyroid hormone (RTH) is a rare genetic disease caused by reduced tissue sensitivity to thyroid hormone. The hallmark of RTH is elevated serum levels of thyroid hormone with unsuppressed thyrotropin (TSH). The most common form of RTH results from minor defects in the ligand-binding domain of the TRb gene, resulting in impaired T3-induced transcriptional activity. This study aimed to characterize clinical and genetic features of THD suspected cases in our clinic.

Eighteen patients were evaluated with THD who were admitted to our clinic with different complaints or abnormal thyroid function tests. Clinical features, biochemical and hormonal values of all cases were recorded. 7-10. Exons of THRβ gene were scanned by the Sanger sequencing method.

The mean age of patients (7 males and 11 females) was 7.61 (4 days-17 years and 5 months). There was at least one symptom of all patients, except 2 cases. Malnutrition and palpitation were the most common findings (8/18-9/18). The most frequent manifes-

tation is not goiter incompatible with the literature (3/18). The most symptoms were 7 cases with frequent defecation, 6 cases with excessive sweating, 4 cases with short structure and 4 cases with trembling. The body mass index was <-2 SD in 4 cases. Neuromotor or mental retardation in 4 cases, attention and learning deficit in 2 cases, and psychosis in 1 case were the other symptoms. Thyroid autoantibodies were positive in 3 cases. In the screening of the last 4 exons of the THR1 gene, mutations were detected in 12 cases, for M313V in 3, E324K in 3, P453T in 2, R438P in one, and Phe234 silent mutations in 2 patients. Phe245 synonym mutation was present one case.

THD is a dominant negative inherited disease with no phenotypic- genotype correlation.

Misdiagnosis due to clinical variability is reason the wrong treatment. The clinical and genetic characteristics of pediatric18 cases were examined in this study.

P1-P259

A Novel Mutation of IGSF1 Gene

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Introduction: Mutations in *IGSF1* result in X-linked congenital central hypothyroidism, macroorchidism and a variable spectrum of anterior pituitary dysfunction, most commonly including hypoprolactinaemia. We identified a novel hemizygous *IGSF1* mutation (c.3191T>C, p.L1064P) in a 17 year-old adolescent, inherited from his heterozygous mother.

Case: A novel hemizygous IGSF1 mutation (c.3191T>C, p.L1064P) was identified by direct sequencing in a 17 year-old male adolescent with central hypothyroidism (fT4 8pmol/L (8-21pmol/L), TSH 1.8 mU/L (0.35-3.5 mU/L). This variant was novel, absent from the Exac database and predicted to be probably damaging by Polyphen2. IGSF1 deficiency is almost universally associated with macroorchidism, and he exhibited testicular enlargement (volumes ~ 35ml). Additionally, he had hypoprolactinaemia (26 mIU/L (44 - 479 mIU/L), consistent with previous reports that basal prolactin is subnormal in ~60% affected males. His mother who was euthyroid was subsequently found to be heterozygous for the same variant.

The Proband was also obese (BMI 31.6 kg/m^2) and had learning difficulties. Although both are recognized consequences of untreated hypothyroidism, and obesity may be associated with the IGSF1 deficiency syndrome, he also had a paternally-inherited 16p11.2 microdeletion. The relevant section included the *SH2B1* gene which has been implicated in a microdeletion syndrome associated with developmental delay, obesity, ADHD, autism and behavioral problems and could explain some of his problems such as developmental delay and obesity.

Conclusion: We described a male with central hypothyroidism, macroorchidism and hypoprolactinaemia due to a maternally-inherited mutation in *IGSF1* (c.3191T>C, p.L1064P). Asymptomatic individuals in families with IGSF1 mutations who are detected by family screening need close follow up since their endocrinopathy could progress with time as happened with our patient who was initially euthyroid and progressed to central hypothyroidism.

P1-P260

Multinodular Goiter in Childhood: a Diagnostic Gateway for Screening *DICER1* Syndrome

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Background: DICER1 is a member of the Ribonuclease III family that plays a crucial

Background: DICER1 is a member of the Ribonuclease III family that plays a crucial role in the biogenesis and the maturation of microRNAs. Pathogenic germline *DICER1* variants cause a hereditary cancer predisposition syndrome with a variety of manifestations: in addition to first described pleuropulmonary blastoma (PPB) and ovarian sex cord-stromal tumours, individuals may also develop benign (multinodular goiter MNG, cystic nephroma..) or malignant tumours as differentiated thyroid carcinoma from infancy to adolescence and early adult. Average penetrance seems low to 15% except for MNG recently described as 15 to 75% at 40 years (male and female respectively).

Objective: To investigate whether MNG could be a pointer for familial *DICER1* variants screening

Methods: We report a families' serie whose diagnosis for *DICER1* syndrome was done on childhood MNG history (or in index patient or in siblings presenting with benign (15) and/or malignant (9) tumours). We screened germline DNA samples from probands and relatives for *DICER1* variants using Next Generation Sequencing tools. For 3 families the unique manifestation over generations was related to MNG. Personal and family history, clinical examination, thyroid ultrasonography, thyroid function and autoimmunity were evaluated.

Results: We identified 8 different pathogenic DICER1 variants in 9 index patients and 25 relatives: In all cases but one, the germline *DICER1* pathogenic variants associated to MNG have been already described in the literature or located in the enzymatic site of the enzyme. In one family, infant history of pulmonary cystic adenomatoid malformation in the context of MNG at 11 for the proband but also father and uncle, led us to explore the *DICER1* gene and identified a novel heterozygous variant in the exon 20, c.3104C>G, p.Pro1035Arg. Histological sections rereading in view of the familial thyroid history corrected the initial diagnosis in PPB.

Conclusion: GMN is uncommon in children. Its diagnosis before adulthood, recurrence within a family or its association with children benign or malignant tumours should make them suspect of anomalies in the DICER1 protein as proposed in recent international recommendations. Children and adolescents diagnosed with GMN should be referred in genetic counselling. Early detection of *DICER1* variants has important consequences in terms of tumour screening and therapeutic strategies.

P1-P261

A Novel *DICER1* Mutation Identified in a Family with the Multinodular Goiter of Children

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Background: Nontoxic multinodular goiter (MNG) is frequently encountered in the general population,but little is known about the underlying genetic susceptibility to this disease. Recently, germline mutations in *DICER1*, a gene that codes for an RNase III endoribonuclease, have been identified in familial MNG with and without Sertoli-Leydig cell tumor of the ovary.

Objective: We reporteda family exhibiting various thyroid diseases in which a *DICER1* germline mutation was revealed first in the proband with the childhood onset MNG and subsequently in the family members.

Patients: The patient presented to our hospital with a cervical mass at the age of 6 years.Thyroid ultrasonography revealed a mixed type tumor with the size of 15 mm in the right lobe, showing tendency to grow. During the following two years, two nodules appeared in the right lobe, one in the isthmus and another in the left lobe. Fine-needle aspiration biopsy of the nodule in the right lobe with unclear boundaries showed that the nodule was benign. A diagnosis of MNG was made. Total thyroidectomy was performed at the age of 8 years because of a significant increase in thyroglobulin level, an increase in tumor mass, and discomfort during swallowing. Her mother had her thyroid nodule removed at the age of 15 years, and a total thyroidectomy was performed on a cervical tumor that was diagnosed as poorly differentiated thyroid carcinoma and MNG when she was 39 years old. Her mother's sister also had a thyroid nodule removed at the age of 15 years and ovarian surgery when she was approximately 30 years old. Additionally, the patient's maternal grandmother had partial removal of the thyroid gland when she was 20 years old and is currently undergoing treatment for Graves' disease. As a result of *DICER1* mutation analysis, c.4509C> G (p.Y1503X) was identified as the heterozygous allele for the patient, her mother, and maternal grandmother.

Discussion & Conclusion: We speculated that the novel *DICER1* mutation was pathogenic because of the nonsense mutation, and because the mutation positive patients demonstrated a history of thyroid nodules. Although *DICER1* mutation patients have reported familial thyroid differentiated cancer, there is no report of poorly differentiated thyroid carcinoma, suggesting that an additional somatic mutation might be responsible for neoplastic transformation. *DICER1* mutation analysis is considered to be very important in the treatment protocol and for the management of complications in childhood onset MNG.

P1-P262

Subclinical Hypothyroidism, Thyroid Nodule or Cyst in Prepubertal Children: How Many Children Were Diagnosed at Age 6?

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Purpose: We investigated the prevalence of subclinical hypothyroidism (SCH) and its risk factors in prepubertal children at age 6. We also evaluated the prevalence of thyroid nodule or cyst and its relationship with SCH in prepubertal children.

Methods: From the Environment and Development of Children (EDC) cohort study, 458 prepubertal children (243 boys, mean 5.8 years) who visited at age 6 were included in this study. Serum concentrations of free thyroxine (fT4), triiodothyronine (T3) and thyroid stimulating hormone (TSH) were measured. With the use of ultrasound, thyroid volume (Tvol) and the presence of thyroid nodule or cyst were analyzed.

Results: SCH was detected in 27 children (5.9%). SCH group had lower birth weight z-scores ($p = 0.03$) and higher proportions of family history of thyroid disease ($p = 0.04$) and multiple birth ($p = 0.02$) than normal group. SCH group had lower fT4 levels (1.1 ng/dL vs. 1.2 ng/dL, $p = 0.008$) and higher TSH levels (6.3 mIU/L vs. 2.3 mIU/L, $p< 0.001$) than normal group. After adjusting for birth weight and multiple birth, family history of thyroid disease was independently associated with SCH (OR 4.8, $p = 0.024$). When neck ultrasound was performed in 216 children, thyroid nodule and cyst were detected in 13 (6.0%) and 49 (22.7%) children, respectively. Children with thyroid nodule or cyst had significantly higher Tvol than those without ($p = 0.009$). No significant differences in age, sex, birth history, BMI z-scores, and proportion of family history were found according to presence of nodule or cyst. Tvol was positively correlated with TSH levels ($r = 0.30$, $p=0.032$), significantly higher Tvol in SCH group than normal group (mean 3.3mL vs. 2.9mL, $p = 0.009$). However, the relationship of SCH with presence of thyroid nodule or cyst was not significant.

Conclusion: In prepubertal children at age 6 years, SCH and thyroid nodule were detected in 5.9% and 6.0%, respectively. Family history of thyroid disease was independent predictor for SCH. Although the relationship of SCH with thyroid nodule or cyst was not significant, higher Tvol was significantly related to SCH and presence of thyroid nodule or cyst at age 6.

P1-P263

Expression of ZnT8 Transporter in Thyroid Tissues from Patients with Immune and Non-immune Thyroid Diseases

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Introduction: Zinc homeostasis is regulated by ZnT and Zip zinc transporters. Zinc transporter 8 (ZnT8) is localized in insulin containing secretory granule membrane and transports zinc from the cytosol into the vesicles. ZnT8 was identified on peripheral lymphocytes, in subcutaneous adipose tissue, in a pancreatic β-cells and extra-pancreatic endocrine glands including pituitary, adrenal and thyroid. Autoantibodies to the ZnT8 are detected in the majority of type 1 diabetes patients. A few recent studies showed that ZnT8 Ab may occur in patients with autoimmune thyroid diseases. There is lack of data about expression of ZnT8 transporter in human thyroid tissues.

Aim of the study was to compare the expression of ZnT8 transporter in thyroid tissues from patients with immune and non-immune thyroid diseases.

Material and methods: The study was performed in thyroid tissues after thyroidectomy from patients with thyroid nodular goiter (n=17, mean age 17.8 years ± 4) and cases with Graves' disease (n=20, mean age15.6 years ± 2.8). The ZnT8 expression protein was evaluated using immunohistochemistry. The specimens were paraffin embedded tissues, derived from the pediatric patients, who had thyroid nodular goiter or GD. The antibody against ZnT8 was goat polyclonal antibody (Santa Cruz Biotechnology USA; sc-98243). The antigen was retrieval was done using high pH (PTLink DAKO) and antibody was incubated in 4°C overnight in 1:50 dilution. The patients with pancreatitis were as positive controls. The intensity and the proportion of stained cells were determined by examining the entire slide and section as: + (low staining intensity in less than 10% cells in the section); ++ (moderate staining intensity in 10-40% cells in the section); +++ (high and diffuse staining intensity in more than 50% cells in the section).

Results: The staining intensity of examined cells in thyroid tissues from patients with: thyroid nodular goiter ++; C cells hyperplasia ++; GD +++. The positive control (patients with pancreatitis) +++.

Conclusions: Expression of ZnT8 transporter was identified in the thyroid tissues from paediatric patients with Graves' disease and nontoxic nodular goiter and was found both in thyroid follicular cells and C cells. Predominant expression of ZnT8 in immune than in non-immune thyroid disorders may suggest potential role of ZnT8 as a new thyroid autoantigen but it requires further study on a larger cohort.

P1-P264

Thyroid Nodules in a Childhood Cancers Survivors Population: A Monocentric Experience

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Thyroid nodules are rare in pediatric age with an incidence of 1,8-3 %. However, the risk of thyroid cancer is much higher in the pediatric population compared with adults.

Among the pediatric cancer survivors there is an increased risk of developing a secondary malignancy and the thyroid cancers account for about 10% of these secondary tumors.

From 2004 to 2017, we have recruited 43 patients (22 females; 21 males) with thyroid nodules among a population who had presented an hematologic or solid tumors before 18 years old. The mean age at the first thyroid nodule detection was 17,3 ± 5 years (range: 8,9-33,1).

We considered "thyroid nodule" every solid lesion larger than 4 mm at ultrasound evaluation. The fine needle aspiration biopsy (FNAB) was performed in thyroid nodules larger than 7 mm and/or with malignant sonographic findings (32 patients; 74.4%). According to Bethesda System, we identified 12 Tir2 (37,5%), 14 Tir3 (43,7%), 2 Tir4 (6,3%) and 4 Tir5 (12,5%). Five of 6 patients with Tir4 and Tir5 cytology underwent total thyroidectomy with an histological diagnosis of papillary carcinoma (in one patient surgery was not possible for localized scleroderma).

Thirteen of 14 patients with Tir3 cytology underwent surgery (emithyroidectomy and/or total thyroidectomy) with an histological diagnosis of thyroid papillary carcinoma in 8 patients (**61,5%**).

Totally, we diagnosed 14 thyroid carcinomas in our population (32,6%). We found a statistically significant difference in the percentage of malignant nodules between patient submitted to radiotherapy (local RT or Total Body Irradiation) and patients submitted to only chemotherapy (36,6% vs 22%).

We demonstrated that patients with malignant nodules received a dose of radiotherapy inferior to patients with benign nodules (12,2 ± 1,1 Gy vs 22,2 ± 15,7 Gy; p=0,022), according to previous studies which indicated that thyroid cancer risk after a first childhood malignancy is curvilinear with radiation dose, increasing at low to moderate doses and decreasing at high doses.

We did not find any statistically significant difference between the dimensions of malignant and benign nodules (12,9 ± 5,7 mm vs 11,4 ± 5,6) probably due to an early ultrasound finding of those lesions.

Finally, dividing the population in two groups according to age at the diagnosis of the first malignancy (<8 and ≥8 years old), we showed that in the younger group the timing of thyroid nodule's onset is superior to the older one (10,8 ± 3,3 vs 8,4 ± 5,3 years).

P1-P265

HLA Alleles and Amino Acid Variants of HLA-A, -B, -C, -DRB1, -DQB1, -DPB1 Molecules in Early-onset Autoimmune Thyroid Disease

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Objective: We try to investigate the polymorphisms and amino acid variants of HLA-A, -B, -C, -DRB1, -DQB1, -DPB1 molecules in early-onset AITD.

Methods: The genotypes of HLA-A, B, C, DRB1, DQB1, and DPB1 on AITD were analyzed in 102 Korean children with AITDs (Graves' disease (GD) = 62, Hashimoto¢s disease (HD) = 40) and 142 healthy control using sequence-based typing. Analysis of variant amino acids was performed across the genotyping results with a resolution of 4 digits from the ImMunoGeneTics database.

Results: In AITD, the allele frequencies of HLA-A * 0207, -B * 4601, -DPB1 * 0202 were higher and those of HLA- Cw * 0602, -Cw * 1403, -DRB1 * 0701, -DQB1 * 0202, -DQB1 * 0501, -DQB1 * 0604 were lower than in controls. In GD, those of HLA- -B * 4601(OR = 4.0, Pc = 0.005), -DPB1 * 0202(OR = 4.4, Pc = 0.013), -DPB1 * 0501 (OR = 4.1, Pc = 0.005) were higher than in controls. In HD, those of HLA-A * 0207(OR = 5.6, Pc = 0.005), -and -DPB1 * 0202(OR = 7.2, Pc = 0.0002) were higher than in controls. Between HD and GD, HLA-DPB1*0501 showed a significant difference (Pc = 0.001). The risk of AITD in the presence of HLA-A*0207, -B*4601 and -C*0102 (OR = 6.2, Pc = 0.001) and HLA -DRB1*0803-DQB1*0601-DPB1*0202 are increased and HLA-A*3001, -B*1302 and -C*0602 (OR = 0.1, P = 0.003) is decreased. In analysis of amino acid variant of HLA molecules in patients with GD, Leu35 (OR = 30.2, P = 0.000001) and Glu55 (OR = 30.2, P = 0.000001) presented in both -DPB1*0202 and- DPB1*0501 increased than control. Cys99 (OR = 3.6, Pc = 0.019) in HLA-A molecules, Ala24 (OR = 3.7, Pc = 0.018), Lys66 (OR = 4.0, Pc = 0.0003), Arg69 (OR = 3.7, Pc = 0.0003), Val76 (OR = 3.7, Pc = 0.0002) in HLA-B molecules, Lys6 (OR = 2.2, Pc = 0.018), Phe9 (OR = 2.2, Pc = 0.035), Cys99 (OR = 2.2, Pc = 0.035), Tyr116 (OR = 3.0, Pc = 0.007) in HLA-C molecules, Ser57 (OR = 3.1, Pc = 0.001), Leu74 (OR = 3.1, Pc = 0.002) in HLA-DRB1 molecules, Asp57 (OR = 15.7, Pc = 0.002) in HLA-DQB1 molecules are increased in patients with GD than control.

Conclusion: Significant differences in the amino-acid signatures of HLA-molecules were observed between early-onset AITD patients and controls.

P1-P266

Childhood Thyroid Autoimmunity and Relation to Islet Autoantibodies in Children at Risk for Type 1 Diabetes

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Background: The aim was to determine prevalence and age at seroconversion of thyroid autoimmunity and relation to islet autoantibodies, gender and HLA-DQ genotypes in children followed from birth because of increased genetic risk for type 1 diabetes.

Methods: In 1874 10-year-old children followed in the Diabetes Prediction in Skåne (DiPiS) study, blood samples were analysed for autoantibodies against thyroid peroxidase (TPOAb), thyroglobulin (TGAb), glutamic acid decarboxylase 65 (GADA), three variants of Zink transporter 8 (ZnT8R/W/QA), insulinoma-associated protein-2 (IA-2A), insulin (IAA) and HLA-DQ genotypes. Prospectively collected samples from 2 years of age were analysed for TPOAb and TGAb and confirming samples at 11-16 years of age for TPOAb, TGAb, TSH and FT4, in children positive for thyroid autoantibodies at age 10.

Results: The prevalence of thyroid autoimmunity was 6.9%, overrepresented in girls ($p<0.001$), also having higher TPOAb titers at 10 years ($p=0.049$). TPOAb was related to GADA ($p=0.002$), ZnT8R/W/QA ($p=0.001$), IA-2A ($p=0.001$) and multiple islet autoantibodies ($p<0.001$), while TGAb was related to ZnT8R/W/QA ($p=0.021$) and multiple islet autoantibodies ($p=0.039$). In boys, TPOAb was related to GADA ($p=0.002$), IA-2A ($p=0.001$), ZnT8R/W/QA ($p=0.001$), IAA ($p=0.009$) and multiple islet autoantibodies ($p=0.001$) and TGAb to GADA ($p=0.013$), IA-2A ($p=0.005$), ZnT8R/W/QA ($p=0.003$) and multiple islet autoantibodies ($p=0.001$). In girls, TPOAb was related to multiple islet autoantibodies ($p=0.022$), while no other associations were found. Titers of IA-2A were related to both TPOAb ($p=0.021$, rs 0.36) and to TGAb ($p=0.011$, rs 0.40). In boys, but not in girls, titers of GADA and TGAb correlated ($p=0.009$, rs 0.38) as did titers of IA-2A and TPOAb ($p=0.013$, rs 0.51). Thyroid autoimmunity appeared already at 2 years of age, both frequency and titers increased with age. In the confirming sample, 94% were still thyroid autoantibody positive. Abnormal thyroid function or thyroxine treatment was found at follow-up in 22.3 % of the children who were thyroid autoantibody positive at 10 years of age.

Conclusion: Thyroid autoimmunity and high TPOAb titers were more common in girls. However, the relation between thyroid and islet autoantibodies and correlations between titers were stronger in boys. These data suggest that while girls may develop autoimmune thyroid disease independent of islet autoantibodies, the risk for boys to develop thyroid disease may be dependent on concomitant islet autoantibodies and an increased risk for type 1 diabetes.

P1-P267

Evaluation of Serum Concentrations of Selected Cytokines OPG and sRANKL in the Diagnosis of Autoimmune Thyroid Disease in Children

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Chronic autoimmune thyroiditis (cAIT) and Graves' disease (GD) is the most common autoimmune disorders in children, associated with induction of inflammation and autoimmunity process. OPG, a cytokine receptor which mediates suppressive effect on osteoclastogenesis and its soluble ligand RANKL (sRANKL) are regulators of inflammation and may be a link between bone, autoimmune disease, and vasculature.

Aim of the study: We hypothesized that cytokines OPG and sRANKL play a crucial role in modulating an immune response in both, thyroid disorders in children.

Methods: We studied serum OPG and sRANKL in 22 newly diagnosed children with cAIT, 22 GD children and 20 healthy subjects with normal fT4, fT3, TSH and negative antithyroid Abs. Thyroid function (TSH, fT4, fT3), autoimmune (ATG, ATPO, TRAb) and anthropometric (weight, height, BMI, BMI-SDS, Cole index) parameters were evaluated. OPG and sRANKL concentration were measured at the beginning of disease (before treatment) by ELISA. Nonparametric statistical test and ROC analysis were performed to assess the data.

Results: In our study, no significant difference was observed between sRANKL serum concentrations in studied groups ($p=0.33$, Kruskal-Wallis test). OPG concentrations were significantly higher (ANOVA $p=0.013$; Newman-Keuls $p<0.01$) in children with GD: (mean±SD) (4.48±2.01 pmol/L) compared to control group (3.02±1.17 pmol/L); whereas no significant difference between children with cAIT (3.79±1.28 pmol/L) vs. control group (Newman-Keuls $p>0.05$) and cAIT vs. GD (Newman-Keuls $p>0.05$) was observed. In children with hyperthyroidism we identified significant positive correlation between OPG and sRANKL ($r=0.54$; $p<0.01$) as well sRANKL and ATPO($r=0.46$p $p<0.05$). In a cAIT group sRANKL positively correlated with thyroid hormones: fT4 ($r=0.53$; $p<0.05$) and FT3 ($r=0.52$;$p<0.05$) and negatively with TSH ($r=-0.51$; $p<0.05$). Significant positive correlation between sRANKL and the age of children ($r=0.47$; $p<0.05$) was found in a control group. ROC curve indicates good efficacy of OPG to discriminate groups of hyperthyroid and healthy children (AUC=0.716; $p=0.017$) at the cut-off point of 4.54 pmol/L with low sensitivity (54.5%) but high specificity (90.0%). In these groups of children, AUC of sRANKL did not differ significantly from 0.5 ($p=0.458$).

Conclusion: Based on the performed study we suggest that OPG may be considered as a useful biochemical marker of hyperthyroidism in GD children.

P1-P268

Analysis of Zinc- Transporter ZnT8 Autoantibodies in Children and Adolescents with Autoimmune Thyroid Diseases

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Background: Recent studies have revealed the presence of zinc and the expression of zinc transporter (ZnT) family members in most endocrine cell types. It was demonstrated that ZnT family plays an important role in the synthesis and secretion of many hormones. Moreover, recently ZnT8 was described as a newly islet autoantigen in type 1 diabetes.

Material and methods: The study was performed in the group consisting of patients with 44 Graves' disease (GD) (mean age, 14.4±3.1), 66 Hashimoto's thyroiditis (HT) (mean age, 13.0±3.7), 166 with T1DM (mean age, 12.4±4.1), 36 with both T1DM and GD or HT (mean age, 13.2±4.3), and 58 healthy controls (mean age, 13.3±3.5). GAD, IA-2, IAA, ZnT8, 21OH antibodies' concentration were evaluated in the peripheral blood.

Results: ZnT8 Ab was found in 4 patients (9.1%) with GD while 4 patients (9.1%) were positive for GAD Ab, two patients (4.5%) were positive for IA-2 Ab and one patient (2.2%) was positive for IAA. Of these, one GD patient was positive for all four diabetes associated antibodies and one was positive for GAD Ab and ZnT8 Ab, two GD patients (4.5%) were positive for ZnT8 Ab only. In the case of HT patients, 6 (9.1%) were positive for ZnT8 Ab, while 4 patients (6.1%) were positive for GAD Ab, 4 (6.1%) were positive for IA-2 Ab and 3 (4.5%) were positive for IAA Ab. Of these, one HT patient was positive for all four diabetes associated antibodies, 2 had 3 diabetes associated antibodies (ZnT8 Ab, IA-2 Ab, GAD Ab or IAA) and one had 2 diabetes associated antibodies (GAD Ab and IAA), 3 HT patients (4.5%) were positive for ZnT8 Ab only.

Conclusions: These results show the presence of ZnT8 autoantibodies not only in patients with type 1 diabetes mellitus but also with Graves' disease and Hashimoto's thyroiditis. Further longitudinal studies in a large cohort are necessary.

P1-P269

The Association Between TSHR, IFIH1 and ETV5 Polymorphisms with Graves' Disease and Diabetes Mellitus Type 1 in Children

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Background: Many organs of human body are attacked by autoimmune processes and countless number of genes are involved in their pathogenesis. Diabetes mellitus type 1 (T1DM) attaching pancreas is a common autoimmune disease in childhood. Among autoimmune thyroid diseases (AITD) we can distinguish less frequent in children population- Graves' disease (GD). Thyroid stimulating hormone receptor (TSHR) gene encodes membrane protein responsible for thyroid metabolism. Interferon induced helicase (IFIH1) gene tends to be related to development of many autoimmune diseases. ETV5 transcription factor is considered to be obesity-associated loci.

Objective and hypotheses: Identification of genetic variants enabling differentiation between GD and T1DM in children.

Method: The study was performed among 170 patients with GD and 194 with T1DM. Three single nucleotide polymorphisms (SNPs): Rs 179247-TSHR, Rs 1990760- IFIH1 and Rs 7647305-ETV5 were genotyped by TaqMan SNP genotyping using QuantStudio 12 K Flex OpenArray plates.

Results: Rs 179247 A alleles were more frequent in GD in comparison to T1DM patients ($p<0.05$ with OR=1.35). Rs 1990760 C alleles were more frequent in GD in comparison to T1DM patients ($p=0.003$ with OR=1.6). Rs 7647305 C alleles were more frequent in GD in comparison to T1DM children ($p<0.001$ with OR=1.8).

Conclusion: When comparing GD with T1DM, Rs179247 A/G, Rs 1990760 C/T and Rs7647305 C/T polymorphisms could contribute to GD development in children. The main risk factor for Rs 179247 is A allele, for Rs 1990760 is C allele and for Rs 7647305 is C allele.

Thyroid P2

P2-P376

Long Term Monitoring of Graves Disease in Children and Adolescents: Single Center Experience

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Introduction: Antithyroid Drugs (ATD) are generally preferred at the onset of treatment with no consensus on the duration of ATD (propylthiouracil, methymasole) treatment Graves disease in children.

Objective: Examining the effectiveness of ATD treatment on children and adolescents and determining the risk factors of remission and relapse.

Method: A total of 45 cases with ages varying between 1-18 years diagnosed with Graves disease during 2003-2017 were included in this retrospective study. The average age of diagnosis was 12,5 years with a total of 36 female (80%) and 9 male patients. ATD treatment was started on all cases. While 22 cases were treated with methymasole (average starting dose 0,65 ± 0,24 mg/kg/day), 23 cases were administered with propylthiouracil (PTU) treatment (average starting dose 3,88 ± 1,37 mg/kg/day). In accordance with the 2009 FDA suggestion, treatment was changed to methymasole (MMI) for 5 cases who were undergoing PTU treatment. Whereas titration treatment was applied on 9 cases (20%), blockage-replacement treatment was preferred for 36 (80%) of the cases. ATD treatment was stopped for all cases undergoing medical treatment at the end of an average treatment period of 23,2 ± 13,2 months (10-73 days).

Results: The cases were classified into 2 groups as remission and relapse groups. While remission was attained in 24 (53%) of the cases, relapse was observed in 21 (47%) cases. The average duration for initial treatment was 23.2± 13.2 months (10-37 months). The period of time until the end of the initial treatment was longer in the remission group (26.91±16.18 months) in comparison with the relapse group (19.09±7.14 months) (P=0.01). The total ATD treatment duration was longer at a statistically significant level in the remission group (38.14 ± 14.35 months) in comparison with the relapse group (26.95± 16.13 months) (P=0.03). While ATD treatment was started again in 10 of the cases with relapse, remission was attained in 5 of these cases. Of the cases in which relapse was observed, 4 were subject to surgical treatment and 2 were subject to RAI treatment. Hypothyroidism developed in one case after surgical treatment and in 2 cases after RAI treatment.

Conclusion: Long-term initial ATD treatment until remission and long-term total ATD treatment were evaluated as a positive parameter for the Graves disease in children independent of age, gender and pubertal state.

P2-P377

Effects of Thyroid Autoimmunity on Non-Alcoholic Fatty Liver Disease in Euthyroid Girls with Hashimoto's Thyroiditis

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Introduction and Aim: The aim of this study was to investigate whether autoimmune Hashimoto's thyroiditis (HT) increases the incidence of non-alcoholic fatty liver disease (NAFLD). In addition, the relationship between autoimmunity and the following factors was evaluated: Body Mass Index (BMI), body parameters measured by Bioelectric Impedance Analysis (BIA), and metabolic syndrome parameters.

Methods: 43 newly diagnosed euthyroid girls with HT (14.4±2.1years) were included. The control group consisted of 41 age- and BMI-matched healthy girls. At enrollment, all subjects underwent physical examination including blood pressure, standing height, weight, waist circumference (WC), and hip circumference measurements. The lipid profile, liver function tests, glucose, insulin, high sensitivity C-reactiveprotein (hs-CRP), thyroid functions, and thyroid antibodies were measured. Thyroid and liver ultrasonography (US) were performed and body parameters were measured by BIA.

Results: Grade 1 steatosis was detected by liver US in 3 patients (7%) in the HT group while the control group was completely normal. There was no significant difference between the two groups in terms of NAFLD (p= 0.085). There was no significant difference between the two groups in terms of anthropometric variables except for systolic and diastolic blood pressures, which were significantly higher in patients even though they were still within the normal range.

The median thyroid stimulating hormone (TSH) value of the patient group was higher [2.88(0.43-5.57) μLU/mL] than the control group [1.98 (0.96-4.24) μLu / mL] (p = 0.017). However, once again, these higher values were still within the normal range. There was no statistically significant difference in metabolic parameters (ALT, AST, GGT, cholesterol, triglyceride, glucose, insulin and HOMA-IR) between the two groups. When we compared the BIA parameters between patient and control groups, there was no statistically significant difference (p> 0.05).

A multivariate logistic regression analysis didnot find that the independent variables BMI-SDS, age, waist circumference, hip circumference, TSH, Anti-TPO, anti-Tg antibodies, and systolic blood pressure affect the presence of NAFLD.

Conclusion: In conclusion, our study revealed that HT patients had increased NAFLD compared to the control group, but this difference wasnot statistically significant. The two groups were considerably homogeneous in terms of thyroid function, metabolic risk factors, and anthropometric variables except for systolic and diastolic blood pressures, which were significantly higher in patients. These observations suggest an atherogenic role of thyroid antibodies. As thyroid autoimmunity increases atherosclerosis via an inflammatory mechanism, it could also have a role in NAFLD development in a similar manner.

P2-P378

The Prevalence of Clinically Significant Anti-TPO Positivity in Children with HLA-Conferred Susceptibility to Type 1 Diabetes

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Background: The increased prevalence of anti-thyroid peroxidase antibodies (anti-TPO) and autoimmune thyroiditis in children with type 1 diabetes (T1D) has been previously well described. However, the necessity for screening for anti-TPO in children who have not been diagnosed with T1D yet, but have a HLA-conferred susceptibility to T1D, has not been reported. A 3% prevalence of anti-TPO in healthy children has been shown in studies using a cut-off value of > 100kU/L for clinically significant anti-TPO level. The aim of this study was to evaluate the serum levels of anti-TPO and the prevalence of clinically significant anti-TPO positivity in children with HLA-conferred susceptibility to T1D.

Methods: Serum concentrations of anti-TPO in 111 subjects (57 boys) aged 8-9 years with a HLA-conferred susceptibility to T1D were studied. None of them had a known thyroid disease, one of the subjects had already a diagnosis of T1D. The test was performed with ECLIA method. As no universal reference ranges for anti-TPO in children have been agreed upon, we used the test manufacturer's reference range of < 18 kU/L for this age group. The lower detection limit of the test was 5 kU/l. Clinically significant anti-TPO positivity was set at a concentration of >100 kU/L. The statistical analysis was performed with Excel using the Mann-Whitney test, p <0.05 was considered statistically significant.

Results: Eleven samples of anti-TPO (9.9%) were over the reference range. In 2 cases (1.8%), both girls, anti-TPO was >100 kU/L, suggesting a very likely autoimmune thyroiditis. Those two subjects had normal thyroid function tests. The lowest detected anti-TPO was 7 kU/L, the highest 354 kU/L. Nine out of 11 risen anti-TPO concentrations belonged to girls. Girls had significantly higher median anti-TPO concentration than boys (12.5 vs 10.0 kU/L; p = 0.0001).

Conclusion: In children with HLA-conferred susceptibility to T1D the prevalence of clinically significant rise of anti-TPO levels was similar to previously reported data in healthy children. However, almost 10 percent of those children have anti-TPO levels above the reference range. Further studies are necessary to clarify the clinical significance of this finding.

P2-P379

Encephalopathy Associated with Autoimmune Thyroid Disease: A Case Report

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Background: Encephalopathy associated with autoimmune thyroid disease (EAATD) is very rare in pediatrics. Contributing factors include: Sudden change is thyroid levels, cerebral

vasculitis,endothelial inflammation or immune complex deposition, global cerebral hypoperfusion, as well as cerebral tissue-specific autoimmunity.

The case: A 16-year-old female was diagnosed with hyperthyroidism and treated with Radio Iodine Ablation (RIA). Her total T4 level was followed from hyperthyroid levels of 18.6 ug/dl (239.4 nmol/L) until hypothyroid 3.2 ug/dl (41.2 nmol/L). Her TSH remained suppressed. Therapy with Levothyroxine of 1.6 microgram/kg/day was started when she had low T4 level and made the patient euthyroid within 1 month.

The patient started having emotional lability symptoms with sudden crying, mild confusion, disturbed sleep pattern and deteriorated school performance. The mother of the patient felt that her daughter „ became a different person". There was no history of fever. EAATD was suspected. Diagnostic workup revealed high anti-thyroid peroxidase antibody titers (Anti TPO) and anti-thyroglobulin (TG) antibodies in the cerebrospinal fluid (CSF). MRI of the brain was normal. The patient was initially treated with a course of Hydrocortisone orally. When symptoms persisted, Intravenous Immunoglobulin (IVIG) therapy was given after which, the patient had remarkable improvement of her symptoms.

Discussion: The diagnosis of EATTD may be delayed due to the wide range symptoms of autoimmune thyroid conditions. It is important to recognize the association of autoimmune thyroid disease and encephalopathy as a separate medical condition since symptoms of both hyper and hypothyroidism can be associated with neuro –psychiatric symptoms. EAATD occurs mostly with thyroiditis but can actually happen with hyperthyroidism and Graves' disease. The diagnosis of EAATD should be considered in all patients with signs of encephalopathy of unknown origin when associated with an autoimmune thyroid disease.

Symptoms can be very variable and may include: Headache, confusion, involuntary movements, altered consciousness, decreased verbal fluency, dysarthria, hallucinations, altered hearing, cognitive impairment, disturbed sleep pattern, emotional lability and seizure. The sudden change from hyper- to- hypothyroidism state could contribute to the symptoms on top of the antibodies-mediated neuro pathology. Most of the reported cases appear to be steroid responsive while immune therapy with IVIG can be considered in persistent cases.

Careful follow up is warranted since some cases of EAATD may recur and the evolution of the disease in the long-term is unpredictable.

P2-P380

Celiac Disease Screening Should Be Routinely Offered in Pediatric Population with Autoimmune Thyroid Disease

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Background and Hypothesis: Autoimmune thyroid disorders (AITD), including Hashimoto's Thyroiditis (HT) and Grave's disease (GD), are known to cluster with other autoimmune disorders (AID). There seem to exist both a pathophysiological basis of immunomodulator genes and epidemiological indications of a higher prevalence of AID including Celiac disease (CeD) in patients with AITD, compared to that in the healthy pediatric population. CeD is asymptomatic in a large proportion (ranging from 33% to 67%) of patients at the time of diagnosis. The hazard of complications, such as malignancy, which worsen the quality of life and increase mortality, is lower when diagnosis is made at a younger age, due to longer adherence to a gluten-free diet. Taking all the above into account, we should consider if screening children with AITD for CeD on a regular basis should be recommended.

Objective: To determine the prevalence of CeD among asymptomatic pediatric patients with AITD and no other co-morbidities as to justify CeD screening in this population.

Methods: Children and adolescents with AITD and no other co-morbidities followed at our Pediatric Endocrinology Outpatient Clinic were serologically tested for CeD with Immunoglobulin A (IgA) tissue Transglutaminase antibodies (IgA-tTg), as well as for their IgA serum levels, in order to exclude IgA deficiency. Intestinal biopsy for a definite diagnosis of CeD was offered to those with a confirmed positive IgA-tTg titer.

Results: Eighty-eight patients (62 girls and 26 boys), 80 of which had HT and 8 had GD, with a mean age of 11.80 ± 3.14 years were included in the analysis. Three of them (3.41%), all of which were female diagnosed with HT, were found positive for IgA anti – tTg in two samples and had the diagnosis of CeD confirmed by an intestinal biopsy. The proportions of CeD diagnosis in HT patients or female HT patients alone were even higher (3.75% and 5.36%, retrospectively). Finally, another 2 female patients with HT were found to have transient seropositivity for IgA anti-tTg, with borderline positive results in the first test and negative in the repeating one. No differences regarding age, age at diagnosis, years since diagnosis, anti-thyroid antibodies titers or anthropometric parameters were observed between those diagnosed with CeD and the rest of the studied population.

Conclusions: The relatively high prevalence of CeD in patients with AITD in this study justifies the screening for CeD in this specific pediatric population and especially in girls with HT.

P2-P381

Autoimmune Thyroiditis in Klippel-Feil Syndrome with Arnold Chiari and Syringomyelia

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Introduction: Klippel-Feil Syndrome (KFS), prevalence of 1:40000, is characterized by congenital fusion of cervical vertebrae; three major features are short neck, low hairline at the back of the head and a limited range of motion in the neck. The phenotypic expression is variable, presenting with other vertebral abnormalities (congenital high scapula, scoliosis, kyphosis, spina bifida, hemivertebrae) or extra skeletal symptoms such us deafness, renal, heart or neurological abnormalities like neuroschisis and syringomyelia. Most cases are sporadic, but an autosomal dominant form, linked

to a mutation in the gene GDF6 (8q22) or to a chromosomal rearrangement involving the long arm of chromosome 8, has been described.

Case Study: A girl was referred to our department at the chronological age (CA) of 10.3 yrs with a suspect of Turner syndrome, due to the presence of webbed neck and progressive deceleration of growth velocity. The girl, born in Russia, was adopted at the CA of 14 months. Clinical examination showed short neck, thelarche Tanner stage II, pubarche Tanner stage II, hyperlordosis and valgus elbow. The height was 134 cm (-1.1 SDS), weight 28 kg (-1.3 SDS).

Pelvic ultrasound showed normal uterus and ovaries, karyotype was not performed.

Due to the presence of short neck, cervical x-ray was performed: the images showed fusion of the cervical vertebrae C2 and C3, confirming the suspect of a Klippel-Feil syndrome.

The brain MRI showed Arnold-Chiari (AC) type I malformation associated to syringomyelia from C2 to C7.

Blood investigations showed markedly elevated TSH values (> 75 μU/ml, range 0.4 -4.0) and low values of FT3 (2.5 pg/ml, range 2.5-3.9) and FT4 (4.1 pg /ml, range 5.8-16.4). Serum antitireoglobulin and antiperoxidase antibodies were both elevated: ATG > 3000 U/ml (range < 45), ATPO 298 U/ml (range <35). Thyroid ultrasound showed increased thyroid size with markedly heterogeneous and hypervascular echogenicity with slightly thickened isthmus. The patient was started on thyroid replacement therapy.

Conclusion: To our knowledge, association of KFS with AC malformation, syringomyelia and autoimmune thyroiditis has not been reported in the literature. We believe that the presence of thyroiditis in our patient represents a random association, since neither in our patient nor in the literature there are data supporting the hypothesis of an increased incidence of autoimmune disorders in these patients. Nevertheless, we suggest to evaluate also thyroid function in these patients to rule out the presence of abnormalities.

P2-P382

Neonatal Monitoring of Newborns Born from Mothers with Graves' Disease. Results of a Retrospective Monocentric Study

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Background: Neonates born from mothers with Graves' disease are at risk to develop hyperthyroidism due to placental transmission of TSH-receptor antibodies. Neonatal hyperthyroidism should be effectively diagnosed and treated to prevent severe complications of this disease (cardiac symptoms, poor weight gain, severe neurological manifestations).

Objectives: To describe the post-natal follow-up of neonates born from women with Graves' disease.

Method: 33 neonates (17♀, 52%), born from 32 women (1 twin pregnancy) with Graves' disease diagnosed before (n=23) or during pregnancy (n=9) referred to our hospital between 2006 and 2015 were included in this study. Symptoms of hyperthyroidism, thyroid function tests, TSH-receptor antibodies (TRAK) titers were collected during the follow-up. Data are reported in median [Q1-Q3] values.

Results: Seven women (22%) have had thyroïdectomy and/or IRA therapy. During pregnancy, 24 women (75%) were treated with anti-thyroid drugs (21 received PTU). Maternal TRAK titers were available in only 22 (68%) women at the last trimester of pregnancy or at birth and were positive in 21 (95.5%, TRAK: 15 [3.5-35] UI/L). At birth, gestational age was 38 [37-39] weeks, 7 neonates were born preterm and 3 were SGA. 3 neonates had birth defects (hexadactily, biventricular dilatation, unilateral kidney hypoplasia+ureteral duplicity). 14 neonates had goiter and 2 exophthalmia. 25/31 neonates (80.6%, 2 missing data) were TRAK+ within the first 10 days.

During the post-natal follow-up: 15 newborns did not require ATD. Their thyroid function tests at 3-5 post natal days were: TSH: 3[1.2-5.7] mU/L, FT4: 26.8 [15.5-30.6] pM/L, FT3: 6.6 [6.3-8.1] pM/L, TRAK:6.8[2.2-10.9]UI/L. Among them, 3 neonates developed central (n=1) or primary (n=2) hypothyroidism and were treated with L thyroxin within the first post-natal month. 18 neonates (54.5%) had overt hyperthyroidism (TSH: 0.1 [0.0-0.9] mU/L. FT4: 50 [37-54] pM/L. FT3: 11.6 [10.0-13.0] pM/L, TRAK: 12[6-35] UI/L) requiring treatment. Carbimazole was initiated at the age of 4.5 [3.0; 8.0] days, at a baseline dose of 0.8 [0.6-1.0] mg/k/d for a duration of 1.9 [1.3-2.5] months. 10 babies received beta-blockers and 7 combined treatment with L-Thyroxin. Treatment was well tolerated. Craniostenosis was observed in 1 neonate.

Conclusion: Repeating thyroid function tests in the first postnatal weeks was effective to detect hyper or hypothyroidism in neonates born from mothers with Graves disease. ATD was well-tolerated and effective to protect infants from the severe consequences of thyrotoxicosis.

P2-P383

A Successful Switch Experience from High-dose PTU to MMI on day 4 of Graves' Thyroid Storm in a 14-Year-Old Girl

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Background: The standard pharmacological treatment strategy of thyroid storm according to 2016 Japan Society of Pediatric Endocrinology Guideline. Although thiamazole (MMI) is recommended be used as the first choice in Graves' disease, the effect of propylthiouracil (PTU) to block the conversion from T4 to T3 in peripheral tissues encourages clinicians to use against thyroid storm in its very early phase, and switch to MMI later. Nevertheless, the optimal timing of the switch has not been established to date and recently, pediatric cases with thyroid storm are quite rare in developed countries.

Case: The patient was initially diagnosed as having Graves' disease at age 8 years in a rural area of Philippines and prescribed

with MMI. She quit hospital visiting soon after the diagnosis. At age 12 years, she continuingly had fatigue and palpitation. At age 14 years, the family moved to Japan. On the day of onset, she had a strong dyspnea and was unable to lie flat. She was brought to the tertiary care center to be diagnosed as thyroid storm and transferred to PICU in our hospital.

The patient was fully conscious and orthopneic. Bilateral exophthalmos and diffuse goiter were noted. Both the fT3 and fT4 were beyond the measurable range. The patient was treated with dexamethasone 8mg, PTU 1,200mg and iodine 200mg. Four days after the treatment, fT3 was decreased to the measurable range (8.0pg/mL). We immediately switched PTU to MMI 80mg. On 6th day, we reduced the dose of MMI into 60mg, switched dexamethasone to hydrocortisone. On 11th day, the symptoms and test results further improved and we reduced MMI into 30mg along with introduction of levothyroxine to prevent hypothyroidism and suspended iodine. On day 16, the patient was discharged from the hospital.

Discussions: In this case, high dose PTU rapidly suppressed fT3 within 4 days. Free T3 drop to measurable range can be a good indicator of optimal timing of switching PTU to MMI. Relatively higher dose of MMI as 80mg might be required to keep suppressing the thyroid just after the switch.

P2-P384

Graves's Disease During Pregnancy: The Impact on the Fetus and the Newborn

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Introduction: Graves's disease is frequent in women, its prevalence being 0.5-2% and its incidence 0.1-1% during pregnancy. Both TSH anti-receptor antibodies and the synthetic antithyroid drugs cross the placenta, increasing the risk of hypo- and/or hyperhtyroidism. Our objective is to describe the thyroid status of fetus and newborns from women with Graves's disease referred to our Department.

Materials and Methods: We included children of women affected with Graves's disease referred to the pediatric-endocrinology department of Bicêtre Paris Sud hospital between 2006 and 2017. Clinical and biological parameters have been recorded during first days of life. Results have been presented as means with intervals [minimum; maximum] at birth or at the treatment's introduction. The reference range of TSH at birth is 1.5-10 mUI/L and of fT4 is 13.5-34 pmol/l.

Results: 12 newborns have been included. 7/12 had hyperthyroidism (TSH : 0.2 mUI/L [0-1.5], fT4 median: 76.2 pmol/L [48-100]). 2 of these 7 presented neonatal hypothyroidism (TSH median: 60.2 mUI/L [40.2-84.14], T4 median: 4.65 pmol/L [2.3-7]) that evolved towards hyperthyroidism at days 9 and 10 and 5 had neonatal hyperthyroidism. One of them was treaded by L thyroxin during 10 days. 1 out of 12 had fetal hypothyroidism but had normal biological parameters at birth and 4 had no thyroid anomalies (TSH median 5.6 mUI/L [1.81-7.46] T4 median 17.4 pmol/L [15.2-20.6]). Synthetic antithyroid drugs were initiated in patients with hyperthyroidism at day 8 [1-14] for a mean duration of 41 days [11-120]: 5/7 with propyl thiouracyl at 5.2 mg/kg/d [1-10], and 2/7 with carbimazole at 1 mg/kg/d. Their mean level of antibodies was 24.7 UI/L [13-50] compared to 4.55 UI/L [1.3-7.6] in newborns with normal T4 and fT4 (*p=0.01)*.

Conclusion: In 11 years, we have had 8 children with a fetal and/or neonatal thyroid dysfunction. We confirmed the predictive value of the antibody plasma level for the development of hypo- and/or hyperthyroidism. The French Society of Endocrinology recommends a fT4, TSH and antibodies screening in cord blood, at days 3 and 5 in order to look for hyper- and/or hypothyroidism. In this cohort, several neonates developed hyperthyroidism after day 5 suggesting that a longer biological follow up may be needed until the disappearance of antibodies.

P2-P385

Thyroid Hormone Receptor β (THRB) Mutation: Two New Cases of Heterozygous Mutation with Significant Family History

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Introduction: Resistance to thyroid hormone (RTH) is a relatively uncommon disorder that is usually associated with mutations in thyroid hormone receptor (*THR)* beta, although rarely *THR* alpha mutations have been described. RTH beta (RTHB) is often inherited in an autosomal dominant pattern. We describe two cases of RTHB to highlight the significant variations in both clinical presentation and family history.

Case 1: A two year old patient presented with a three week history of diarrhoea, weight loss and lethargy. On examination the patient was tachycardic, dehydrated and had evidence of faltering growth (weight 8.95kg, SDS -2.8). Thyroid function taken at the time of admission showed a raised TSH of 6.35mu/L [0.3-3.8mu/L], raised Free T4 of 29.1pmol/L [9-19pmol/L] and a raised triiodothyronine (FT3) of 8.1pmol/L [4.29-6.79pmol/L]. Detailed evaluation revealed a family history of failure to thrive and childhood thyroid illness in the father and paternal aunt (who also has had thyroid surgery). In view of the biochemistry and family history, the patient underwent genetic analysis that revealed M334R mutation in *THR* confirming a diagnosis of RTH (beta). The patient was initially commenced on a short course of carbimazole and propranolol prior to genetic confirmation but the treatment was subsequently discontinued. On further follow-up she was noted to be symptom free and gaining weight adequately.

Case 2: A five year old patient was referred to the endocrine clinic with poor weight gain [weight 13.8kg (-2.37SDS)]. Thyroid function tests revealed raised TSH [5.93mu/l, 0.3-3.8] and raised FT4 [28.6pmol/l, 9-19]. On examination, the patient was euthyroid and asymptomatic. Further investigations revealed that the patient's mother had an elevated T4 of 21.3pmol/L and elevated T3 of 8.8pmol/L with the TSH in the normal range. Patient's 8 year old sister had a T4 of 24pmol/L and T3 of 12pmol/L with a normal TSH. Subsequent genetic analysis of the patient and family showed a single base change in Exon 10 [c.1357C>T Pro453Ser] of *THR*

confirming RTH (beta). The patient did not require any treatment and remains under regular follow-up with good weight gain.

Conclusion: These cases demonstrate the highly variable presentation of RTHB. The combination of elevated serum levels of free T4 and TSH should suggest a diagnosis of RTHB. The inheritance pattern highlights the importance of thorough family history. Timely genetic analysis would help to confirm the diagnosis and avoid any unnecessary treatment.

P2-P386

Triac Treatment Response to Thyroid Hormone Resistantance

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Aim: Resistance to thyroid hormone (RTH) is a disease characterized by decreased sensitivity to thyroid hormone in the peripheral tissues such as cell membrane, metabolism, or nuclear receptor. In THRB gene mutation induced RTH, the effect of T3 on TRβ mutant receptors in the liver and the pituitary decreased, on TRα receptors located in the brain and heart increased. Triac's activity is similar to T3.

Case: A 1-month-old girl patient was admitted because of detection of elevated TSH level in the national screening program. With regards to her family history there was no thyroid disease in the family and in the mother of the patient during pregnancy. The patient's physical examination revealed a live gaze, anterior fontanel 3x3 cm, body weight of 3500g (10-25 p), height 52 cm (25-50 p), pulse: 190/min, blood pressure : 90/pulse, thyroid stage 0, and puberty tanner stage 1. In his laboratory, sT3: 8.62 pg/ml (2.76-4.38), sT4: 3.31ng/dl (0.75-1.49), TSH: 7.86 μIU/ml (0.77-5.64), thyroglobulin: 105 ng/dl(1.6-59.9), İodine(urine): 12.7 ug/dl, TSH receptor antibody (TRAB): 8.36 U/L (0-14), thyroid autoantibodies were negative. Her mother tested normal for thyroid functioning. In the genetic analysis of the patient suspected of thyroid hormone resistance, the P453H c.1358C> A mutation was detected heterozygously at the 10th exon of the THRB gene. Triac therapy began at 0.5 mg/kg/ day (1750 mcg/ day) In the follow up examination, the patient's pulse rate decreased to normal and sT3: 6.09 pg/ml (2.76-4.38), sT4: 1.41 ng/dl (0.75-1.49),TSH: 7.44 μIU/ml (0.77-5.64).

Conclusion: In RTH due to THRB gene mutations, Triac binds to mutant TRβ receptors, reducing the effect of TRα receptors on the decrease in thyroid function tests and the decrease in fT3 levels. Like in our case, cases of high levels of fT3 have been reported in the literature when clinical recovery was obtained with Triac therapy. This effect is thought to be secondary to the cross-reaction. In view of this, or this reason, triac dose titration should take into account clinical improvement as well as thyroid function tests.

P2-P387

Phenotype and Genotype of Four Patients with Thyroid Hormone Resistance Syndrome Due to Mutations in the *THRB* Gene

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Background: Resistance to thyroid hormone (RTH) is a dominantly inherited rare disorder (1:40000) mainly due to mutations in the *THRB* gene that lead to a decreased end-organ responsiveness to thyroid hormone. Clinical and molecular characteristics of four patients with RTH are described.

Patients & Methods: Four patients from three non-related families were studied; two boys (8.3 and 9.2 years old) and 2 adults (35 year old male and 27 year old female, the mother of the younger boy). RTH diagnosis was confirmed by sequencing analysis of the *THRB* gene.

Results: The four patients presented with various phenotypes. All individuals had persistently elevated circulating free thyroxine (FT4) and/or free triiodothyronine (FT3) associated with non suppressed thyroid stimulating hormone (TSH). They were clinically euthyroid and all had non-autoimmune goiters of various sizes. Antithyroid drugs were previously administered in both adults without successful suppression of the thyroid hormones. The 35 year old male was initially diagnosed with atrial fibrillation and treated with beta blockers. He had mild degree of cognitive impairment. The 27 year old female had resting tachycardia with no other symptoms of thyroid dysfunction. Her 8.3 year old son was investigated because of positive family history for RTH. He had been diagnosed with attention deficit disorder and also had resting tachycardia. The oldest boy underwent thyroid function tests as a part of investigation for obesity, learning difficulties and hyperactivity disorder. Direct sequencing analysis of the *THRB* gene revealed three previously reported mutations: p.Arg438Cys mutation was found in the two related patients, p.His435Leu was found in the 35 year old male and p.Pro453Thr was found in the oldest boy.

Conclusions: Common mutations in the *THRB* gene are characterized by various phenotypes; clinically asymptomatic, thyroid hormone deprivation suggestive symptoms or thyroid hormone excess symptoms. RTH can be suspected in both children and adults with elevated thyroid hormones and not suppressed TSH. Prompt molecular diagnosis and genetic counseling could prevent unnecessary tests and inappropriate treatments.

P2-P388

Clinical Course in a Girl with Two HTPO Mutations – Homozygous c.1268G>A (p.Gly393Arg) and Heterozygous c.208C>G (p.Ala70Pro): 27 Years of Follow Up

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Of the several genetic defects responsible for thyroid dyshormonogenesis, mutations in TPO gene are the most prevalent causes of inherited defects in CH. Prevalent mutations are in exons 8-11 (catalytic site).

Case presentation: girl, born at 16d after term, before the introduction of the neonatal screening, with asphyxia, BL 55 cm, BW 4 kg. Because of insufficient weight gain, feeding difficulties, prolonged jaundice she was referred to a pediatric endocrine clinic highly suspicious for congenital hypothyroidism (CH). At d 42 classical clinical signs of CH were fully present, the clinical diagnosis was confirmed by the hormonal constellation, a gland in situ was present as well (table). L-T4 treatment was introduced, the dosages increased gradually up to 75 mcg/d. At 11 yrs the treatment was discontinued by the mother and permanent primary CH with an eutopic thyroid were reconfirmed. The therapeutic strategy changed (gradual increment of L-T4, not until "toxic" dosages), a stable euthyroid situation was achieved, the adherence of the patient and the family improved. Normal growth and development, very good school and academic results were evident during the complex follow up including the entire transition period. The patient presents a suitable candidate for the hTPO study (permanent severe CH, eutopic thyroid, measurable Tg). A homozygous mutation c.1268G>A (p.Gly393Arg) and a heterozygous missense c.208C>G (p.Ala70Pro) were found by Sanger sequencing. The homozygous mutation is new, undescribed in the databases. A stop-gain mutation, with the functional consequence of a protein lacking the catalytic site and therefore inability of effective thyroid hormone synthesis (p.Gly393*Ter), on the same position has been described. The missense heterozygote c.208C>G (p.Ala70Pro) in exon 4 is a rare variant (Exac MAF=0.007) with unknown clinical significance and may also contribute to the phenotype as it is predicted as possibly damaging and deleterious by Polyphen and SIFT prediction programs.

Table 1. Hormonal data (for Abstract no P2-P388)

Age	NTSH mu/l	TSH mU/l	T4 nmol/l	Tg ng/ml	fT4 nmol/l
42d		>200	33	ND	
11yrs	107	139	<20	22.6	<1.2

Conclusions: early molecular genetic studies are important for patients with primary CH and eutopic thyroid glands for refining the treatment strategy; increased risk for thyroid cancer should be kept in mind. Genetic consultation and possibilities for having healthy offsprings in patients diagnosed before screening introduction is nowadays part of the complex personalized care. The patient contributes to the genotype-phenotype data in CH due to hTPO mutations.

P2-P389

A Neurological Disease Mimicking Central Hypothyroidism: MCT8 Deficiency

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Introduction: Monocarboxylate transporter 8 (MCT8) is necessary for the transport of T3 to neurons. The case presented here is a male infant with neuromotor retardation initially treated for central hypothyroidism who showed no benefit from treatment and a final diagnosis of MCT8 deficiency was made.

Case Report: A male infant at 13 months of age was brought to the clinic because he was unable to sit without support. The perinatal history revealed that he was born after uneventful delivery with birthweight of 3650 gr as the first child of non-consanguinous parents. On physical examination, body weight was 9.5 kg (-0.74 SDS), length was 75cm (-0.92 SDS), and head circumference was 45 cm (-1.59 SDS). Neorological examination showed hypotonicity in the trunk and spasticity in the lower extremities. He had head control but he was unable to sit without support.

In the thyroid function tests, free T4 (fT4) was low (0.68 ng/dl; N: 0.8–1.9 ng/dl) and TSH was normal (2.8 mIU/L; N: 0.4–5.0 μU/ml). The other anterior pituitary hormones as well as the brain MRI and EEG were normal.

With the diagnosis of central hypothyroidism, L-thyroxin replacement treatment was started at 3 mcg/kg/day. The dose was increased to 8 mcg/kg/d during monthly follow-up, because no increase was observed in the fT4 level. At the end of 3 months, fT4 was low (0.74 ng/dl), TSH was normal (2.1 mIU/L) and free T3 (fT3) was high (5.3 pg/ml).

Despite the increase in fT3, low fT4 level and retarded neuromotor development led us to consider MCT8 deficiency (Allan-Herndon-Dudley syndrome). The L-thyroxin replacement treatment was terminated and further diagnostic workup was planned. The genetic analysis showed c.670 G>A (A224T) hemizygote mutation on the SCL16A2 gene. The family was given genetic counselling and the patient was followed up with supportive physical therapy.

Conclusion: Mutations in the SLC16A2 gene, which encodes MCT8, cause Allan–Herndon–Dudley syndrome that is characterised by abnormal thyroid hormone levels and severe neuromotor retardation. The syndrome is defined in male patients because of X-linked transmission. The characteristic thyroid hormone abnormalities in MCT8 defect are high fT3, low fT4, and normal/high TSH. In male children with retarded development and neurological findings, this syndrome should be considered when evaluating thyroid function tests.

P2-P390

Multinodular Goiter in Childhood: Look for DICER1 Mutation

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Introduction: Multinodular goiter (MNG) is a common disorder of the thyroid gland, characterized by thyroid enlargement due to the development of multiple hyperplastic nodules. It is infrequent in children. Here, we present the case of two families with novel DICER1 mutations and familial history of nodules in adolescence.

Observations: A 10-year-old female presented a MNG. TSH, Free T3, Free T 4 were in the normal range and thyroid autoantibodies were negative. Familial history included an MNG operated at the age of 15 in her brother and at the age of 19 in her father. Fine needle cytology of the thyroid was of undetermined significance. She underwent a thyroidectomy, and histology revealed a benign follicular adenoma. Based on familial history and young age, a hereditary predisposition syndrome was suspected and genetic testing of DICER1 was undertaken. An heterozygous germ-line DICER1 variant was identified in Exon 4 (c.322C>T, p.Gln108Stop). This variant was predicted to be deleterious with a premature stop codon and the loss of protein function.

A 2-year-old girl presented a pleuropulmonary blastoma. Familial history showed that her mother had a left unilateral retinoblastoma at the age of three, and thyroid nodules leading to a thyroidectomy at the age of 15, and that her sister also had a thyroidectomy at the age of 7 for nodules. Genetic screening of DICER1 showed an heterozygous germ-line mutation in Exon 17 (c2692del, p.Glu898Lysfs*10) in the girl and her mother.

Discussion: Thyroid nodules and MNG are uncommon in pediatric population. Familial cases, or the association with familial tumors, should prompt the search for DICER 1 mutation. DICER1 syndrome is a pediatric cancer predisposition condition causing a variety of tumor types in children and young adults. Recent recommendations have been established for detecting pleuropulmonary blastoma, ovarian sex cord-stromal tumors and other DICER1-associated tumors.

P2-P391

Application of Elastography in Assesment of Different Benign Thyroid Lesions in Children and Adolescents

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Introduction: Elastography is a noninvasive imaging technique based on estimation of the tissue flexibility. There are two methods of elastography: Static Elastography and Shear Wave Elastography. Scale of deformation under pressure is presented as a colourful map – elastogram, where red colour signify soft tissues, green colour signify middle tough tissues and blue colour signify tough tissues. Analysis of elastograms enable us to present results as ROI1/ROI2 index. In adult patients decreased flexibility is characteristic for malignant lesions (except follicular thyroid carcinoma) and benign lesions are flexible in elastography.

Aim of Study: The aim of our study was to evaluate the deformation in elastography of different benign lesions.

Materials and Methods: In a prospective study between February 2013 and December 2017 112 patients with lesions in thyroid were examined. We compared ROI1/ROI2 index with results of fine needle aspiration cytology (FNAC) to determine any correlations. Elastography parameters were acquired with Toshiba Aplio MX SSA-780A system and analyzed while comparing of the stiffness of ROI 1 (of healthy tissue) to ROI 2 (of the nodule).

Results: All 112 patients were benign in cytological examination. In 34 patients with lymphocytic thyroiditis ROI1/ROI2 index was 2.47 with SD 1.42. In 78 patients with nodular goiter, colloid nodular goiter, nodular goiter with oxyphilic metaplasia, partially cystic nodular goiter, lymph node, lymphatic tissue with single Hodgkin like cells, lesion resembling haemorrhagic cysts ROI1/ROI2 index was 3,55 with SD 2.99 and it was statistically significant higher than in patients with lymphocytic inflammation ($p = 0.048$).

Conclusion: Our results suggest that all benign lesions in thyroid in children were usually soft in elastography and the lymphocytic thyroiditis in children seems to be more soft than the nodular goiter.

P2-P392

Clinical Characteristics and Predictive Factors for the Detection of Thyroid Cancer in Children with Thyroid Nodules

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Thyroid nodules in children are less common than adults. However, pediatric thyroid nodules have higher rate of malignancy compared with adults, and also have increased risk of metastasis and recurrence. In this study, we analyzed clinical features, laboratory findings, and thyroid ultrasound (US) of children with thyroid nodules to determine predictive factors of thyroid cancer.

Total 268 patients under 18 years of age with thyroid nodule whom visited Severance Children's Hospital from January 2005 to May 2017 were retrospectively reviewed. Patients were divided into thyroid cancer group and benign nodule group, and clinical, laboratory, US data had been compared. Variables with statistical significance were used to analyze predictive factors of thyroid cancer.

Among the 268 patients, 101 patients were diagnosed with thyroid cancer, and the remainder of 167 patients were set to be benign nodule group. Thyroid mass was more often palpated in thyroid cancer group, whereas grade 2 goiter was more often seen in benign nodule group. The size of thyroid nodule was larger in thyroid cancer group. Nodule with microcalcifications, regional lymph node alterations, irregular margins, and intranodular blood flow on US were significantly related to thyroid cancer. Palpable thyroid nodule, nodule with microcalcifications, and lymph node alterations showed statistical significance in predicting thyroid cancer, while mixed echogenicity on US suggested benign nodule.

In conclusion, palpable thyroid nodule, nodule with microcalcifications, and lymph node alterations are predictive factors of thyroid cancer, so further evaluation including fine needle aspiration biopsy should be considered in patients with these findings.

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Thyroid Nodules in Prader-Willi Syndrome

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Objectives: Prader-Willi syndrome (PWS) is a complex multisystem disorder due to loss of expression of paternally derived genes in the PWS critical region on chromosome 15q11-q13. The majority of the cases are due to the deletion of this region (del15), while 20-30% are caused by a maternal uniparental disomy of chromosome 15 (UPD15). The clinical picture is characterized by neonatal hypotonia and feeding difficulties in early infancy, early development of hyperphagia with progressive development of severe obesity (if uncontrolled), short stature, behavioural problems, cognitive impairment, psychiatric illness, and multiple endocrine abnormalities. Disturbances in the hypothalamic-pituitary-thyroid axis are observed with variable frequency in PWS. Hypothyroidism is the most frequent alteration, and may be of central or peripheral origin. Other thyroid abnormalities in PWS subjects are rarely reported, including congenital hypothyroidism caused by an ectopic sublingual thyroid gland and fetal goiter. Because data on the ultrasonographic examination of the thyroid gland in PWS subjects are not currently available, this preliminary study aims to evaluate the thyroid morphology and function in transition individuals and young adults with PWS.

Methods: Twenty subjects with genetically confirmed PWS [15 patients with del15 and 5 individuals with UPD15, 12 females, aged 30.6±5.9 yr (mean+SD) (range 18.0-39.0 yr), Body Mass Index (kg/m^2) 46.7±8.8 (range 35.8-63.5] were studied. Thyroid function tests, including antithyroid antibodies, and thyroid ultrasonography (TUS) were performed in all subjects.

Results: Eighteen PWS subjects were euthyroid, while 1 female had central hypothyroidism and 1 female showed an overt hyperthyroidism. Antithyroid antibodies were negative in all subjects. TUS demonstrated a mild hypoechogenicity in 6 cases (30%) and a hyperechogenic pattern in 1 female. Six PWS had nodules with a diameter >5 mm (30%); 2 females had a single nodule, while 2 nodules were found in 3 females and 1 male. In 2 patients there were parenchymal microcalcification. Thyroid vascularization was reduced in 5 subjects.

Conclusions: Our results seem to demonstrate that alterations in thyroid structure can frequently be observed in patients with PWS. In this light, screening for altered thyroid morphology should be a routine element of care for individuals with PWS.

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Early Medullary Thyroid Carcinoma (MTC) in an infant with Multiple Endocrine Neoplasia Type 2B (MEN2B, RETS Mutation codon 891)

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Introduction: An age-related progression from C-cell hyperplasia to medullary thyroid carcinoma (MTC) is associated with various germ-line mutations in the rearranged during transfection (RET) proto-oncogene that could be used to identify the optimal time for prophylactic surgery. In 207 patients from 145 families there was a significant age-related progression from C-cell hyperplasia to MTC. Thus, early diagnosis and prevention are particularly crucial.

Case description: We describe a 24 months Qatari male who was diagnosed with medullary thyroid cancer. At age 22 months he was screened for RET proto-oncogene because his mother found had MEN2B proven germline RET mutation. Physical examination showed stable vital signs, coarse facial features, enlarged lips and thickened gum, disproportionate short stature with decrease U/L ratio and height SDSD = -3.69. There was no goiter or cervical lymphadenopathy. No skin pigmentation. No palpable abdominal mass. The genetic screening showed a germline RETS mutation in

codon 891. Mother was anxious to minimize the future risk and therefore wish to undertake thyroidectomy as early as possible. Therefore, we request screening for MTC at age of 24 months. Unfortunately the screening showed positive findings for MTC. Thyroid U/S revealed a small foci of globular dystrophic calcification in the left lobe concerning for an early medullary cell carcinoma. Abdominal U/S was normal. Labs showed very high serum level of basal Calcitonin but normal CEA, PTH and Free T4 and TSH levels. Skeletal survey showed normal finding. The patient has been considered for early total thyroidectomy.

Discussion: Patients with MEN2B and RETS mutation in codon 891mutation have moderate gene penetrance and the recommended age to begin annual screening for MTC is 5 years and the suggested timing of prophylactic thyroidectomy is childhood or young adulthood. This infant, with this mutation, had evident MTC at the age of 2 years that raises concern about late screening for these patients.

Conclusions: We report for the first time the occurrence of MTC at an early age (2 years) in an asymptomatic toddler with MEN2B, with RETS mutation in codon 891. The recommended delayed screening may miss cases of MTC in these children.

P2-P395

Serum Level of Biotin Rather Than the Daily Dose Is the Main Determinant of the Interference on Thyroid Function Assays in Patients with Biotinidase Deficiency

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Introduction: High doses of biotin are reported to cause incorrect results in various immunoassays in some patients. However, there is no systematic study regarding biotin interference in childhood.

Aim: To assess thyroid function with different methods in subjects with biotinidase deficiency, to determine the factors causing interference, and to investigate the efficiency of the methods for overcoming interference.

Method: The study included children with biotinidase deficiency who were regularly treated with biotin [Group 1, n=44, female/male: 26/18, median dose: 10 mg/day (25-75p; 10-10), age: 1.83 years (1.04-2.90)] and healthy subjects [Group 2, n=30, female/male: 16/14, age: 1.05 years (0.37-3.37)]. Blood samples in Group 1 were obtained two hours after the morning biotin dose. Serum fT3, fT4, and TSH levels were measured using both biotin-containing (Beckman Coulter) and biotin-free methods (Siemens Advia Centaur XP). Serum biotin levels were measured (in duplicate) with an ELISA-based kit. Streptavidin coated particles were used to remove biotin for serum samples of cases with biotin interference.

Results: Age, gender, weight, and height were similar between two groups. The measurements were first performed with Beckman Coulter. In Group1, TSH levels were normal in all of the cases but remarkably high levels of fT3 and fT4 were found in 26 (59.1%) and 25 (56.8%) patients, respectively. Thyroid hormone functions were all normal in Group2. The clinical features including biotin doses were similar (p=0.955) between interference-positive (Group 1A, n=26) and remaining (Group 1B, n=18) patients except significantly higher serum biotin levels Group 1A [221 µg/L (145-349) vs. 49 µg/L (38-71), p <0.001]. Serum biotin levels in Group 1 showed a strong positive correlation with fT3 (r=0.867) and fT4 levels (r=0.905). The serum biotin level of 80.35 µg/L was found to be the best cut-off value for predicting interference (96.2% sensitivity and 94.4% specificity) with a discriminative ability of 0.987±0.01, p<0.001 (95% CI: 0.962–1.000). When analyzed with Siemens Advia Centaur XP, all thyroid function tests were normal in both groups except one patient (2.27%) with high fT3 level in Group 1. Repeated tests with Beckman Coulter after neutralization of biotin with streptavidin magnetic particles in serum samples of the cases in Group1A revealed no interference.

Conclusion: Interference is an important problem in thyroid function tests in children receiving biotin treatment for biotinidase deficiency. Serum levels of biotin rather than the dose are the main determinant of interference, which can be eliminated by choosing appropriate laboratory methods.

P2-P396

Thyroid Function Tests and Affecting Factors in Twins and Triplets

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Aim: To evaluate thyroid function tests and affecting factors in twin and triplet newborns.

Method: 655 newborns from 320 multiple gestations(305 twins/15 triplets) were evaluated retrospectively with respect to thyroid function tests (FT4, TSH). The effects of birth order, birth weight SDS, gestational age, maternal thyroid disease, gestational diabetes, assisted reproduction, dopamine were analysed.

Results: Gestational age was 25.0-37.1weeks(Mean: 33.0±2.2). 38.6% of pregnancies were resulted from assisted reproduction. 10% of babies were SGA. Mean TSH was 5.3±10.9µIU/ml and 5.6±7.5 µIU/ml; mean ft4 levels were 1.53±0.37 and 1.49±0.34ng/dl for the first and second born twins respectively(p:0.35 for TSH; p:0.14 for ft4). The frequency of hypothyroidism was 1.07% (7/655).Only one twin (dizygotic)was concordant for hypothyroidism. SGA(59/549) babies had higher TSH(6.7±5.4 vs 5.3±9.7 µIU/ml; p:0.001). Maternal thyroid disease, gestational diabetes and hypertension were detected in 10.5%, 14.5% and 11.7% of pregnancies. Mean TSH was higher in neonates with maternal thyroid disease (7.5±11.5 vs 5.3±8.8 µIU/ml) but the difference was statistically insignificant.There was no difference in TSH and fT4 values of babies born from pregnancies with assisted reproduc-

tion. fT4 was lower in babies with dopamine treatment(1.38±0.4 vs 1.52±0.34 ng/dl; p:0.021).A positive correlation was detected between TSH and dopamine treatment duration. A positive correlation was also present between fT4 and gestational age. fT4 and TSH levels were similar in tiplets and birth order did not affect thyroid function tests.

Conclusion: There is a high frequency of hypothyroidism in twins and triplets Although there are many confounding factors, thyroid function tests do not differ in twins and triplets.

P2-P397

Hypothyroidism in a Child During Treatment with Nivolumab for a Glioblastoma

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Objective: The programmed cell death 1 protein (PD1) is a T lymphocyte membrane receptor, which when bound to its ligand PD – L1 inactivates the cytotoxic T lymphocyte, thereby down regulating the immune response. Cancer may upregulate PD – L1 on the cell surface, further downregulating the immune response. Nivolumab, a so called check point inhibitor, is a PD1 antibody, and when bound to PD1 keep the cytotoxic T lymphocyte active. Cytotoxic T lymphocyte activation by nivolumab has proven effective in treating hypermutant tumors. However, activating cytotoxic T lymphocytes may cause hormonal side effects. We describe a child developing primary hypothyroidism during treatment with nivolumab for an inoperable glioblastoma.

Methods: Case story.

Results: At the age of five years the patient was diagnosed with a frontal malignant nerve sheet tumor. After tumor resection, he was treated with radiation therapy 36 Gy with tumor bed boost of 25.2 Gy. Six years after initial diagnosis, the tumor recurred. At that time, the tumor was subtotal resected, histology showed glioblastoma WHO grade IV. Re-irradiation with 36 Gy in 20 fractions and a boost of 18 Gy was initiated with concomitant temozolomide treatment. Four months after initiated treatment MRI showed new tumor progression. Tumor was found to have a mutational load of more than 34000 mutations and treatment with nivolumab 3 mg / kg every second week was initiated. After four months MRI showed almost complete tumor regression, but at the same time the child had developed primary hypothyroidism and treatment with tablet L-thyroxin was initiated. No other hormonal organs were affected.

Conclusion: Check point inhibitor treatment for different cancers has become an option in adults, and may also be an option for cancer treatment in children where the opportunities of conventional treatment are exhausted. We describe a child developing hypothyroidism during successful treatment with the check point inhibitor nivolumab for glioblastoma. When treating with check point inhibitors, patients should be monitored on regular basis for hormonal deficits, particularly for hypothyroidism and hypopituitarism.

P2-P398

Diagnosis and Clinical Course of Amiodarone Induced Hyperthyroidism in Three Adolescent Patients

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Amiodarone induced hyperthyroidism is a known side effect of amiodarone treatment. In the pediatric population long-term amiodarone treatment is rarely indicated because of its severe side effects including thyroid function impairment and therefore treatment is restricted to therapy resistant arrhythmias. In the literature scarce data is available on management and therapy of amiodarone induced thyroid dysfunction at a young age.

We present three adolescent patients developing amiodarone induced hyperthyroidism in the months after amiodarone therapy. Interestingly the gap between amiodarone treatment and development of symptoms and or diagnosis of hyperthyroidism was between three and ten months. In two patients hyperthyroidism was transient and resolved without treatment. These two patients, one boy and on girl were almost asymptomatic. In contrast in one male patient overt and severe hyperthyroidism developed. Treatment with thiamazole was not effective and control of hyperthyroidism was only achieved under prednisone treatment, which had to be continued for nine months. Clinical evaluation proved an amiodarone induced destructive thyroiditis in this patient.

Amiodarone induced thyroid dysfunction is frequent also in pediatric patients with long-term amiodarone treatment. Patients and clinicians should be aware of the impact of amiodarone on thyroid function during and also in the months and maybe years after treatment. Careful follow-up is needed, as symptoms might aggravate the underlying cardiac disease in these patients. Amiodarone induced thyrotoxicosis often resolves without treatment but can be challenging in some cases.

P2-P399

Allogenic Bone Marrow Transplantation in Children: Effect on Thyroid Function

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Objective: To report the incidence of thyroid dysfunction of patients who underwent allogenic BMT during childhood.

Patients and Methods: 82 patients (56 boys) who were transplanted from an HLA matched donor at a mean age of 7.5 ± 4.8 years (range 0.18-17.5 years) were followed prospectively having measurements of fT4, TSH twice yearly, using chemiluminescence. Patients with elevated TSH higher than 8 μIU/ml had a repeat evaluation in a month time. Thyroid sonogram was performed yearly in patients who have received radiation therapy (RT) and at least once in patients with no history of RT. The initial diagnosis included acute lymphocytic leukemia (ALL), acute myelocytic leukemia, thalassemia, Fanconi anemia, aplastic anemia. The conditioning regimen consisted of Busulfan(16mg/Kg) + Cyclophosphamide(200mg/Kg) +/-Fludarabine(100mg/m^2) and antithymocyte globulin. Four patients received total body irradiation (TBI). Seven patients received CNS prophylaxis with 12 Gys for ALL.

Results: The age of the last evaluation was 11.97 ± 5.17 yrs and the years post BMT were 4.47± 3.24. Fifty patients (60.9 %) patients had normal thyroid function. Twenty five patients (30.4%) had primary hypothyroidism as evidenced by TSH levels higher than 8 μIU/ml and low or low normal fT4 levels verified with a second measurement and they were started on replacement therapy with L-thyroxine. One patient had TSH higher than 10 μIU/ml which returned to normal and she has normal thyroid function up since. Among the patients with hypothyroidism 2 had received TBI and 3 had received 12Gys prophylaxis RT. Four patients (4.8 %) had compensated hypothyroidism as evidenced by TSH level range greater than 5 and less than 8 μIU/ml. None of them had progressed so far to overt hypothyroidism. One patient with a history of TBI, borderline elevation of TSH and low fT4 was considered to have central hypothyroidism and he was started on replacement therapy. One of the hypothyroid patients who had received TBI had a thyroid nodule for which he had an FNA consistent with a dysplastic nodule BETHESDA 1. One of the normothyroid patients who had also received TBI had papillary Ca and underwent thyroidectomy.

Conclusions: Thyroid dysfunction is quite common complication of BMT in this pediatric population. The exact mechanism is not clear. Patients who have received radiation prior to BMT are at increased risk. Patients who underwent BMT should have evaluation of thyroid function routinely in order to prevent overt hypothyroidism.

P2-P400

Follow-up in Children with Non-Obese and Non-Autoimmune Subclinical Hypothyroidism

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Introduction: Subclinical hypothyroidism is a form of thyroid dysfunction in which TSH level is high while serum free thyroxin (fT_4) and free triiodothyronine (fT_3) are within normal reference range. In this study, it was aimed to investigate effects of subclinical hypothyroidism on anthropometric characteristics, blood pressure, glucose and lipid metabolism by evaluating course of subclinical hypothyroidism during follow-up without treatment.

Methods: The study included patients aged 3-18 years with BMI<85th percentile and negative thyroid auto-antibodies (anti-TPO and anti-Tg) who were diagnosed as subclinical hypothyroidism. These patients were assessed at time of diagnosis, on month 3 and at year 1 during follow-up.

Results: Mean age was 9.65±2.89 years (range:4.5-16.24) in 25 cases with subclinical hypothyroidism. At time of diagnosis, 22 cases with subclinical hypothyroidism were asymptomatic. These patients were observed without treatment. Thyroid autoantibodies were negative at time of diagnosis and year one in all patients. The mean TSH level was 6.92±0.92μIU/ml in the diagnosis, 4.77±1.57μIU/ml in the third month and 4.51±1.79μIU/ml in the first year of follow-up. 73.7% of subclinical hypothyroidism was recovered. There was no significant difference among fT_4 levels obtained at time of diagnosis, on month 3 and at year one. While there was no significant difference between fT_3 levels obtained at time of diagnosis and on month 3, fT_3 levels at year one were significantly lower than those obtained at time of diagnosis (p=0.014) but were comparable to those obtained on month 3. There was no statistical significant difference between heart rate, diastolic blood pressure, lipid profile, fasting blood glucose, fasting insulin level, HOMA-IR, hemoglobin, white blood cell, platelet, CRP levels and thyroid volume in diagnosis and in the first year of follow-up. In the first year of follow-up, systolic blood pressure and high sensitive CRP value were significantly higher than the diagnosis. However, it was seen that these values were similar in the ongoing group with subclinical hypothyroidism.

Conclusion: We observed that subclinical hypothyroidism was recovered in 68.2% on month 3 and 73.7% of children at year one among patients with non-otoimmune subclinical hypothyroidism, normal BMI and TSH level of 5.5-10 μIU/mL. We concluded that there was no progression to overt hypothyroidism during one-year follow-up and that subclinical hypothyroidism had no effect on height SDS, BMI SDS, blood pressure, glucose and lipid metabolism during follow-up without treatment in this group of patients.

P2-P401

Clinical Management of Childhood Hyperthyroidism: A Longitudinal Study at a Single Center

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Background: The approach to clinical management of Graves' disease (GD) is debatable.

Objective: This study aimed to identify predictors of remission in pediatric GD.

Methods: A longitudinal study of 36 children and adolescents with Graves´ disease followed from 1997 to 2017 at a single pediatric tertiary hospital was performed. Clinical and biochemical parameters, including comorbidities, treatment with anti-thyroid drugs (ATD) or definitive therapy [radioiodine (RIT) and thyroidectomy], and remission as the main outcome were collected. We performed a multivariable logistic regression analyses to identify likely predictors of remission, and a Kaplan-Meier survival curve to compare outcomes between groups.

Results: Among patients, most were female, in late puberty, with exuberant symptoms at onset. Eleven also suffered from Down syndrome (DS). Thirty-four patients (94%) started on methimazole from disease onset, and 25 (69%) received it as only therapy, with a mean duration of 2.7±1.8 years. Six crossed to RIT and three underwent thyroidectomy; no DS patient received definitive therapy. Remission was higher in DS patients (45% vs. 25%, p=0.24), but afterwards (3.9±2.5 vs. 2.3±1.4 years, p<0.05); no significance in relapsing (20% vs. 15%). Females were less likely to reach remission (p<0.05); serum free T4 at onset was higher (p<0.05) in patients who required definitive therapy. Thyroid-stimulating immunoglobulin (TSI) values normalized in exclusively ATD therapy, especially from two years on (p<0.05).

Conclusions: 1. Males were more likely to achieve remission; 2. TSI values may normalize in Graves' disease, notably from the second year of treatment; 3. Children with Down syndrome may benefit with conservative management in GD. Larger prospective multi-centered studies should confirm these findings.

P2-P402

Association of Thyroid Stimulating Hormone and Free Thyroxine with Cardiometabolic Risk Factors in Euthyroid Korean Children and Adolescents Aged 10–18 years: The Korean National Health and Nutrition Examination Survey 2015

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Objective: The present study aimed to evaluate the association of free thyroxine (FT4) and TSH with insulin resistance indices in euthyroid Korean children and adolescents using nationally representative data.

Methods: A total of 259 children and adolescents were included in data from The Korean National Health and Nutrition Examination Survey 2015

Results: TSH levels were significantly positively associated with HOMA-IR (β=0.106, *P*=0.039) whereas TSH levels were marginally associated with fasting insulin levels (β=0.085, *P*=0.098). FT4 levels were significantly negatively associated with HOMA-IR (β=−0.121, *P*=0.018) and fasting insulin (β=−0.128, *P*=0.012) after adjustment for confounding variables including gender, age, BMI SDS, SBP, DBP, T-C, TG, HDL-C, LDL-C, anti-TPO antibody, house income, smoking, alcohol intake, and physical activity. TSH (β=0.103, *P*=0.043) and FT4 (β=−0.119, *P*=0.020) were significantly associated with HOMA-IR whereas FT4 (β=−0.128, *P*=0.012) were significantly negatively associated with fasting insulin levels.

Conclusion: Our results suggest that free thyroxine (FT4) and TSH is related to insulin resistance in children and adolescents

P2-P403

Asymptomatic Hyperthyrotropinaemia in Children, Does It Correlate to True Thyroid Gland Dysfunction?

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Introduction: Thyroid stimulating hormone (TSH) abnormalities are a frequent laboratory test finding, which may hinder thyroid dysfunction. One of the most accurate laboratory methods for testing thyroid function (TFTs) is the *radioimmunoassay* (*RIA)* method. *RIA* is an immunoassay that uses radiolabelled molecules in a stepwise formation of immune complexes. It is a very sensitive in vitro assay *technique* used to measure concentrations of substances, usually measuring antigen concentrations (for example, hormone levels in blood) by use of antibodies.

Aim: The purpose of the study was to examine whether a random finding of hyperthyrotropinaemia (raised TSH with normal levels of FT4) is an indication of a thyroid gland disorder.

Subjects and methods: 48 healthy children (25 boys, 23 girls) were referred to the Paediatric Endocrinology Outpatients of a Tertiary Centre for hyperthyrotropinaemia found when TSH was performed either randomly, or due to family history of thyroid disorder or due to various symptoms (short stature, constipation, obesity). None of the children were on replacement therapy with levothyroxine. It was checked whether repeat and/or further testing of TFTs had been performed prior to referral and the laboratory method used to confirm results. All subjects had TFTs (TSH, Free T4, thyroglobulin, anti-TPO, anti-Tg) performed with the RIA method. Statistical analysis performed with SPSS, significant p value <0.05.

Results: Mean age of children was 8.9 years (median 9.7y, range 1-15 years old). At referral 28 children (77.5%) had abnormal TSH values (>5 mU/L, method ELISA), mean 6.59mU/L(range 5.05 to 12.35mU/L). Only 13 (27%) had TFTs repeated, 8(16.6%) had also a thyroid ultrasound performed. After testing with the RIA method, 20 children (41.6%) had raised TSH, and only one child had TSH>10mU/L. In the end, 11 children (22.9%) received replacement treatment with levothyroxine. Significant difference was observed between the mean TSH values at referral and the ones tested with RIA method (6.22mU/L and 4.55mU/L respectively, p<0.05). No statistical significance was observed between males' and females' TSH mean values either at referral or when tested with RIA, 5.83 mU/L and 6.69 mU/L (p=0.11), and 4.67mU/l and 4.42mU/L respectively, (p=0.76).

Conclusions: The enhanced sensitivity and specificity of TSH assays have greatly improved the assessment of TFTs. In mild hyperthyrotropinaemia (TSH>4.05mU/L, <10mU/L), clinical assessment of the patient is recommended. Abnormal thyroid function needs to be confirmed with an accurate method as RIA.

P2-P404

Hearing Loss Among Patients with Congenital Hypothyroidism

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Background: A high rate of hearing impairment has been reported in patients with congenital hypothyroidism (CH). However, this association has only been explored in a few studies with inconclusive findings.

Objectives: To assess the prevalence of hearing impairment among patients with CH and determine whether hearing impairment is related to delay in supplemental therapy, etiology of CH or other parameters.

Methods: Audiometry was undertaken prospectively for 65 patients with CH and 49 healthy patients aged 3 to 30 years. All patients with hearing impairments underwent otolaryngologist examination, and brain stem response audiometry was performed in patients with sensorineural loss.

Results: Hearing impairment was found in 18 patients (27.7%) with CH, among them 4 (6.2%) with sensorineural and 14 (21.5%) with mild conductive hearing loss. None of the controls had hearing loss. The etiology of CH in patients with sensorineural hearing was TPO mutation (2 patients), ectopic sublingual thyroid (1) and thyroid agenesis (1). Among patients with conductive hearing loss, the etiologies of CH were ectopic gland (6 patients), TPO mutation (4), thyroid agenesis (1), TSH resistance (1) and transient CH (2). In comparing patients with hearing loss to patients without hearing loss, no differences were found in time of diagnosis, initiation of L-T_4 therapy, screened TSH levels, gender, ethnicity or CH etiologies. Mean screened TT_4 levels were lower in patients with hearing loss (3.58 *vs*. 5.21 μg/dL, respectively), but this difference was non-significant.

Conclusions: We found a high prevalence of hearing loss among patients with CH. Both sensorineural and conductive hearing loss were found, with a higher rate for the latter. Hearing loss was not related to the etiology of hypothyroidism or delayed initiation of therapy; nevertheless, it is possible that non-adherence to thyroid supplement therapy has a role in hearing impairment. Our findings indicate that every child with CH must undergo audiometry, and long-term hearing follow-up is required.

P2-P405

Predictors of Permanent Congenital Hypothyroidism in Children

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Background: Congenital hypothyroidism (CH) is one of most common endocrine disease in childhood. If unteated, it is one of the leading causes of childhood intellectual disability. CH can be permanent, or can be transient in which thyroid function is spontaneously recovered. It is also known that among children with congenital hypothyroidism, the proportion of transient cases is higher in preterm than in full term babies. But there are few, if any, large studies which evaluated the risk factors of permanent congenital hypothyroidism. And most of previvous studies involved only full-term infants. So, in this study, we investigated the proportion of permanent hypothyroidism and the difference between transient and permanent hypothyroidism group, in CH patients including both term and preterm infants. We also tried to find out the predictive factors of permanent hypothyroidism.

Methods: In CH patients, we gathered information about demographic characteristics and information about thyroid function test and levothyroxine medication by retrospective chart review. Discontinuation of levothyroxine was tried when the patients were 3 years of age. Thyroid function test was followed up for more than 6 months after discontinuation. We compared the clinical charac-

teristics between permanent and transient group and investigated the risk factors for permanent CH.

Results: Patients were 82 infants who were born between July 2005-July 2014 and treated for congenital hypothyroidism in Gyeongsang National University Hospital (52 preterm and 30 full-term infants). Fourty-two (51.2%) were males. Eleven (13.4 %) were permanent hypothyroidism. There was no difference in proportion of permanent cases between preterm and full term groups (9.6 vs 20.0 %, p=0.198). Compared with transient cases, those with permanent hypothyroidism had higher levethyroxine dose at 1 yr, 2yr and at discoutinuation. levothyroxine dose at discontinuation of 2.88 μg/kg could suggest permanent CH at a sensitivity of 90% and a specificity of 71%, with an area under the ROC curve of 0.864.

Conclusion: Majority of CH patients discontinued successfully. Higher levothyroxine dose at discontinuation was found to be a predictive factor of permanent hypothyroidism.

P2-P406

Absence of Uptake on Scintigraphy Does Not Always Correlate with Athyreosis: Re-evaluation of Patients Diagnosed with Athyreosis Over a 10 Year Period in the Republic of Ireland

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Background: Thyroid imaging is recommended to determine the aetiology of congenital hypothyroidism (CHT). Currently scintigraphy is the gold standard imaging modality. Negative scinitigraphy despite the presence of thyroid tissue may lead to a spurious diagnosis of athyreosis. Few centres routinely perform both scinitgraphy and ultrasound so that the incidence of misclassified athyreosis is unknown.

Aim: To describe the incidence of sonographically normal thyroid glands in patients scintigraphically diagnosed with athyreosis using technetium (^{99m}Tc) and to determine if these patients have a distinct clinical phenotype when compared to patients with CHT who have normal uptake on scintigraphy.

Methods: All infants who screened positive for CHT and commenced levothyroxine treatment in the Republic of Ireland between 2007 and 2016 were identified. We identified all patients diagnosed with athyreosis on thyroid scintigraphy. Patients with no uptake on scintigraphy were invited to attend for a thyroid ultrasound scan if this had not been done previously. We re-evaluated the patients found to have a normal gland on ultrasound to establish if they had transient or permanent CHT.

Results: Four hundred and eighty-eight patients were diagnosed with CHT over this ten year period in the Republic of Ireland (incidence 1:1538 live births). Seventy-three patients had a presumed diagnosis of athyreosis with no uptake on scinitigraphy in the newborn period. Sonography demonstrated thyroid tissue (3 hypoplastic thyroid glands, 15 normal glands) in 18/73 (24.6%) patients who had negative scinitgraphy. Ten of the 15 patients with a normal gland on ultrasound were eligible for re-evaluation (aged over 3 years) and of these 6 (60%) had transient CHT.

Conclusion: Absence of uptake on scintigraphy does not always correlate with athyreosis. Almost one quarter of patients with no uptake on scinitgraphy had thyroid tissue on ultrasound and of these 60% had transient CHT. Ultrasound should be performed in all patients with no uptake on scintigraphy.

P2-P407

Bannayan-Riley-Ruvalcaba Syndrome with PTEN Mutation in a Patient Affected by Congenital Hypothyroidism Due to TPO Gene Alteration

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We present the case of a 7-year-old female affected by permanent congenital hypothyroidism and Bannayan-Riley-Ruvalcaba syndrome.

The patient was born at 31+4 gestational weeks because of premature rupture of membranes. At birth her auxological parameters were adequate for gestational age with a 75th percentile head circumference. She was diagnosed with congenital hypothyroidsm (TSH 1016 mcu/mL, FT4 <0,4 ng/dL) with an in situ gland caused by a homozygous mutation of the TPO gene (ins.GGCC395, exon 8). This variation was inherited from both parents: the mother suffered from non-autoimmune hypothyroidism and celiac disease and the father had normal thyroid function. Physical examinations, thyroid function tests, and ultrasounds of the neck were regularly performed.

Beginning at 7 months of age, facial abnormalities such as frontal bossing and hyperthelorism were observed, as well as an increasing head circumference (>97° percentile). The patient also presented with a mild delay in neuromotor development (first steps at 18 months, first words at 24 months). The first brain MRI preformed showed no alterations. At 2 and a half years old, a dorsal and a periumbilical lipoma were observed and subsequently surgically removed. At 6 years old, a thyroid ultrasound revealed for the first time five nodules in the right lobe and four in the left one and a brain MRI identified a suspected orbital hemangioma.

After genetic counselling, the sequencing analysis of PTEN gene was performed showing the presence of a heterozygous mutation (c.635-1G>C) coding for a truncated protein causing Ban-

nayan-Riley-Ruvalcaba syndrome (BRRs). In consideration of the increased risk of developing thyroid cancer, the patient recently underwent total thyroidectomy: 21 adenomatous nodules were described at the histological exam. In 8/8 nodules, the immunohistochemical analysis revealed a loss of nuclear expression of PTEN.

The clinical features of our patient (face abnormalities, macrocephaly, subcutaneous lipomas, hemangiomas, and multinodular goiter) represent some of the several phenotypic expressions of BRRs. Mutations in the tumor suppressor gene PTEN cause an increased oncologic risk thus prophylactic total thyroidectomy should be considered in selected patients.

P2-P408

The Congenital Hypothyroidism Screening Programme in a Sigle Italian Centre: A 5-Years Retrospective Study

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Congenital hypothyroidism (CH) occurs in approximately 1:2,000-1:3,000 newborns in Italy. Lowering of the TSH cut-off was the most important factor contributing to the increase of CH incidence in Italy.

The aim of this study is the determination of the prevalence of CH in northwest Sicily, evaluated by the single screening centre of the Children Hospital "G. Di Cristina", ARNAS, Palermo.

From January 2013 to December 2017, 79.699 newborns were screened testing TSH from blood spots. The neonates with TSH≥6mU/L were recalled measuring serum fT4, fT3, TSH, anti-TG and anti-TG antibodies, and thyroid echography. To evaluate the effect in lowering the TSH cut-off, we compared the cases of confirmed CH (transitory or permanent), considering a different TSH cut-off (≥6-<7; ≥7-<10; ≥10).

The number of screening in 2013 was 17.472: 941 (5.9%) were recalled; 50 (0.29%) were confirmed as having CH. Considering a TSH cut-off ≥6-<7, 7/50 (14%) patients were affected; considering a cut-off ≥7-<10, 17/50 (34%); considering a cut-off ≥10, 26/50 (52%). The number of screening in 2014 was 16.020: 680 (4.24%) were recalled; 40 (0.24%) were confirmed as having CH. Considering a TSH cut-off ≥6-<7, 3/40 (7.5%) patients were affected; considering a cut-off ≥7-<10, 13/40 (32.5%); considering a cut-off ≥10, 24/40 (60%). The number of screening in 2015 was 15.502: 627 (4.04%) were recalled; 62 (0.40%) were confirmed as having CH. Considering a TSH cut-off ≥6-<7, 10/62 (16.1%) patients were affected; considering a cut-off ≥7-<10, 20/62 (32.2%); considering a cut-off ≥10, 32/62 (51.6%). The number of screening in 2016 was 15.670: 659 (4.21%) were recalled; 80 (0.51%) were confirmed as having CH. Considering a TSH cut-off ≥6-<7, 10/62 (16.1%) patients were affected; considering a cut-off ≥7-<10, 26/80 (32.5%); considering a cut-off ≥10, 35/80 (43.75%). The number of screening in 2017 was 15.037: 838 (5.57%) were recalled; 98 (0.65%) were confirmed as having CH. Considering a TSH cut-off ≥6-<7, 28/98 (28.5%) patients were affected; considering a cut-off ≥7-<10, 40/98 (40.8%); considering a cut-off ≥10, 30/98 (30.6%). Considering a TSH cut-off ≥6-<7, 58/330 (18%) CH were identified by the screening, otherwise impossible to be precociously evaluated. There were no statistically significant differences in permanent or transitory CH in the 3 groups. The relieve of low cut-off for CH minimize the risk of underdiagnoses.The high incidence of CH in our population could be linked to geographical endemic.

P2-P409

Do Insulin Like Growth Factors Also Influence Growth in Children with Congenital Hypothyroidism: A Cohort Analysis

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Introduction: Congenital Hypothyroidism if not treated timely presents with growth & developmental delay. Thyroid hormones and Growth hormone- Insulin like growth factor 1 axis (GH-IGF-1) together are critical for somatic and skeletal growth. Hypothyroidism and derangement in this axis leads to profound growth retardation and delayed skeletal maturation. Limited studies suggest that thyroxine directly regulates IGF-1 independent of GH in congenital hypothyroidism.

Objective: To evaluate levels of insulin like growth factors in children with congenital hypothyroidism and their role on growth parameters.

Methods: 13 children with congenital hypothyroidism 1 month- 18 years old recruited after taking consent &approval of Institutional ethics committee. Anthropometric measurements-height, weight and body mass index (BMI) recorded and interpreted on WHO growth charts for < 5 years & new IAP growth charts for ≥ 5 years. Those with GH deficiency central hypothyroidism and deranged liver functions were excluded. Estimation of thyroid profile(T3, T4 and TSH) done by electro-chemiluminiscence and IGF-1, IGF binding protein-3 by enzyme linked immunoassay DRG kits. Statistical analysis done using software version SPSS 17.0.

Results: 13 children (9 males, 4 females) had mean age 7.76 ±3.6 years, height 112.68±22.11 cm (-2.1SD), weight 21.46±9.41 kg (-0.58SD) and BMI 16.15±2.43 (+0.26SD). 7/13(53.8%) children were stunted (<-2SD). Mean T3, T4, was 2.73±1.48pg/ml, 5.36±4.72µg/ml and TSH was raised 12.91±18.05µIU/ml. TSH had negative correlation with height (r=0.47, p=0.05). IGF-1 was 103.34±81.38 ng/ml and IGFBP-3 2260.62±1594.25 ng/ml, significantly lower than age and sex matched normal population (p<0.05). Height correlated positively with IGF-1 (r=0.104). Significant positive correlation observed with T4 7 IGF-1 (r=0.564, p=0.045) and T3, IGFBP-3 (r=0.66, p=0.014).ROC analysis showed IGF1 levels below 93.2ng/ml had 85.7% sensitivity & 66.7% specificity predicting stunting (AUC=0.679)& IGFBP3 levels of 1730ng/ml had 57% sensitivity & 83.3% specificity. IGFBP3 levels of 2168ng/ml predicted poor control.

Conclusion: Height was most affected growth parameter in the cohort of congenital hypothyroidism. Mean T3, T4 normal and

TSH was elevated. IGF-1 and IGFBP-3 significantly low with positive correlation with TSH. Growth retardation observed seems to be attributed significantly to reduced levels of insulin like growth factors. Low IGF1 levels predict & associated with stunting. IGFBP3 predicts poor control. Insulin growth factors play significant role in stunting in poorly controlled congenital hypothyroidism

P2-P410

Study of Hearing Function in Children with Congenital Hypothyroidism Attending Alexandria University Children's Hospital

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Introduction: Congenital hypothyroidism (CH) is the most common congenital endocrine disorder in childhood and is one of the most common preventable causes of mental retardation. Thyroid hormones (TH) are essential for normal development of auditory system. Deficiency of TH during fetal and early postnatal sensitive periods of ear development, results in various degree of congenital hearing impairments or even in deafness if TH substitution is not instituted within a critical time window. Hearing impairment in hypothyroidism can be conductive or sensorineural type. Thyroxine deficiency is responsible for the delay and abnormalities in the auditory brainstem response (ABR), so ABR is used in young children to estimate hearing level and monitor neural conduction.

Aim of the study: The aim of this work is to study the hearing function, frequency and type of hearing impairment among children with congenital hypothyroidism. Patients and methods: The study was conducted on 41 Children with congenital hypothyroidism aged 3 years and more attending the endocrinology clinic in Alexandria University Children's Hospital in Egypt. Thorough history and clinical examination were done with emphasis on age of diagnosis and start of treatment, and symptoms of hearing impairment. Thyroid functions were performed. Pure tone audiometer and acoustic impedance were done to evaluate the hearing and middle ear function.

Results: It was found that 10 children (24.4%) had hearing impairment; four of them had bilateral conductive hearing impairment and three with sensorineural hearing loss. The mean age of children with hearing impairment was 7.8 years, they started treatment at the mean age of 5 months. Three out of these ten children still had slight high TSH levels. Most of the cases with hearing impairment had mild degrees by pure tone audiometer.

Conclusion: Early screening and treatment of hearing impairment in children with congenital hypothyroidism is important to prevent speech and language development problems.

P2-P411

Awareness of the Risks of Acquired Iodine Deficiency in Strict Vegan Diets

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Background: Iodine deficiency is the most common cause of acquired hypothyroidism worldwide but rare in developed countries. Incidence of iodine deficiency may be rising due to increased popularity of vegan diets. There is minimal information on official health promotional webpages alerting to this risk.

Case presentation: We present a 2.5yr old boy and his 6yr old sister from a family who adhere to a strict vegan diet and additional dietary restriction including a gluten free diet. Both children have been on a vegan diet since birth and neither underwent neonatal screening. The children's parents saw a private paediatrician as the younger brother had thin fine hair and his growth had tailed off <0.2nd for height and weight was 0.4-2nd. The girl had a goitre and so a thyroid US was arranged and both had thyroid function tests, which showed in boy: TSH:187miu/L, FT4<4pmol/L, negative antibodies and in girl:TSH: 7.04iu/L, FT4: 16pmol/L, negative antibodies, US showed diffusely enlarged goitre. Both children were commenced on iodine supplements and multi-vitamins, in addition the boy was given Vit B12 and iron due to further deficiencies. The biochemistry laboratory at the hospital picked up the boys results and as could not see a referral to endocrinology made an urgent referral themselves. Both children had been commenced on supplements for 2 months when first seen at the hospital. The results for both children showed normalisation of their thyroid function [Boy:TSH:0.44 mIU/L, FT4: 15.2 pmol/L; Girl:TSH:2.10miu/L, FT4:22.3pmol/L]. Both children were referred to a dietitian for formal assessment of their diet and advice on appropriate supplementation. The parents reported that they had gone onto NHS and other health webpages for Vegan children and had followed advice given, however had not seen anything documented about iodine supplementation. They reported that there was a lot of information out there promoting vegan diets as a healthy lifestyle choice and had not noticed any warnings regarding hypothyroidism from iodine deficiency being clearly highlighted. Other deficiencies such as iron, protein, Vit B12, Omega-3 and calcium are well documented.

Conclusions: This case highlights the risk for iodine deficiency in children on vegan diets and the risk of acquired hypothyroidism and goitre. Recognition in developed countries of the risk of hypothyroidism in Vegan children needs to be made more widespread. Doctors should ensure adequate supplementing with iodine in children on vegan diets.

P2-P412

Thyroid Function in the Korean Obese Children and Adolescents: Korea National Health and Nutrition Examination Survey 2013 to 2015

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Purpose: In recent years, there has been an increasing focus on thyroid function in pediatric obese patients, but no nationwide study evaluating the relationship between thyroid function and obesity has yet been conducted in Korea. We aimed to evaluate thyroid dysfunction in obese Korean children. Methods: We analyzed the association between obesity and thyroid hormone levels among 975 Korean boys and girls aged 10–18 years, who participated in the Korean National Health and Nutrition Examination Survey VI (2013 to 2015). Results: Average serum thyrotropin (TSH) and serum free thyroxine (fT4) levels in the non-obese group were 2.7 ± 0.1 μIU/mL and 1.3 ± 0.0 ng/dL, and in the overweight group were 3.1 ± 0.2 μIU/mL and 1.2 ± 0.0 ng/dL. Serum TSH level was significantly higher in the abdominal obesity group than that in the normal group (P = 0.023). FT4 levels were significantly lower in both the overweight and abdominal obesity groups than that in the normal group (P < 0.001, P = 0.014). Serum TSH levels were associated positively with abdominal obesity and levels of high-density lipoprotein cholesterol and triglyceride. Serum fT4 levels were negatively correlated with abdominal obesity (P = 0.014). Conclusion: Korean children with abdominal obesity showed increased TSH and decreased fT4 levels compared to normal children.

Thyroid P3

P3-P361

Prevalence and Demographic Profile of Thyroid Disorders in Indian Children

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Introduction: Thyroid hormone abnormalities are the commonest endocrine disorder in India and also the commonest preventable cause of mental retardation.

Aim: To determine the prevalence, clinical profile, etiology and associated co-morbidities of thyroid dysfunction in children.

Materials and Methods: This is a retrospective study, performed in our tertiary care Pediatric Endocrine Center at Indraprastha Apollo Hospital, Delhi, India from patients' record of 7 years from January 2011 to December 2017. All the patients referred to pediatric endocrine clinic with abnormal thyroid function test report were included in this analysis.

Results: Total of 522 (F:M=1.8:1) patients were referred with abnormal thyroid function test report, out of which 98 (18.77%) were diagnosed to have subclinical hypothyroidism, while 18 (3.44%) patients had hyperthyroidism. 6 patients had secondary hypothyroidism. Among the patients with hypothyroidism, most common presenting age was 12-13 years of age followed by 0-1 year of age, while commonest presenting feature was short stature (53.06%) followed by lethargy, constipation. The commonest etiology of hypothyroidism was found to be dyshormonogenesis. A host of co-morbidities was observed along with thyroid dysfunction. There were 4 patients with Turner syndrome, 10 with Downs syndrome.

Conclusion: thyroid disorders can have a varied spectrum ranging from subclinical to hyperthyroidism. Apart from short stature a thyrid profile should be done in syndromic children for early diagnosis and treatment.

P3-P362

Graves' Disease in a Pediatric Population: Results from the Last 17 Years at a Pediatric Endocrinology Unit

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Introduction: Graves' disease (GD), the main cause of hyperthyroidism in children, is caused by thyrotropin receptor stimulating autoantibodies (TRABs) that activate thyroid hormone synthesis, secretion and thyroid growth. Therapeutic options are anti-thyroid drugs (ATD), 131-I or thyroidectomy. This study reports the experience of a Tertiary Pediatric Endocrinology Unit.

Methods: Review of GD patients diagnosed from January/2001 to October/2017. Results were expressed as mean and standard-deviation, statistical significance at <0.05.

Results: 21 patients, 19 girls, 38% diagnosed in the last two years. At diagnosis, mean age was 11.94±3.50 years, 6 patients (28.6%) presented ophthalmopathy, FT4 and FT3 levels were increased 7.70-fold (0-35) and 2.13-fold (0-5.7); mean TRABs titer was 27.54-fold (0-188) and normal in 2 patients. All patients had thyroid volumes above 97th percentile. Five patients (23.8%) presented thyroid disease family history and 3 (14.3%) had other auto-immune disease.All patients received ATD as first treatment: 23.8% (n=5) propylthiouracil (PTU) (before 2011), 71.4% (n=15) tiamazol (TMZ) and 1 carbimazole.Mean time treatment since diagnosis until TSH normalization was higher for PTU (6.5±0.71 (6-7);4.39±2.94 months (0.81-10.0) - *p=0.049)*. Time to thyroid hormones normalization was similar for both drugs (PTU 3±1.4 (2-4);TMZ 3.28±2.99 months (0.4-10) - *p=0.844)*. Both ATD had similar TRAbs titers when thyroid function normalized(*p=0.199)*. No adverse effects were reported with TMZ. One PTU treated patient developed hepatitis.Mean treatment duration was: PTU 40.60±35.54 and TMZ 28.90±13.20 months, *p=0.282*; remission rate was 19%, similar for both ATD (*p=0.217*). After TSH normalization, ATD maintenance mean time was: PTU 20.5±2.1 and TMZ 24.51±14 months, *p=0.323*. A 2nd treatment was tried in 3 patients; 2 relapsed and were proposed for definitive treatment. Definitive treatment was used in 8 patients (38%), 131-I in 6 (28.6%), with no adverse reactions, and surgery (total/subtotal thyroidectomy) in 2

(9.5%). One patient needed a second 131-I dose. After surgery, 1 patient developed persistent hypoparathyroidism. Seven patients (33.3%) maintain ATD treatment (mean time 22.94±9.0 (14-36) months); 2 finished ATD 2 months ago.

Conclusions: As recommended by 2011 international guidelines, TMZ was the first treatment. Despite a rapid achievement of euthyroidism, treatment duration was longer and only 19% patients entered remission. We found an increase in diagnosis in the last years that conditioned our results. Definitive therapy had a high rate of success without adverse effects.

P3-P363

Acquired Severe Hypothyroidism in Children – Forgotten or Unbelievable Diagnosis in a Time of Large and Easy Availability of Thyroid Tests?

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In a time of widespread availability of thyroid lab tests plenty of patients are reported to endocrine clinics because of isolated slightly increased TSH value and many papers are dedicated disscussion of precautions to treatment in subclinical hypothyroidism. Simultaneously in the same places other patients develop severe hypothyroidism without proper diagnosis. What is the reason of missing diagnoses?

The Aim: Clinical characteristics of severe hypothyroidism in children.

Identification of the reason of delayed diagnosis of severe hypothyroidism.

Methods: Patients with severe acquired primary hypothyroidism were enrolled to the study. The basic criterion was elevated TSH above 100 mIU/L. We analysed the clinical symptoms, time of diagnosis, referral reason, kind of thyroid disease and results of laboratory tests.

Results: In years 2007-2018 twenty one patients of our clinic met above criteria. Severe hypothyroidism was diagnosed in 20 patients with autoimmune atrophic thyroiditis and one patient with thyroid ectopy. The mean age at diagnosis was 10,32 ± 3,53 years. Female predominance was 5:2. None of patients had goiter. Reported symptoms in order of the most frequent: slow rate of growth (77%), weight gain (60%), anaemia (40%), dry skin (37%), myxoedema (33%), loss of appetite (33%), constipation (27%), weakness (27%), somnolence (25%), lower physical activity (20%), hair loss (20%), noticeable bradycardia (20%), feeling cold (13%), hypertrichosis (13%), pituitary hypertrophy (5%). The mean time from the occurrence of the symptoms to the diagnosis ranged from 3 months to 6 years (the mean value 22,9 ± 20,32 months, median – 19 months). TSH level at the time of diagnosis was 499,02 ± 234,55 uIU/ml, (range: 171,22 – 921,66 uIU/ml) normal range of method: 0,58–3,59 µIU/ml. The mean level of fT4 – 0,348 ± 0,11ng/dl (normal range 0,78–1,31ng/dl), the mean fT3 level – 1,33 ± 0,79 pg/ml, (normal range 2,17–3,77 pg/ml). Anti-TPO antibodies : the mean value 2165 ± 2565,35 IU/ml (normal range <5,6 IU/ml) and anti-Tg antibodies: the mean value 854,5 ± 1189,65 IU/ml (normal range <4,1 IU/ml) were detected. In one patient anti-TSH receptor antibodies were detected (ECLIA, Roche). The patients before the endocrine consultation were evaluated by specialists of dermatology, cardiology, alergology and haematology.

Conclusion: Despite the patients presenting typical symptoms of hypothyroidism the diagnosis was delayed in majority of them. The lack of goiter can be the potential reason why thyroid disease is not considered at the beginning of diagnostic process.

P3-P364

Thyroid Disorders and Autoimmunity in Children and Adolescents with Type 1 (T1DM) and Type 2 Diabetes Mellitus (T2DM)

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Hypothyroidism is prevalent among pediatric patients with T1DM and is associated with a more aggressive form of the disease. Patients with T1DM and hypothyroidism have higher rates of DKA, develop the disease at younger ages, and require higher insulin doses. T2DM patients are also more prone to thyroid disorders. The prevalence of thyroid dysfunction in adults with T2DM patients was reported to be 12.3% in Greece and 16% in Saudi Arabia and has been reported to be associated with insulin resistance. However, the prevalence of thyroid disorders and autoimmunity has not been reported in children with T2DM.

Aims: To report the thyroid status and autoimmunity in children and adolescents with T1DM and T2DM diagnosed between 2012 and 2016 in Doha, Qatar.

Patients and Methods: This was a cross-sectional descriptive study thyroid function (Free thyroxine (FT4) and TSH) and antithyroid peroxidase antibody (ATPO) in a cohort of children and adolescent (aged 2-16 years) with T1DM (n= 396) and compare them with those for children with non-familial T2DM (n = 50) at their first presentation at Hamad General Hospital Diabetes Center, Doha, Qatar.

Table 1. (for Abstract no P3-P364)

	T1DM	T2DM
Number of patients	396	50
T4 (<11 pmol/L)	10.6%	10 %
TSH (5.6-10 U/ml)	3.5%	8%*
TSH (>10U/ml)	2.5%	6 %*
ATPO (>100 IU/ml)	27.2%	34.6%*
ATPO (>100IU/ml) + NL TFT	22.7%	23.1%
ATPO (>100IU/ml) and T4 <11pmol/L) or TSH >10U/ml)	3.4 %	7.7%*
ATPO (>100) + subclinical (TSH 5.6-10)	7.29 %*	3.8 %
ATPO (<100) + hypothyroid (T4 <11 or TSH >10)	6.64 %	7.7 %

*$p < 0.05$.

Conclusion: At first presentation, children and adolescents with T2DM had a similar prevalence of hypothyroidism compared to children with T1DM. In addition, children with T2DM had a higher prevalence of subclinical hypothyroidism and ATPO positivity versus T1DM children. Early detection of thyroid dysfunction in children with type 2 diabetes mellitus should be performed routinely, given the high rate of newly diagnosed cases.

P3-P365

The Reference and Follow-up Signs and Symptoms of the Cases Who Are Diagnosed as Hyperthyroidism

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Objective: Hyperthyroidism is rarely seen in the childhood. In this study,we evaluated the reference sign and symptoms and following laboratory and treatment results of the hyperthyroidism cases.

Method: Data of the 78 patients were extracted from hospital records retrospectively.Patients' height,weight,BMI and laboratory results at the time of diagnosis are recorded. Antithyroid drug doses at the 2th, 6th, 12th months after diagnoses are compared to initial treatment doses.

Results: Graves's disease was detected 79% of the patients.Other causes are Hashimoto tiroiditis, subclinical hyperthyroidism and neonatal hyperthyroidism. Antithyroid drugs are initial treatment in all patients. According to etiology of hyperthyroidism, anthropometric and hormone measurements, antithyroid drug doses were given on the Table. Remission is seen in 37 patients.Patients are followed up mean 65±3.7 months.Antithyroid therapy was stopped mean 30.4±14 months later in 22 patients.Hypothyroidism with antithyroid therapy was performed in 46 patients median 2(6) months later and L-thyroxin was added their therapy.Side effects of the antithyroid drugs are seen as urticeria due to methimazole in one patient and the elevation of liver function tests due to propylthiouracil in one patient.Seven patients had relapse. Two patients who have the failure to achieve remission clinically and one patient who has follicular neoplasia suspicion underwent to total thyroidectomy.

Conclusion: In this study,the most common cause of hyperthyroidism is Graves disease that is detected incidentally in one third of the patients. Almost half of the patients achieve remission with antithyroid drug therapy.

P3-P366

Clinical Features in Childhood Graves' Disease

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Introduction: Hyperthyroidism is a disorder of the thyroid function in childhood that causes symptoms such as low school performance, headache, hyperactivity, palpitation, systolic hyper-

Table 1. (for Abstract no P3-P365)

		Graves disease	Hashimoto thyroiditis	Subclinical hyperthyroidism
Anthropometric measurements				
Height (cm)		153.9±16	156.7±7	157.9±10
Weight (kg)		47.1±17	22.7±10	49.8±10
BMI		19.3±4.1	17.02±1.6	19.7± 2.3
Physical examination findings				
Goiter	Grade 0(n (%))	15 (24.2%)	2 (22.1%)	3 (60%)
	Grade I-III	10 (16.1%)	1 (11.1%)	1 (20%)
Laboratory findings				
At the diagnosis	TSH (uIU/mL)	0.01(0.05)*	0.02±0.008	0.4±0.1
	fT3 (pg/mL)	10.9(18.5)*	7.4±1.9	3.6±0.1
	fT4 (ng/mL)	3.5 (3.8)*	2.1 (29.3)*	1.01±0.05
Antithyroid drug dose (mg/kg/d)				
At the diagnosis	Propylthiouracil	6.3±3	4.1±2	1.7
	Methimazole	0.44±0.2	0.39±0.2	-
	Propranolol	1.1±0.7	1.11±0.1	0,5
Final admission	Propylthiouracil	6.3±5.2	3.2±1.0	-
	Methimazole	0.3±0.1	0.59±0.3	0.19±0.03
	Propranolol	0.7±0.1	0.43	-
	L-thyroxin	1.4±0.8	1.22±0.7	-

*Median.

tension, heat intolerance, diarrhea, weight loss inspite of tremendous appetite and tremor. Hyperthyroidism is very rare in childhood. Graves' disease is responsible for 84% of pediatric cases and is the most common cause.

Method: The demographic characteristics, referral complaints, physical examination findings, laboratory findings, ultrasound findings and treatments of Graves cases in Gazi University Pediatric Endocrinology Department between 1990-2016 were examined retrospectively.

Results: Among 24 cases diagnosed with Graves' disease 87.5%(n:21) were girls and 12.5%(n:3) were boys with a mean age of 10.7 years(min 3.6 years- max 16.5 years). The most frequent complaints among the cases were palpitation (50%), followed by irritability, sweating, weight loss (41.7%) and the rarest heat intolerance. When physical examination findings were examined, 66.7%(n:16) cases of tachycardia was observed, with hypertension at 41.7%(n:10), tremor at 25% (n:6), goiter at 29.2% (n:7), and 50% (n:12) ophthalmopathy was detected. Of the cases, while 45% (n:11) was prepubertal, 54.2% (n:13) was pubertal. The comparison of symptoms of the pubertal and prepubertal according to examination and laboratory findings of the cases are given in Table 1. Thyroid ultrasonography revealed 54% (n:13) cases of goiter, with parenchymal heterogeneity at 95.8% (n:23) and parenchymal homogeneity found to be 4.2%(n:1). In all cases, 54% (n:13) of them with medical treatment were treated with block-replacement therapy, 2 patients who did not benefit from the treatment were treated with radioactive iodine and 2 other patients with surgical therapy.

Discussion: While Graves' disease is common in children during pubertal period, the number of prepubertal and pubertal cases in our study were similar. The most frequent symptom was palpitation and the most common physical examination was tachycardia. Ophthalmopathy was seen in 50% of the cases. Thyroid parenchymal features were an important parameter in the differential diagnosis of hyperthyroidism. Parenchymal heterogeneity was detected in 95.8% of our cases inspite of the parenchyma is generally homogenous in thyroid ultrasonography of Graves cases.

P3-P367

General Characteristics of Autoimmune Thyroid Diseases and Evaluation of Accompanied Morbiditis

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Aim: Thyroid hormones are necessary for neurological and psychological well-being in addition to normal growth and development in children and adolescents. Hashimoto thyroiditis is the most common cause of goiter and acquired hypothyroidism and Graves' disease is the main cause of hyperthyroidism in children and adolescents. These two diseases are evaluated in the group of autoimmune thyroid diseases and will be evaluated because of their frequent occurrence in childhood and puberty.

Method: A hundred and fourty two patients aged between 1 and 18 years with autoimmune thyroid disease were studied. The age of onset, application complaints, hypothyroidism, euthyroidism or hyperthyroidism, goitre stages, physical examination findings, family history, accompanying diseases, thyroid function tests, autoantibodies recorded. Clinical, laboratory, ultrasonographic evaluation was performed at the time of admission and after the diagnosis of autoimmune thyroid disease. The time of application and follow-up findings were compared between themselves.

Results: Twenty-seven (19%) of the patients were female and 115 (81%) were female. Median age was found at 14. 00. Of the patients, 130 (91. 5%) were over 10 years old and 106 (74. 6%) were girls. 129 (91%) of the patients were pubertal and 105 (74%) of them were girls. 103 (73%) of the patients were hypothyroid, 26 (18%) were hyperthyroid and 13 (9%) were euthyroid. When the goiter status was examined 101 (71%) patients were found to be stage 0. 122 patients (86%) with Hashimoto and 20 patients (14%) with Graves' diagnosis were the most common complaints of autoimmune thyroid disease were malaise (26%). There was a significant correlation between positivity of levothyroxine and sT4 values in male and female patients with Hashimoto's thyroiditis ($r =. 01$, $r =. 24$, $p <0. 0$). There was no significant relationship between anti-TMAB and anti-Tg levels in male and female patients($p>0,05$). When female patients diagnosed with Graves' disease were examined, there was a significant positive correlation between Metimazol and duration of PTU acquisition and TSH level ($rbayan\_TSH =. 0,48$; $p <0. 01$). No significant correlation was found between anti-TSHR level of Metimazol and PTU in male and female patients ($p> 0,05$).

Conclusion: Clinical and laboratory findings may vary during diagnosis and follow-up in children and adolescents with autoimmune thyroid disease. Close monitoring of events is important. We think that these findings will be helpful for the general features, treatment and follow-up of autoimmune thyroid diseases.

P3-P368

Amiodarone Induced Hyperthyroidism in a Pediatric Patient

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Introduction: Thyroid dysfunction is the most common side effect of amiodarone therapy, ranging from subclinical changes to overt clinical thyrotoxicosis (AIT) and/or hypothyroidism (AIH). Two major types of AIT have been described: type I usually develops in multinodular goiter or in preexisting Graves' disease where an overload of iodine is responsible for the overproduction of thyroid hormones, and type II presents as a destructive thyroiditis, with release of pre-formed thyroid hormones. However, many cases are mixed-form AIT, encompassing several features of both type I and type II.

Case Report: 16 year old, male, with type 1 truncus arteriosus who underwent several cardiac surgical interventions. He was started on amiodarone (200mg/day) in August 2015 due to parox-

ysmal supraventricular tachycardia; he was referred to us in October 2017 for hyperthyroidism: he had lost 4kg in weight in the previous 3 months, but had no heat intolerance, diarrhea or other symptoms. Laboratory evaluation revealed: TSH <0.01 uUI/mL [reference values (RV) :0.47-3.41; FT4 2.83pg/mL (RV: 0.89-1.32); FT3 7.92pg/mL (RV: 2.25-3.85); negative antithyroid antibodies; the thyroid ultrasound was normal. The distinction between the 2 types of amiodarone-induced hyperthyroidism could not be done clinically. The patient was started on thiamazole (0.25mg/kg/day) and a month later, in view of no significative improvement in thyroid function and slight changes in hepatic enzymes, amiodarone was replaced by sotalol.

Five months after starting thiamazole, the patient had gained 5kg and thyroid hormone levels had improved (TSH 0.02 uUI/mL; FT4 0.78pg/mL; FT3 2.83pg/mL). Thiamazole dose was then decreased and treatment was stopped 1 month later.

Conclusion: This is a rare case of AIT in pediatric age. If possible, amiodarone should be replaced by other antiarrhythmic drug, as was the case with this patient. Nevertheless, therapy with thiamazole has to be continued due to the long half-life of amiodarone in the body. It is also important to distinguish the type of AIT when planning therapy, as steroid therapy could be started when findings indicate type II or mixed-type AIT.

P3-P370

Thyroid Carcinoma in Children: 7 Years' Experience of a Single Center

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Introduction: Thyroid cancer is the most common pediatric endocrine cancer, constituting 0.5%–3% of all childhood malignancies. Cancer can be present in multinodular thyroid disease but the majority of malignant nodules are solitary. Thyroid malignancies in children are almost always well differentiated.

Aim: Prevalence, clinical features, pathological profile and therapy of thyroid cancer in children.

Patients and Method: Retrospective study of patients admitted with diagnosis of nodular goiter in the Endocrinology Department, St. Spiridon Hospital, Iasi, Romania, between 2011-2018. Demographic data (sex/age), clinical examination, thyroid ultrasonographic features, hormonal profile, treatment (surgery or active surveillance) as well as histological aspects were recorded.

Results: In a period of 7 years 35 children (26 girls and 9 boys) were admitted for nodular goiter. Age stratification showed 6 (17, 1 %) patients aged 12, 7 (20%) patients aged 15 and 8 (22%) patients aged 16. Only 20 patients presented clinical evident nodular goiter and in 15 patients the thyroid ultrasound revealed nodular lesions in one or both lobes. According to the ultrasound structure has been found: 2 patients with solitary micro nodule (< 1cm) in the right thyroid lobe, 3 patients solitary micro nodule in the left thyroid lobe, 3 patients with polymicronodular aspect, 8 patients with solitary macro nodule (>1cm) in the right thyroid lobe, 8 patients with solitary macro nodule in the left thyroid lobe, 3 patients with multiple macro nodules in both lobes, 1 patient with cystic lesion (>1cm), 4 patients with micro cystic lesion, 2 patients with nodular Hashimoto thyroiditis and one patient with micro nodules in Graves' Basedow disease.

Surgery was performed in 16 cases (45,6%) with the following results: follicular adenomas 6 cases, Graves disease + follicular adenoma 1 case, toxic adenoma 1 case, follicular carcinoma 1 case, Graves disease + papillary carcinoma 1 case, papillary carcinoma 4 cases, medullary carcinoma (MEN 2a) 1 case and well differentiated tumor of uncertain malignant potential 1 case. The total number of patients with thyroid carcinoma was 8 with a prevalence of 20%.

Conclusions: Nodular goiter is more frequent at the age of 12, 15 and 16. The prevalence of thyroid cancer is quite high (20%) with predominance of papillary carcinoma. The clinical examination and thyroid ultrasound are mandatory in diagnostic algorithm of thyroid carcinoma.

P3-P371

Autoimmune Thyroiditis (Hashimoto Thyroiditis) in a Known Case of Autoimmune Hemolytic Anemia

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Background: Chronic, autoimmune thyroid diseases are sometimes combined with autoimmune hematologic diseases, such as pernicious anemia, autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP). Hashimoto thyroiditis is one of the most common autoimmune diseases.

Case report: seventeen years old female adolescent complaining of delayed puberty and short stature. She is a known case of autoimmune hemolytic anemia diagnosed at age of ten years old and was on corticosteroids for four years till she underwent splenctomy after which she was controlled with no medications other than long acting pencillin monthly. Her examination revealed goiter so thyroid function tests were done including autoantibodies and ultrasonography (U/S) neck, surprisingly her result was TSH: 232 uIU/ml Normal range (N.)(0.7-6), free T4 : 0.21 ng/dl (N. 0.9-2), anti-peroxidase : more than 600 U/ml (N.up to 43),antithyroglobulin antibody : more than 4000 U/ml (N. up to 115) and U/S features suggestive of thyroiditis. One month later after starting Eltroxin, she had her first menses also her laboratory follow up results improved dramatically. Assessment of other autoimmune associations as Celiac disease, Addison's disease and type 1 diabetes were negative.

Conclusion: we concluded that Patients with autoimmune hematological diseases should be evaluated by thyroid function tests, including those for thyroid auto-antibodies, to prevent the development of overt hypo- or hyperthyroidism and other autoimmune diseases.

P3-P372

Dento–Maxillary and Periodontal Changes in Puberty / Adolescence in Subclinical Hypothyroidism of Autoimmune Cause

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Introduction: The development of the dentomaxillary system in children involves a normal thyroid function. Juvenile hypothyroidism has different complications depending on the congenital or acquired nature of it.

Objective: To identify periodontal changes under the conditions of chronic autoimmune thyroiditis and subclinical hypothyroidism.

Material and method: the study group comprised 24 young patients, 15 girls and 9 boys (15.2 ± 2.8 years) with chronic autoimmune thyroiditis and subclinical hypothyroidism; the control group included 36 young patients (21 girls and 15 boys - [16 ± 2.1 years]) without thyroid pathology.

Results: Facial changes: microretrognathia - 12 cases (52%), pale and infiltrated lingual and jugal mucosa; 14 children (60.8%) - lingual mycotic detritus; 8 children (34.7%) - „geographic" tongue.

Occlusive disorders: frontal malocclusion in the sagittal plane - 19 children (80%); frontal reversed occlusion - 8 cases (34.7%), open occlusion - 4 cases (17.4%), lower *proalveolodentition* with interdental spacing - 17 children (68%).

Dental malposition: reversed overlap - 11 cases (47.8%), eruption of central upper incisors in vestibular position - 1 case (4.3%); bilateral ectopic canine - 1 case (4.3%); dentoalveolar incongruence -1 case (4.3%).

Dental eruption chronology: delayed eruption - 19 patients (78.2%), prolonged mixed dentition - 14 patients (60.8%); taurodontia - upper molars – 1 case (4.3%).

Periodontal changes: pathological tooth mobility, pathological diastemas, gingival retreats, true periodontal pockets - 8 cases (34.7%).

Compared to the control group: occlusive disorders -3.4%, dental malformations -7.8%, periodontal changes- 1.8%.

Conclusions: Subclinical hypothyroidism in chronic autoimmune thyroiditis induces and intensifies dento-maxillary and periodontal changes at puberty.

Key words: subclinical hypothyroidism, chronic autoimmune thyroiditis, periodontitis, puberty.

P3-P373

Hypovitaminosis D and Chronic Autoimmune Thyroiditis Mammary Echostructural Involvements in Puberty

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Introduction: Benign breast pathology has a frequent onset during puberty-adolescence.

Objectives: Differential evaluation of breast echostructure in puberty stage III/V, on Tanner scale, depending on the presence of thyroid autoimmunity and hypovitaminosis D.

Method: Assessment of BIRADS score from 2 to 4 in three groups of girls associating premenstrual mastodynia: Group 1 - including patients with chronic autoimmune thyroiditis and normal vitamin D values; Group 2 - patients without thyroid pathology with moderate and severe vitamin D deficiency; Group 3 - patients with chronic autoimmune thyroiditis and moderate to severe vitamin D deficiency.

Results: The BIRADS 4 score was statistically significant ($p < 0.001$) in the group with chronic autoimmune thyroid disease and among those with hypovitaminosis D. The intensity of the BI-RADS score was significantly ($p < 0.001$) in favor of elevated serum levels of antithyroglobulin antibodies compared to antimicrosomal antibodies.

Conclusions: Mammary echostructural changes with pubertal onset may be correlated to thyroid autoantibodies and hypovitaminosis D by a mechanism that requires ascertainment.

Key words: chronic autoimmune thyroiditis, hypovitaminosis D, benign mastopathy.

P3-P374

Two Contrasting Cases of Solitary Thyroid Nodules in Adolescent Girls

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Introduction: Thyroid nodules are uncommon in the paediatric population, present in 5% of children but 35% of adults. However, up to 25% of paediatric nodules are malignant, compared to 5% in adults. It can be challenging to differentiate malignant nodularity from benign clinically, particularly in the presence of a thyroid disorder. We present two contrasting cases of adolescent girls with solitary thyroid nodules.

Case 1: A 13-year-old girl was referred to paediatric endocrinology with lethargy and headaches, with routine bloods which had uncovered biochemical hyperthyroidism (TSH 0.05mU/L [0.4-4.0]; T4 10.5pmol/L [9.0-25.0]; T3 elevated). She had a previous history of osteochondritis dissecans and a family history of hypothyroidism. On examination, she was euthyroid and a right-sided nodular goitre was palpable. Conservative management was

planned as the patient was asymptomatic. An USS revealed a solitary, well-defined nodule (42x27x18mm) in the right lobule which was isoechoic, heterogeneous, and contained internal vascularity. Reactive cervical nodes were noted. The nodule was "hot" on scintigraphy, and FNAC indicated a Hürthle cell carcinoma. A repeat USS demonstrated increased vascularity suggesting the carcinoma was active. She was referred for a right hemi-thyroidectomy five months after she first presented.

Case 2: A previously well 14-year-old girl was referred to paediatrics by her GP with lethargy and constipation. Routine bloods demonstrated biochemical hypothyroidism (TSH: 10.5mU/L [0.4-4.0], T4: 8.7pmol/L [9.0-25.0]). A microcytic iron-deficiency anaemia was also noted and treated. Further symptoms included weekly panic attacks, frequent headaches and dizziness on exertion. On examination, a neck swelling was noted. Hashimoto's thyroiditis was diagnosed and treated with levothyroxine. An USS showed a diffusely enlarged, heterogeneous thyroid gland the thyroid gland with a 15mm hypoechoic nodule on the right, which was attributed to her Hashimoto's thyroiditis. However, a further USS revealed the nodule contained peripheral vascularity, and FNAC was suspicious for follicular carcinoma. A diagnostic thyroid lobectomy found an irregular 17mm nodule containing a 5mm area of papillary microcarcinoma.

Discussion: The presentations of these two girls have a number of similarities and differences. While both girls presented with lethargy and a thyroid nodule, the initial diagnoses were distinct opposites. Both nodules were found to be malignant, but neither girl presented any "red flag" symptoms clinically. US features – contrasting in these cases – can be ambiguous. The commonalities and differences of these presentations demonstrate that paediatric thyroid nodules must be thoroughly investigated, even in the context of a thyroid disorder.

P3-P375

Congenital Hypothyroidism – Diagnose Early and Keep Going

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Background: Serious mental and physical retardation are sequelae of untreated congenital hypothyroidism. These complications have become rare since the introduction of neonatal screening in Germany.

Case report: Here we report about a girl with congenital hypothyroidism, who suffered from extreme short and thickset stature, rough facial features and straw-like hair at the age of 12 years. She had been detected in newborn screening with a TSH of 132 IU/ml. Thyroid replacement therapy had been instituted with a sufficient dose at day 6 of life. At her first presentation in our clinic at the age of 12 years she reported to take L-thyroxin at a dose of 50 µg per day (1.25µg/kg/d). Her height was 127.6 cm (-3.71 height SDS), which is 15 cm below the third percentile. Her bone age was 6½ years, hence more than 5 ½ years retarded. Her weight was 36 kg and BMI 22.1 kg/m² (SDS 1.13) and the head circumference was 53.9 cm (SDS 1.06). Her mother reported her to be in good condition, calm, fit with normal school performance. She denied symptoms of hypothyroidism such as constipation, insomnia or increased appetite.Menarche had occurred at the age of 11 even though the clinical pubertal status was still B1, P2 and pelvic ultrasound showed prepubertal ovaries and uterus.The mother reported that at frequent evaluations by her primary care pediatrician, thyroid function tests had been performed but the dose of L-thyroxin had not been adjusted. The laboratory results at presentation showed an elevated TSH of 68 mIU/l with fT4 of 12.84 pmol/l, which is in the lower normal range. Hence, we saw the clinical picture of insufficiently treated congenital hypothyroidism and we adjusted the dose of L-thyroxin to 100 µg/d. During the next months the thyroid parameters normalized, the girl became more vivid, her "menses" stopped, her puberty development made normal progress and she showed a catch-up growth of nearly 12 cm in one year. Nevertheless, the mother missed follow-up dates also at our institution and had to be actively contacted to show up. The child maltreatment group in the hospital was informed.

Conclusion: This case report shows that an insufficiently treated child with congenital hypothyroidism can show nearly all symptoms of the disease. Therefore it's highly important to reassure sufficient treatment of these patients preferably at a center of pediatric endocrinology continuously and in the long term.

P3-P376

An Impressive Recovery of Arrested Growth and Puberty in a 13 Year Old Boy After Being Treated for Simultaneously Diagnosed Severe Hypothyroidism and Coeliac Disease

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Background: Individuals with celiac disease are more likely to develop autoimmune thyroid disease compare to the general population and vice versa. Undiagnosed in childhood and adolescence, both diseases compromise final height. Clinical experience shows that near complete catch-up growth is possible in infants and young children, but not in children near or in puberty.

Objectives: To report on the impressive acceleration of arrested growth in a 13 year old male with short stature and arrested puberty, after successful treatment for severe hypothyroidism and coeliac disease.

Case Presentation: A 13 years old boy, presented to our Pediatric Endocrinology clinic for evaluation of short stature. He was bullied at school for being very short and felt constantly tired. He was born at term with a normal birth weight and length (Wt: 3.95 Kg, Lt: 50cm.).There were limited data on his previous growth measurements. On examination: Height was 134cm (-3,5 SDS) and Wt was 37 kg. His pubertal status revealed testicular volume of 10 ml and pubic hair Tanner stage 3. He had a bone age of 7 years at the Chronological Age of 13 years. The Mid Parental Height was

180 cm and the Target height: 175,5 cm-185,5 cm. Laboratory tests revealed positive thyroid antibodies, a TSH of 500 μIU/ml, coeliac disease antibodies positive and an increased prolactine. An MRI showed an enlarged pituitary. Coeliac disease was confirmed with a jejunal biopsy. He was commenced on thyroxine and gluten free diet. His compliance was excellent. Today he is 15 years old. He has gained 28 cm in 2 years. He is now 162 cm, (-1,6 SDS).His testicular volume has increased to 20 ml each and fortunately he has a delayed bone age (2 years).

Conclusion: Despite the patient's late presentation for short stature and concomitant late diagnosis of hypothyroidism and coeliac disease, he is expected, after treatment, to reach his lowest target height. Our patient is an example of impressive ''catch up growth'' in puberty and highlights the importance of therapy compliance.

P3-P377

A Very Rare Thyroid Hormone Resistance Case Having Heterozygous Mutation in THRB Genes

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Objective: Thyroid hormone resistance is a rare autosomal dominant disease. In the pathogenesis of this disease mutations have been reported in two types of thyroid hormone receptors, called alpha and beta. Deletions or mutations in cofactors required to demonstrate receptor effect also reported in the beta receptor gene. The symptoms vary according to the cases. Here; a case of thyroid hormone resistance which is noticed by chance and not treated is presented.

Case: A 10-year-old girl was diagnosed with thyroid hormone resistance. There was late speech and walking in patient's history. Body weight: 25 kg (10p), height: 137.5 cm (25p), system examinations were normal. In laboratory tests, free T4: 2.86 ng / dl (0.61-1.45), free T3: 9.37 pg / ml (2.5-3.9), TSH: 4.18 uIU / ml (0.34-5.60), thyroglobulin: 110 ng/ml (3.5-77), thyroid antibodies negative. In the genetic test for thyroid hormone resistance; THRB c949G>A (p.A317T) (p.Ala317Thr) (Heterozygous) mutation was detected. This mutation was very rarely seen in the literature. Thyroid and genetic tests were normal in parents. In the metabolic parameters; bone age was in accordance with calendar age, and lipids were at normal level. The case is followed without treatment.

Conclusion: In this study; a very rare form of thyroid hormone resistance is diagnosed by chance as a result of abnormal thyroid tests. Late speech and walking may be important marker in this type of thyroid hormone resistance.

Key words: THRB, thyroid, resistance

P3-P378

Clinical Case (Children's Endocrinology)

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On the visit of endocrinologist came 16-year-old girl arrives on an outpatient visit to evaluate and treat post-operative hypothyroidism. The patient has complaints about periodic pain in the neck of the scar area.

From an anamnesis it is known that in December 2016, a patient was diagnosed thyroid papillary carcinoma at stage T1b. 07.12.2016. extirpation of total right thyroid lobe on is complete, after receiving a histological answer on March 27, 2017 - total extirpation of the left thyroid lobe. The girl is taking 25 μg levothyroxine once a day in the morning. When evaluating laboratory performance, hypothyroidism is uncompensated. It is recommended to increase the dose of levothyroxine to 75 μg once daily and repeat the US thyroid gland one month later.

Disease history: *After birth* – 2000 year, the girl was found a congenital abnormal formation in the left arm of the right muscle. A partial resection of the tumor with biopsy was performed. Pathogistological response - aggressive fibromatosis, extra-abdominal desmoid tumor, infantile variant. Further treatment was discussed at the congress of hematologists and oncologists, which decided to start chemotherapy following the COS protocol.

2001 year At seven months of age, the girl was subjected to a partial desmotomy tumor excision. Histological response is identical to the previous one. It was decided to make radical surgical treatment.

Year 2011 At the age of ten, a girl was found formation in the left gluteal region. Diagnosis: Liposus regio glutei sinistra.

2016 year. The patient has a colon prolapse of 15 years of age. Surgical treatment was performed and scheduled colonoscopy was prescribed.

Conclusion: suspected colon polyposis. Histological examination of biopsy material: fragments of the large intestine mucosa with crypt tubular structure, mild dysplasia of decay epithelium, polyphony restructuring. Conclusion: Colon tubular adenoma structures.

September 27, 2016 The patient is hospitalized in a regional hospital with complaints of headache that lasts for the second day. There have been dizziness, chills, subfebrile temperature, decreased appetite. Thyroid ultrasonography was performed, in which abnormal formation in the right lobe was detected centrally.07.12.2016. Total extirpation of the right lobe of the thyroid gland of the girl, audit of the left lobe. Thyroid papillary carcinoma (T1b) has been detected in a biopsy histological examination.

Basic diagnosis: family adenomatous polyposis - Gardner syndrome; Thyroid papillary carcinoma, T1b, i.e., total thyroidectomy, post-operative hypothyroidism, compensated.

Complications: secondary hyperparathyroidism; iron deficiency anemia

P3-P379

Thyroid Imaging Study for the Diagnosis of Congenital Hypothyroidism with Thyroid Dysgenesis

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Background: Primary congenital hypothyroidism can be classified into thyroid dysgenesis and thyroid dyshormonogenesis. Thyroid dysgenesis includes aplasia, hypoplasia, and ectopia. About one-third of ectopic thyroid is presented with congenital hypothyroidism, but sometimes it may be difficult to diagnose ectopic thyroid in infancy. Thyroid ultrasonography or scintigraphy can be used to diagnose thyroid dysgenesis, but sometimes it is hard to diagnose correctly by using one of them. The purpose of this study is to evaluate the diagnostic values of thyroid imaging studies in children referred for the suspected congenital hypothyroidism.

Subjects and Methods: Among children who underwent thyroid scintigraphy below 6 years of age between 2002 and 2017, subjects with the impression of congenital hypothyroidism and thyroid dysgenesis were included. Clinical features and thyroid imaging findings were reviewed and diagnostic values of thyroid imaging studies were analyzed based on the final diagnosis.

Results: A total of 19 children with thyroid ectopia or aplasia on thyroid scintigraphy were included in the study after reviewing 64 medical records of children who performed thyroid scintigraphy between 2002 and 2017. There are 5 males and 14 females. The mean age at 1st visit was 4.5±9.8 months. The initial presentation was abnormal neonatal thyroid screening test (n=16, 84%), delayed development and low T4 level (n=1), tongue base mass (n=1), and constipation (n=1). Four subjects were born as premature babies and 1 infant had schizencephaly. Initial results of thyroid sonography were as follows: ectopia (n=6), hypoplasia (n=8), and normal (n=5). The results of simultaneous thyroid scintigraphy were different: ectopia (n=10), invisible (n=9). After re-reading, final diagnosis was established as ectopia (n=9, 47%), hemithyroid (n=1), hypoplasia (n=3), aplasia (n=1), and normal thyroid gland (n=5). Thyroid scintigraphy showed better sensitivity in diagnosing ectopia, whereas sonography had better diagnostic value of normal eutopic thyroid gland.

Conclusions: This study showed that thyroid sonography and scintigraphy had different sensitivity or specificity in diagnosing specific type of thyroid dysgenesis. Thyroid sonography has better diagnostic value in the presence of normal eutopic thyroid gland, whereas scintigraphy is highly sensitive in diagnosing ectopia. Therefore, we recommend to use thyroid sonography as a first imaging modality to detect thyroid tissue, and thyroid scintigraphy will be required if thyroid hypoplasia or aplasia is suspected in thyroid sonography.

P3-P380

A Case of Permanent Congenital Hypothyroidism with Compound Heterozygous Mutations in the DUOX2 Gene

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Introduction: Congenital hypothyroidism is defined as thyroid hormone deficiency present at birth. It is the most common congenital endocrine disorder. Neonatal screening test for hypothyroidism can allow its early detection. The course of disease can be permanent or transient. Some permanent congenital hypothyroidism has been linked to defects in proteins involved in the synthesis of thyroid hormones. One of the critical steps in the synthesis of thyroid hormone is the generation of H_2O_2 produced by dual oxidase at the apical membrane of follicular thyroid cells. This case report describes a permanent congenital hypothyroidism caused by compound heterozygous mutations in the DUOX2 gene.

Case: An 11-year-old-boy was born at 37weeks of gestational age by Caesarean section. Birth weight was 2.8kg. He was transferred to our hospital at 50 days of age due to abnormally low T4 and high TSH in neonatal screening test. Thyroid function test revealed T3 77.8 ng/dL, free T4 < 0.33 ng/dL, and TSH 38 uIU/mL. On physical examination, no major abnormality was found including goiter or neck mass. Thyroid sonography showed normally positioned thyroid gland with normal echogenicity. He has no family history of thyroid disease or autoimmune disease. He was diagnosed with congenital hypothyroidism and started taking levothyroxine 40ug (11.1ug/kg) daily. The boy has been regularly followed up in outpatient clinic until now. His language development was somewhat slower than peers until 3 years old, but showed normal development afterwards. Head circumstance and height were in the normal ranges. He has been adjusted the drug dosage based on weight and checked TFT every 3-4 months. The recent TFT showed T3 152 ng/dL, free T4 1.52 ng/dL, and TSH 8.29uIU/mL with daily thyroid hormone replacement of 135 ug (1.98 ug/kg). The gene study for the evaluation of congenital hypothyroidism using diagnostic exome sequencing identified compound heterozygous mutations of the gene DUOX2. The sequences of DNA c.2444 Thymine and c.1462 Guanine were changed to Cytosine and Adenine. As a result, amino acid was changed from Leucine 815 to Proline and from Glycine 488 to Arginine.

Conclusion: We experienced a case of permanent congenital hypothyroidism with compound heterozygous mutations of DUOX2 gene inherited from the mother (c.2444T>C) and father (c.1462G>A).

P3-P381

Growth Catch-up on Acquired Hypothyroidism Presenting with Growth Delay

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Introduction: Hypothyroidism is a frequent endocrinopathy in pediatric age. The most common manifestation in children is growth delay with decreased height velocity. Symptoms can be insidious and, if not identified ant treated, result in short stature.

Aim: To evaluate stature catch-up after replacement therapy in children with primary acquired hypothyroidism.

Methods: Retrospective study of all children with primary acquired hypothyroidism followed at our tertiary pediatric hospital from 1998-2017 and presenting with growth delay. Statistical analysis: SPSS22®.

Results: There were 14 patients (71% females) with mean age at diagnosis of 10±3,5 years and mean follow-up duration of 4±2 years. Mean family target height (FTH) was 162,3±8,4 cm (-0,9±0,79 sds). At the end of follow-up there was a mean gain of 22,7 cm, corresponding to a total catch-up of +0,90±0,56 sds (p<0,001). This gain was directly correlated with duration of levothyroxine replacement (Pearson 0,9, p<0,001). Statural gain by year was de +0,48±0,44 sds (p=0,001), 0,33±0,42 sds (p=0,02) e 0,06±0,17 sds (p=0,263) in the first, second and third years, respectively. Recovery of stature sds occurred by the third year with no statistical difference between final stature sds and FTH sds (+0,08±0,98, p=0,760).

Conclusions: Replacement therapy with levothyroxine had a significant positive impact on stature gain, allowing children to catch-up their genetic potential.

P3-P382

Thyroid Disease in Children and Adolescences with Down Syndrome– 16 Years of Follow Up in a Single Service

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Introduction: It is well known that thyroid disease (TD) is more prevalent in patients with Down Syndrome (DS). Among the dysfunctions are congenital hypothyroidism (CH), subclinical hypothyroidism (SC-H), Hashimoto's thyroiditis (HT) and Graves' disease (GD).The evaluation of the occurrence of these diseases in patients with DS according to age is still poorly reported.

Objective: Verify the prevalence of TD in children and adolescents with DS according to age, gender and describe the most prevalent disease.

Methods: A retrospective study was carried out to analyze the medical records of patients with DS in follow-up at the DS Ambulatory of the Regional University of Blumenau (SC,Brazil), attended from 2001 to 2016. The chronological age(CA) were evaluated at diagnosis, as well as gender and kind of thyroid disease of the patients. Were analyzed: *f*T4, TSH; Anti-thyroperoxidase antibody (Ac-TPO) and antithyroglobulin antibody (Ac-TG) were measured when TSH was above 6 µIU / mL in patients older than 3 months. In patients with TSH suppressed, below 0.67 µIU / mL, and high *f*T4, were measured anti-TSH receptor antibody (Ac-TR-AB), which when positive, was considered Graves Disease (GD). The patients were grouped according to the diagnosis: Congenital Hypothyroidism (CH), considered until 3 months of life, Subclinical Hypothyroidism(SC-H) when TSH above 6µIU /mL and normal *f*T4, Hashimoto's Thyroiditis(HT), when TSH above 6 µUI / mL and low *f*T4 with Ac-TPO and/or Ac-TG positive, and Graves Disease(GD). They grouped according to the age at diagnosis: 0 to 4 years, 5 to 9 years, 10 to 14 years and over 15.

Results: Thyroid function was evaluated in 81 patients (43 female). TD occurred in 57 patients (70.4%), 29female. The average of CA at the diagnosis was 5.19 years. CH in 6 patients (7.4%); SC-H was diagnosed in 37 patients (45.7%), HT in 9 (11.1%), 3 patients in each group of age below 14y; and GD in 5 (6.2%), 1 patient below 4y, 2 patients between 5-9y and 2 between 10-14y. Patients who developed some dysfunction, 54.4% were diagnosed below 4 years of age.

Conclusion: TD diagnosed in 70.4% of patients with DS. SC-H was the most prevalent TD. The age range of 0 to 4 years was the one with the highest prevalence of diagnosis of TD. HT and GD occurred in all age groups. Due to TDs occurred at all ages, routine dosing of thyroid hormones in these patients is recommended.

P3-P383

Corticosteroid Resistant Immune Thrombocytopenic Purpura, Is It a Marker of Future Graves Disease?

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Introduction: The Immune Thrombocytopenic Purpura (ITP) and Graves Disease (GD) have in common an autoinmune physiopathology. ITP is characterized by a platelet count less than 100 x 10^6/L in the absence of other cause. On one hand, ITP has been associated with thyroid dysfunction, without developing GD. On the other hand, GD might develop with moderate thrombocytopenia, generally more than 100x10^9/L. It is described that in most cases ITP might appear first and then after some years the patient develops hyperthyroidism that points to a GD.

Case Summary: We present the case of a 5-year-old previously healthy female patient who presented petechiae throughout the body without any signs of external bleeding. The peripheral blood count revealed severe thrombocytopenia (3 x 10^9/L). Other causes of thrombocytopenia were ruled out. Corticosteroid treatment was initiated, and therapeutic response was achieved. Four months after the thrombocytopenia relapsed and corticosteroid

treatment was restarted and not effective, therefore Rituximab was indicated. After two years of the initial diagnosis the patient began having distal hand tremors, tachycardia and goiter. An ultrasonography of the thyroid was performed, and it showed a relative enlarged thyroid gland, with high vascularization which can be presented in thyroiditis. Laboratory findings showed suppressed TSH, elevated FT4 levels and positive antithyroid antibodies (TSI and anti-TPO). Methimazole treatment was initiated and euthyroidism was achieved.

Conclusion: Thyroid function should be evaluated if there is any indication of resistance to corticosteroid treatment, since it might be a prediction marker for future thyroid disease.

P3-P384

Neonatal Hypothyroidism Following Transplacental Amiodarone Treatment for Supraventricular Tachyarrhythmia

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Background: The proper function of fetal thyroid gland depends on a proper content of iodine in mother's diet and its transplacental transportation. Fetal iodine overload may be responsible for fetal hypothyroidism. Amiodarone is an iodine-rich antiarrhythmic medication and it contains 37% iodine by weight. Fetal tachyarrhythmia is associated with significant perinatal morbidity and mortality. If left untreated can cause congestive heart failure and non-immune hydrops fetalis. Transplacental therapy with oral antiarrhythmic drugs administered to the mother is usually effective in non-hydropic fetuses.

Aim: Report on long-term follow-up in child with neonatal hypothyroidism following transplacental amiodarone treatment for supraventricular tachyarrhythmia.

Results: During a routine newborn screening test elevated TSH was found (capillary TSH 18,29 mU/L from the first and TSH 19,23 mU/L from the second screening test) in a 9-day old girl. She was born at 40th week of gestation from spontaneous labor with Apgar scores of 10, weight 3520 g, length 53 cm from a young, healthy mother. At the 29th week of gestation it was stated that the fetal heart rate ranged from 230 to 250 beats per minute. The echocardiogram showed a structurally normal fetal heart, no hydrops fetalis was stated. Transplacental oral antiarrhythmic therapy to the mother with amiodarone was started and was continued up to 40th week. After birth the baby had sinus rhythm and did not require any treatment. At the presentation girl's TSH was 20,1 mU/L, fT4- 10 pmol/L. Ultrasound revealed thyroid gland in typical position with normal echogenicity and volume of 0,7 ml. Treatment with L-thyroxine dose of 10 μg/kg per day was introduced. In the next six months the L- thyroxine therapy was adjusted with decreasing doses according to TSH and fT4 evaluations. At the age of 7 months her thyroid hormone levels were normal and L- thyroxine therapy was stopped. The follow-up showed clinical and laboratory euthyreosis. At the age of five she presented a normal growth with the height in the 75th percentile and weight in the 50th percentile. Her mental and intellectual development was normal, and she met all appropriate developmental milestones.

Conclusions: Transplacental amiodarone treatment for supraventricular tachyarrhythmia may result in transient congenital hypothyroidism in newborns. Adequate treatment and precise monitoring of neurodevelopment in this children provide a possibility of good outcomes.

P3-P385

Rare Case Report of Thyroiditis De Quervain in a Six Years Old Girl

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Introduction: Subacute thyroiditis or De Quervain's Thyroiditis is a self-limited inflammatory thyroid disease that is considered to be caused by a viral infection. Its incidence during the first decade of life is extremely rare.

During the acute phase of the disease which lasts 2 to 6 weeks, the inflammatory process results in a temporary release of thyroid hormone with biochemical hyperthyroidism with or without symptoms. This phase is followed by a period with failing hormone production before the thyroid regains his function.

Case report: We describe a case of Thyroiditis De Quervain in a six years old girl. She presented with a 10d history of fever, sore throat, progressive painfull neck swelling and restriction of the neck movement despite treatment with antibiotics over 4 days. Laboratory evaluation revealed high infection parameters and hyperthyroidism. The ultrasound examination of the thyroid gland showed a diffuse inhomogeneous enlargement of the right lobe without evidence of abscess formation. There were no thyroid antibodies detected. The patient was put on NSAID to 5 w. It came to a rapid resolution of symptoms and fever subsided. The thyroid function tests were consistent with euthyreosis within 2 weeks, the ultrasound of the thyroid gland was after 5 weeks completely normal. Virologic studies showed no raised titter against adenovirus or echo virus.

Conclusion: Subacute thyroiditis is reported to be very uncommon in the paediatric population.However it may be underdiagnosed as in that age group viral illnesses are very common. Subacute thyroiditis should be considered in young children as the clinical and ultrasound findings can resemble acute suppurative thyroiditis or thyroid malignoma. Early diagnosis and proper treatment can lead to dramatic improvement of the symptoms and preserve the children from unnecessary diagnostic tests and unnecessary antibiotic treatment. A close follow up in order to monitor the thyroid gland function should be initiated. Nearly all patients show a fully recover.

P3-P386

Papillary Thyroid Carcinoma in a 7 Year Old Boy Presenting with a Goiter Without Microcalcifications and Enlarged Cervical Lymph Nodes

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Introduction: Only 1.8 % of thyroid malignancies occur during childhood, explaining very limited pediatric data. Most frequent in children are papillary thyroid carcinoma (PTC), occurring after exposure to radiation, and presenting as a thyroid nodule +/- cervical lymph nodes. PTC may present as diffusely infiltrating disease of the thyroid with microcalcifications. We report an uncommon presentation of a PTC in a 7 year old boy.

Case report: The boy was referred for a goiter with cervical lymphadenopathies. He had neither a history of exposure to radiation nor a family history of thyroid cancer. He had a grade 2 goiter with multiple enlarged bilateral cervical lymph nodes. Thyroid function tests were normal. Ultrasonography revealed a multinodular, hypervascularized goiter (12.5 ml) and numerous bilateral cervical nodular formations with a thyroid-like ultrasound structure. A FDG18 PET scan showed a hypermetabolic thyroid and hypermetabolic cervical lymph nodes. No other hypermetabolic focus was seen. Blood analysis excluded an inflammatory process; tumor markers (including calcitonin) were negative.

Fine needle aspiration cytology of the thyroid indicated an adenoma without signs of malignancy. Lymph node biopsy and left hemithyroidectomy were scheduled. Intraoperative analysis of the lymph node revealed metastatic thyroid cancer by positive thyroglobulin staining tissue. Thyroidectomy and complete neck dissection were done. Bulky metastatic lymphadenopathy with tumor tissue growing into adjacent structures (trachea) and encasing both recurrent laryngeal nerves (RLN) was discovered. The left RLN had to be resected, 2 parathyroid glands were left in place. Histopathology confirmed a PTC (follicular variant). No genetic mutation was detected (APC, WRN, PTEN, PRKAR1A, DICER1).

Postoperative care was complicated by bilateral RLN palsy. Left arytenoidopexy enabled extubation. The patient was substituted by T3 (Cynomel), Calcium and Alfacalcidiol (postoperative hypoparathyroidism). Right RLN recovered and arytenoidopexy could be unfixed 3 months later. Ablative I(131), 30 mCi was performed 4 months postsurgery. A post-ablative I(131) scan revealed 1 metastatic lung nodule which has not been identified before (staging T4a, N1b, M1). A second ablative I(131) treatment is planned.

Conclusion: Thyroid cancer in childhood is rare, especially presenting as a diffuse infiltration of the thyroid gland. In the presence of lymphadenopathies, thyroid cancer has to be suspected, even without microcalcifications.

P3-P387

Graves' Disease, Methimazole and SLE-Like Reaction: A Case Report

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Background: Graves' disease therapy in young children may be challenging due to lack of therapy options. The safety of Radioiodine Ablation (RIA) has not been proven in children under age of 10 years. Propylthioracil (PTU) therapy has been linked to hepatic failure and became contraindicated in pediatrics.

The case: A 6-year-old female was diagnosed with Graves 'disease and treated with Methimazole (MTZ) and Propranolol. A few days after starting therapy, she developed an urticarial skin rash, dermatography and mask- like erythematous rash around her eyes. Her parents stopped the therapy and sought a second opinion for evaluation of MTZ induced rash, proptosis and hyperthyroidism. Her total and free T4 levels were elevated, TSH level was suppressed, TSII and Anti thyroglobin were strongly positive.

We discussed therapeutic options with the family regarding the development of drug-induced lupus like rash. Since PTU was contraindicated and RIA was not safe, we were left with 2 options: Either re-start therapy with MTZ and antihistamine or thyroidectomy. Parents elected surgical option which was performed successfully and rendered the patient hypothyroid, she was started on Levothyroxine and preventive Calcium therapy.

Conclusion: Treating pediatric Graves' disease remains one of the great controversies in pediatric endocrinology. Most patients get started with antithyroid drug therapy but there is a high failure rate with this treatment and many potential side effects. Propylthioracil -associated liver toxicity made Methimazole (MTZ) the only oral anithyroid medication approved for pediatric use. When patients experience side effects from MTZ therapy, a clear analysis of the risk versus benefits of therapy should be evaluated, if the side effect is only a minor allergic reaction, continuation of therapy while adding an anti- allergic medication could be considered but if the allergic reaction is severe, it may affect the compliance and can even progress further. Severe reactions such as bone marrow suppression and arthritis can also occur. At this point, alternative therapies should be sought. If the patient is less than ten years of age, radioiodine ablation therapy (RIA) may not be safe. Thyroidectomy yields cure rates higher than 97% with low complication rates (1–2%) when performed by an experienced surgeon. Surgeons who perform higher volumes of pediatric thyroidectomy have better outcomes therefore, patients should be referred to surgeons with extensive experiences. Thyroidectomy has been always considered as a last option of therapy for Graves'disease but it should be really a top consideration with young children.

P3-P388

A Rare Case of Pediatric Hyperthyroidism

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Background: Hyperthyroidism is rare in childhood and adolescence and Graves' disease accounts for approximately 96% of pediatric cases of thyrotoxicosis.

Case Report: A 12-year-old girl, with no relevant family or personal history, was examinated for a thyroid mass noticed a few days before. She also reported excessive sweating of the hands and mild psychomotor agitation. Clinical examination revealed, in addition to the right thyroid mass, other signs of hyperthyroidism: tachycardia (115 bpm), hypertension (128/69 mmHg) and hand tremors. Weight was 43.7 kg (25-50th centile), height 163 cm (75-90th centile), BMI 16.4 kg/mq (10-25th centile). She was Tanner stage 4. She regularly used iodized salt. Laboratory evaluation showed elevated free thyroid hormones (FT4 41.2 ng/l, n.v. 8-16, FT3 20.64 ng/l, n.v. 2-5.01) and undetectable thyroid-stimulating hormone (TSH). Antithyroglobulin were positive (269 KUI/l, n.v. <115) while antithyroperoxidase and TSH receptor antibodies were negative. Thyroid ultrasonography demonstrated an enlarged right thyroid lobe with four nodules in its context; the largest, nonhomogenous one measured 3.5 cm and showed intense perinodular and intranodular vascularity. The left thyroid lobe was instead significantly smaller (0.1 ml volume). ^{99m}Tc pertechnate scintigraphy was consistent with a toxic multinodular goiter with suppression of the remainder of the gland. Pretreatment with antithyroid drugs was then started (methimazole at a starting dose of 20 mg daily, about 0.5 mg/kg daily) to obtain at least subclinical hyperthyroidism preoperatively. Heart rate, blood pressure, FT3 and FT4 normalized in two weeks; methimazole dose was gradually reduced to a dose of 7.5 mg daily, about 0.2 mg/kg daily. A mild increase of alanine aminotransferase was observed (<3 x ULN), with a complete normalization within a few weeks. The patient has increased about 6 kg of weight in 45 days and menarche occurred. A hemithyroidectomy was then programmed.

Discussion: Hot thyroid nodules in children are rare, with about 130 case reports described and a higher malignancy rate than in adults (overall rate of cancer 26.4%). In children and adolescents, according to the joint guidelines of American Association of Clinical Endocrinologists, Associazione Medici Endocrinologi and European Thyroid Association, treatment of choice of both cold and hot suspected nodules appears to be surgery. In particular for hot nodules, considering the high frequency of non-definitive reports from cytologic evaluation (FNAC), a direct referral to surgery is suggested. In cases similar to ours, lobectomy with completion thyroidectomy, if necessary, is suggested as a practical option.

P3-P389

Allan–Herndon–Dudley Syndrome in a Patient with Global Delay Development – A Case Report

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Introduction: Allan–Herndon–Dudley syndrome is a rare X-linked inherited disorder characterized by, axial hypotonia, weakness, and severe intellectual disability [1] Allan-Herndon-Dudley syndrome is caused by mutations in the *SLC16A2* gene(also known as MCT8) This gene is located on the chromosome Xq13.2, mutations of the SLC16A2 gene lead to impaired making a protein that transports thyroid hormone triiodothyronine (T3) into nerve cells, for this reason due to T3 accumulation in the blood, development of the nervous system is disrupted thus mental retardation, and delay of developmental milestones will be happened. Diagnosis is suspected by combination of clinical examination and thyroid profile tests; normal TSH, elevated free T3 and decreased free T4 in the blood and confirmed by molecular genetic testing. In this report, a 3, 5 year old boy with AHDS is presented in whom *SLC16A2* gene mutation was detected. To our best knowledge, this is the first report of disease in an Iranian child with AHDS.

P3-P390

Multi Autoimmune Phenomenon in Indian Children with Thyroid Disorder

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Objective: To evaluate the prevalence of autoantibodies associated with hypothyroid disease and to assess the associated comorbid autoimmune diseases in Indian pediatric patients.

Materials and Methods: Children (n = 373) diagnosed with hypothyroidism at Indraprastha Apollo Hospital, Delhi, India were screened for celiac disease (tissue transglutaminase autoantibodies [TTGAb]) which were further confirmed by upper GI endoscopy and biopsy for coeliac disease. They were also tested for TPOAb and other autoimmune diseases.

Results: Of the 373 children, 174 had thyroid peroxidase autoantibodies [TPOAb]), and of these, 14 (8.04%) had autoimmune thyroid disease, 8 (4.59%) had celiac disease, 5(2.87%) had vitiligo and one patient had autoimmune alopecia. Two patients had autoimmune Type1 diabetes with Thyroid disease and coeliac disease.

Conclusions: Early detection of commonly associated autoantibodies at type 1, aids regular follow up, may prevent complications associated with delayed diagnosis and treatment of these disorders.

P3-P391

Levothyroxine treatment of Subclinical (SH) and Overt (OH) Hypothyroidism in Children with Autoimmune Hashimoto Thyroiditis (AHT): A Retrospective Study in Regard with TSH and Free T4 (FT4) at Diagnosis

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Objectives: Assess the dose of levothyroxine in relation to TSH and FT4 levels at diagnosis of AHT in children with SH and OH.

Methods: Eighty eight children (69 girls) with AHT were devised in regard with TSH and FT4 at diagnosis [SH-FT4 >0.9 ng/dl: Group 1: TSH: 4.5-7 mU/l, Group 2: TSH: 7-10 mU/l, Group 3: TSH: >10 mU/l and OH: Group 4: TSH>10 mU/l and FT4 ≤0.9ng/dl]. Mean L-T4 dose was reported in μgr/Kg/day at diagnosis and at 2.4 years of follow up and TSH targeted levels under treatment were ≤4 mU/l.

Results: Mean age at diagnosis was 9.7 yrs (SD, 2.6). Main characteristics are shown in table 1. At diagnosis, FT4 levels were significantly lower only in OH with regard to SH groups. Similarly, L-T4 dose in OH was significantly higher as opposed to SH groups. At 2.4 yrs (SD, 1.2) of treatment all patients were euthyroid and TSH and FT4 levels did not differ significantly between groups. L-T4 dose was significantly higher in OH as opposed to group 1 and group 2 but not group 3.

Conclusions: At diagnosis, L-T4 needs are significantly lower in SH patients as opposed to OH patients. At 2.4 yrs, children with OH receive significantly higher LT-4 doses than those with SH and TSH < 10 mU/l but similar with those of SH and TSH > 10 mU/l.

P3-P392

Hashitoxicosis: A Rare Diagnosis in Childhood

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Aim: To highlight the diagnosis of Hashitoxicosis and its distinction from Graves's disease. Subjects with Hashimoto's thyroiditis are often euthyroid or may experience subclinical or true hypothyroidism. However, in 5 to 10% of children, a transient phase of hyperthyroidism, called Hashitoxicosis, may occur.

Patients-Methods: Three female patients, were referred at the ages of $6^{1}/_{12}$, $9^{6}/_{12}$ and $12^{4}/_{12}$ years respectively. The first patient suffered from Type I diabetes mellitus and during a routine evaluation, severe hypothyroidism was detected due to Hashimoto's thyroiditis. Substitution therapy with L-Thyroxine was initiated. Subsequently she developed subclinical hyperthyroidism and then returned to a hypothyroid status. The second patient passed from a phase of hyperthyroidism to euthyroidism, while the third patient first experienced hypothyroidism, then subclinical hyperthyroidism and later became euthyroid. Thyroid hormone course is presented with the table

Results: In all cases, the diagnosis of thyrotoxicosi was established by careful history and clinical examination and a series of diagnostic tools. Thyroid ultrasound showed mainly structural gland heterogeneity. The presence of positive TSIs (Thyroid-stimulating immunoglobulins) in the first case, made it even more difficult to diagnose. For this reason, a Tc 99m scintigraphy was requested, showing a diffuse and slightly increased intake in both lobes, compatible with Hashitoxicosis. All three patients showed no evidence of clinical hyperthyroidism and were clinically evaluated every 2 weeks. Subclinical hyperthyroidism lasted from about 30 to 90

Table 1. Data are shown as means (SD) (for Abstract no P3-P391)

	Group 1 (n=26)	Group2 (n=26)	Group 3 (n=21)	Group 4 (n=15)	*p
At Diagnosis					
Age (yrs)	10.2 (2.2)	10.4 (2.6)	9.2 (2.8)	8.6 (2.9)	
Height z-score	0.68 (1.1)	0.47 (1.2)	0.25 (0.9)	0.48 (0.8)	
BMI z-score	0.83 (0.8)	0.78 (0.9)	0.88 (0.9)	1.04 (1.1)	
TSH (mU/l)	5.6 (0.6)	8.1 (0.9)	16.5 (12.9)	57.7 (46.4)	*
FT4 (ng/dl)	1.23 (0.2)	1.18 (0.1)	1.16 (0.1)	0.8 (0.1)	*
L-T4 (μg/Kg/day)	1.1 (0.35)	1.03 (0.27)	1.38 (0.37)	1.91 (0.9)	*
At Follow Up (2.4 yrs)					
Age (yrs)	12.3 (1.9)	13.1 (2.5)	11.6 (3.2)	10.7(2.8)	
Height z-score	0.69 (1.0)	0.46 (1.1)	0.43 (0.8	0.76 (0.9)	
BMI z-score	0.65 (0.8)	0.65 (0.8)	0.92 (0.9)	0.89 (0.9)	
TSH (mU/l)	2.5 (1.3)	2.8 (1.3)	2.2 (1.2)	2.1 (0.9)	
FT4 (ng/dl)	1.4 (0.2)	1.3 (0.2)	1.3 (0.2)	1.2 (0.2)	
L-T4 (μg/Kg/day)	1.2 (0.3)	1.2 (0.3)	1.5 (0.4)	1.9 (1.2)	*

*One-Way Analysis of variance (ANOVA), p<0.05.

days. If however patients demonstrate clinical hyperthyroidism, especially cardiovascular signs, propranolol is recommended.

Conclusions: Hashitoxicosis is a rare event that needs to be recognized and managed appropriately. Treatment with antithyroid medications is not required in most cases. Scintigraphy is not always necessary while prospective careful monitoring of patients is essential.

P3-P393

An Assay Led Astray: A Curious Case of Biotin-Induced Hyperthyroidism

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The third child to Burmese parents is born at term in good condition in a suburban hospital. The baby was breast fed from birth and had a normal physical examination without dysmorphic features or palpable liver edge. The parents have had two previous live male births at term, that developed severe jaundice and seizure in the first 24 hours of life; both passed away on day 3 of life.

Due to concerns of possible metabolic condition, the baby was commenced on prophylactic phototherapy, oral pyridoxine, thiamine and biotin. The baby was transferred to a tertiary neonatal intensive care unit on day 2 of life. As part of the general diagnostic work up thyroid function tests were ordered on day 2 and 9 of life. [see Table 1]. Following these results, the baby was commenced on carbimazole and the breast-feeding mother was advised to avoid high iodine-containing foods.

Discrepancy between clinical and biochemical picture, and absence of maternal hyperthyroidism, prompted literature review for possible cause. Concerns of possible biotin-streptavidin interaction prompted re-analysed, the results were completely normal [see Table 1]. Biotin was ceased and thyroid function normalised. Carbimazole was then ceased; 8 doses total were administered.

Biotin has been shown to affect immunoassays that employ biotin-streptavidin bound to assay antibodies, such as the Roche immunoassays. The biochemical results suggesting thyrotoxico-

Table 1. (for Abstract no P3-P392)

	1st visit	After 2 months	After 7 months	After 10 months
1st patient: $6^{1}/_{12}$	TSH:201.1 FT4:0.29 Anti-TPO:96 Anti-Tg:1193	TSH:1.49 T4:10.49 Thyroxine:50µg	TSH:< 0.01 FT4:2.50 Anti-TPO:127 Anti-Tg:196 TSI: positive	TSH:34.63 FT4:0.79 T3:143
2nd patient: $9^{6}/_{12}$	TSH:0.040 FT4:25.72 Anti-TPO:69.7 Anti-Tg:226 TSI: negative	TSH:12,439 FT4:14,56 Thyroxine:50µg	TSH:2,94 FT4:17,78 Thyroxine:50µg	
3rd patient:$12^{4}/_{12}$	TSH:7,68 T4:7,06 T3:138 Anti-TPO:219 Anti-Tg:826	TSH:1,320 FT4:1,34 Thyroxine:50µg	TSH:0,083 FT4:1,34 Anti-TPO:129 Anti-Tg:2655 TSI: negative	TSH:1,330 FT4:1,18 Anti-TPO:67,67 Anti-Tg:1024

Table 1. Biochemical thyroid function and immunoassay over time (for Abstract no P3-P393)

Assay	Vitros	Roche	Roche	Abbott	Roche	Roche	Roche
DOB is day 0	Day 2	Day 9	Day 10*	Day 10*	Day 12	Day 16	Day 23
TSH mIU/L	0.21 (0.5-8.5)	<0.05 (0.43 – 16.10)	0.09 (0.43 – 16.10)	3.81 (0.88-5.42)	1.45 (0.43 – 16.10)	7.05 (0.43 – 8.05)	6.81 (0.43 – 8.05)
Free T4 pmol/L	44.5 (18-27)	>100 (8.5 – 39.8)	>100 (8.5 – 39.8)	19.4 (9.0-19.0)	32.1 (8.5 – 39.8)	19.9 (8.5 – 39.8)	17 (8.5 – 39.8)
T3 pmol/L	9.3 (4.2 – 8.3)	33.4 (3.1-6.8)	19.3 (3.1-6.8)	-	9.2	-	-
				CBZ started	Biotin ceased	CBZ ceased	

* Same serum sample re-analysed.

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sis mislead clinicians with a clinically euthyroid patient. In cases where concerns of antibody-mediated thyroid disease are being considered, biotin may falsely elevated thyroid receptor antibodies, anti-thyroid peroxidase and anti-thyroglobulin antibodies, leading to further confusion regarding 'confirmation' of the diagnosis.

Prophylactic metabolic supplements are prescribed often in neonates with suspected metabolic disorders. This case illustrates the seriousness of assay interference due to exogenous biotin which can mimic biochemical thyrotoxicosis.

P3-P394

A Case of Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis (SREAT) in a Girl with Newly Diagnosed Hashimoto Thyroiditis

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Background: SREAT is a rare entity in children, with about 60 cases described to date. It is characterised by acute encephalopathy, elevated anti-thyroid antibodies and exclusion of other causes of encephalopathy like infection, tumour, toxic or metabolic diseases. Typical presentations in children include behaviour changes, psychosis and seizures. The role of anti-thyroid antibodies in the pathogenesis is not clearly understood, and the titre level does not predict severity of disease and relapse. The treatment of choice is intravenous methylprednisolone followed by oral prednisolone.

Case report: A previously well 11-year-old girl presented to the clinic with short stature and increasing weight gain. She had a diffusely enlarged firm and non-tender goitre. Her free thyroxine was <3.2 pmol/L (8 - 16) and TSH was >450 mIU/L (0.4 - 4). Anti-thyroid peroxidase (TPO) antibodies were elevated at 371 IU/mL (<50). She was treated with thyroxine 50mcg daily. Two weeks later, she presented to the Children's Emergency with behavioural change of 3 days' duration. She was agitated and refused to eat and speak. During hospitalisation, MRI brain and lumbar puncture were normal. An EEG showed generalized cerebral dysfunction. Electrolytes and blood sugar were normal. TSH was 112.71 mIU/ml, free thyroxine 5.7 pmol/L, anti-TPO 145 IU/mL and anti-thyroglobulin 491 IU/mL (<115). Erythrocyte sedimentation rate was elevated at 63 mm/hr (2 - 20). Autoimmune work-up including antinuclear antibody, anti-double stranded DNA antibody, complements and ENA (extractable nuclear antigens) antibodies were normal. Autoimmune encephalopathy panel of the cerebrospinal fluid was negative. In view of her acute encephalopathy, elevated anti-thyroid antibodies and the absence of other causes of encephalopathy, she was diagnosed to have SREAT and treated with 5 days of intravenous methylprednisolone followed by a tapering dose of oral prednisolone. She was also treated empirically with Levetiracetam and 2 days of antibiotics and Acyclovir. On the third day of treatment with methylprednisolone, her behaviour normalised, although she could not recall what the events in the past week. Since recovery, there have been no residual neurological deficits.

Conclusion: The rarity of SREAT may lead to delayed or under-diagnosis. Clinicians should consider SREAT in children with acute encephalopathy and no other causes are found. Failure to treat may lead to coma, death or permanent neurological deficit.

P3-P395

Intellectual Outcome at Childhood in Congenital Hypothyroidism According to Etiology and Treatment Related Factors

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Introduction: The intellectual outcome in children with congenital hypothyroidism detected by neonatal screening is generally good. The aim of this study was to evaluate the intellectual outcome in patients with congenital hypothyroidism at childhood and to identify factors that may affect intellectual development.

Methods: The intelligence quotient (IQ) of 126 patients with congenital hypothyroidism was evaluated at childhood using the Korean Wechsler Intelligence Scale for Children. We retrospectively reviewed their clinical datas to know etiology, thyroid function status, L-thyroxine dose at diagnosis and normalization duration of TSH. Etiology – agenesis, ectopic thyroid, hypoplasia and dyshormonogenesis - was sorted by imaging including ultrasonography and Tc-99m scintigraphy at diagnosis.

Results: The mean IQ of patients tested at childhood was 103.3 ± 11.5. Total IQ, verbal IQ and performance IQ of patients was not significantly different according to etiology. Mean IQ of patients with thyroid agenesis was lower than patients with thyroid dysgenesis, but there was no statistical significance. In multivariate linear regression analysis, pretreatment thyroid function, age at treatment and normalization duration of TSH were not determinants of IQ. L-thyroxine dose was statistically significant determinant of total, verbal and performance IQ.

Conclusion: IQ of children with treated congenital hypothyroidism were within normal range. Pattern of treatment was important for intellectual outcome rather than etiology and severity of congenital hypothyroidism.

P3-P396

Myastenia Gravis in a Girl with Hashimoto Thyroiditis

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Objective: To describe an association of Hashimoto's thyroiditis and myasthenia gravis in a 16 years old girl.

Patient report and methods: A 18-year old girl with persistent hypothyroidism secondary to Hashimoto's thyroiditis and a family history of Hashimoto's thyroiditis (grandmother), diagnosed in

2005 and confirmed by elevation of thyroid stimulating hormone (TSH), low levels of T3, T4 and fT4 levels. The US of the thyroid gland revealed hyperechogenic and hypoechogenic zones.

In 2016 the girl complained of extreme fatigue, and difficulties in opening bottles. The diagnosis of MG was confirmed by electromyographic (EMG) activity (decelerating burst). No serum antibody against acetylcholine receptor (AChR) and MuSK could be detected. She was followed up and treated with pyridostigmine sulphate. She undewent laparoscopic thymectomy and was treated further with corticosteroids and pyridostigmine sulphate (240 mg). In the following 4 months her muscle strength slightly improved, but there was no improvement in her feeling of fatigue.

Conclusion: Patients with autoimmune thyroid disease (AITD) are at a higher risk of developing other autoimmune disease (s). When a patient with AITD presents with new or nonspecific symptoms screening for a second autoimmune disorder should be done. One should exclude MG if AITD patient complains of muscle weakness, fatigue or double vision. In our patient, AITD preceded the occurrence of MG.

P3-P397

Head Circumference, Birth Length, and Weight of Neonates of Mothers with Hypothyroidism

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Background: The number of publication on head size of newborns of hypothyroid mothers is scant.

Aim: To study concomitantly head circumference, birth length and weight in such neonates.

Method: Data was retrieved from computerized medical records of our hospital.

Results: One hundred and thirty nine neonates (82 males and 57 females) from a total of 18,538 deliveries at the Rabin Medical Center during the years 1987-1993 were studied. The female neonates had a significantly smaller head circumference than the males 34.3±1.4 vs 33.8±1.5cm (P0.047) and that neonates of both genders had a tendency to a smaller head circumference than the control population. The birth length and weight were similar to the controls.

Conclusion: The head circumstance (brain size) in neonates of hypothyroid mother tends to be smaller than of healthy mothers. Whether this is due to inadequate treatment remains to be established.

Late Breaking P1

LB-P1

A Second Growth Hormone Receptor Pseudoexon Mutation Causing Frameshift and Severe Postnatal Growth Failure

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Background: Growth Hormone Insensitivity (GHI) is usually caused by mutations in the Growth Hormone receptor (*GHR*). Patients present with short stature associated with high GH and low IGF-I levels and often have midfacial hypoplasia (typical Laron syndrome facial features). Our centre previously described the first *GHR* pseudoexon mutation (42700896A>G, c. 618+792A>G). The inclusion of this 108bp pseudoexon is predicted to lead to in-frame insertion of 36 amino acid residues, between exons 6 and 7. This 36-residue insertion in the dimerization domain of the *GHR* results in defective trafficking rather than impaired signalling, and thus causes a partial loss-of function. As such, the observed phenotype is usually moderate postnatal growth failure (Height SDS -3.3 to -6.0).

Objective and hypothesis: Pseudoexons outnumber exons by 10 to 1 and variants in them may be a major contributor to disease burden in short stature.

Methods: We designed a custom short stature gene panel that interrogates both coding and non-coding regions to uncover such mutations. In vitro splicing assays, using an exon trap vector (pET01, MoBiTec GmbH, Göttingen, Germany) were utilised to mimic the splicing process.

Results: We identified a homozygous GHR variant (g.5:42700940 T>G, c.618+836T>G) in an Italian patient with severe postnatal growth failure, classical Laron phenotype and height SDS -7.5. Both unaffected, non-consanguineous parents were heterozygous for the mutation. This mutation was 44bp downstream of the previous pseudoexon mutation and was predicted *in silico* to create a donor splice site. Splicing analysis of this variant confirmed inclusion of the 152bp mutant pseudoexon in all transcripts with no evidence of normal splicing in contrast to the wild-type pseudoexon which showed no such inclusion. Inclusion of the pseudoexon will lead to a frameshift and premature truncation of the mRNA.

Discussion: This novel pseudoexon inclusion event will result in a truncated message which may be destroyed by nonsense mediated mRNA decay or, if not, will lead to a truncated protein lacking the transmembrane and intracellular domains responsible for anchoring the protein in the membrane and signalling respectively. Given the undetectable GHBP levels in this patient, the former effect is considered most likely. Either scenario will lead to complete loss-of-function, consistent with the more severe growth pheno-

type exhibited by this patient in comparison to the previously described, in-frame, pseudoexon mutation with milder phenotype. Our work highlights the potential for such splicing events to be more commonly causal for this and other rare diseases.

LB-P2

Effects On Growth, Body Composition and Gross Motor and Cognitive Development and Safety of Recombinant Human Growth Hormone in Infants or Toddlers with Prader-Willi Syndrome: A Randomized, Active-Comparator Controlled Trial

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This was a Phase 3, multicenter, randomized, active-comparator controlled, parallel, open-label study (NCT02204163) to evaluate efficacy on growth, body composition and motor and cognitive development and safety of recombinant human growth hormone (rhGH) (Eutropin® Inj., LG Chem, Ltd.) in children with Prader-Willi syndrome (PWS) compared to the approved rhGH (Genotropin® Inj., Pfizer, Inc.). Eligible Korean children with PWS were randomly assigned to receive Eutropin® Inj. (test) or Genotropin® Inj. (control) (both 0.24mg/kg/week, 6 times/week) for 1 year. Body composition was measured by dual energy x-ray absorptiometry, and motor and cognitive developments were assessed by Bayley scale.

Total 34 subjects were randomized into either test (N=17) or control (N=17) group and were all less than 24-months old. The demographic characteristics in the per-protocol set (N=16 and 13, respectively) were similar between the groups, but the mean (standard deviation, SD) age at screening and mean (SD) weight at birth were different: 4.81(2.04) *vs.* 8.04(5.81) months (p=0.0483) and 2.86(0.34) *vs.* 2.49(0.48) kg (p=0.0219) in the test and control groups, respectively. After 52 weeks of treatment, height SDS and lean body mass increased significantly in both groups: mean changes (SD) from baseline in each group, the difference between groups and its 95% confidential interval (CI) were 0.751(0.588), 0.948(0.663), -0.197 [-0.674, 0.279] for height SDS, and 2,377.79(536.25)g, 2,607.10(641.36)g, -229.31 [-677.73, 219.12] for lean body mass, respectively. And percent body fat decreased significantly: mean changes (SD) were -8.12(9.86)% and -7.48(10.26)%, respectively, and the difference between groups and its 95% CI was -0.64 [-8.33, 7.05]. The mean changes in other auxological parameters including head circumferences as well as IGF-1 and IGFBP-3 values were also comparable between the groups. The scores for motor and cognitive developments were also improved in both groups after the 1 year treatment. Incidence rate and patterns of adverse events (AEs) were similar between groups. Most AEs were mild to moderate intensity. One case of sleep apnoea syndrome was reported in test group, but considered not to be related to study drug. The other safety profiles in both groups were also comparable without noticeable findings.

Eutropin® Inj. showed comparable efficacy and safety outcomes in infants or toddler with PWS with Genotropin® Inj. Hence, Eutropin® Inj. is expected to provide safe and clinically meaningful improvement.

LB-P3

Glycemic Impact of Long Term Use of Diazoxide Choline Controlled-Release Tablets in Patients with Prader-Willi Syndrome or with Very High Triglycerides

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DCCR is a once daily tablet formulation of the choline salt of diazoxide, a K_{ATP} channel agonist. DCCR is being developed for the treatment of hyperphagia in Prader-Willi syndrome (PWS), the most common genetic cause of life-threatening obesity. In a phase 2 study, DCCR treatment resulted in significant reductions of hyperphagia and aggressive behaviors. Diazoxide increases glucose by decreasing beta-cell insulin secretion in hyperinsulinemic conditions. However, other effects have been documented in animal models and clinical studies to counterbalance insulin suppressive effects. For example, central K_{ATP} channel agonization leads to partial suppression of hepatic gluconeogenesis and peripheral agonization causes marked and progressive improvements in insulin sensitivity. Since PWS patients are hypoinsulinemic and insulin sensitive, it is presumed that changes in appetite and behavior are due to central effects of the drug.

In PWS and VHTG patients, DCCR treatment resulted in a transient rise in fasting glucose, post-prandial glucose and HbA1c, with regression towards baseline with longer term treatment. In PWS, fasting glucose returned to baseline by Day 97 or 126, depending on titration schedule, target dose, and patient population. Fasting glucose regressed more rapidly than OGTT glucose or HbA1c. Clinical Study PC025 evaluated 13 PWS subjects. In subjects completing the study, change from baseline in fasting glucose at Day 69 was +7.9mg/dL (+9.4%) and then regressed to baseline by the end of treatment (+0.4mg/dL, +0.5%) on Day 98 in those who continued DCCR treatment. In a limited number of PWS patients treated with DCCR for 6 months, HbA1c dropped incrementally toward baseline values. Follow-up of PWS at the end of treatment confirmed that when elevated, fasting and OGTT glucose returned to Baseline values within 4 weeks.

In patients with VHTG treated with DCCR, fasting glucose had increased on Day 84 by 13mg/dL(+12.2%) compared to an increase

of 3.9(3.7%) in the placebo arm. By Day 126, change from Baseline in the DCCR arm was comparable to the Placebo arm (0.9mg/dL, 0.9%, versus 0.8mg/dL, 0.8%). In the DCCR arm, HbA1c rose by 0.18% by Day 84, but returned to baseline (+0.09%) by Day 126.

Diazoxide has historically been used to increase glucose levels in hyperinsulinemic patients, and increased glucose levels in PWS have been seen with short-term treatment. However, counterbalancing effects of K_{ATP} channel agonization appear to cause normalization of glucose levels with longer-term use in the patients studied.

LB-P4

An Updated Evolutionary Study in Glucocorticoid Receptors; Insights from a Comprehensive Phylogenetic, SNP's and Mutation's Analysis of the Nuclear Receptors Family

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Background: Protein subfamilies within the Nuclear receptor (NR) family share common domain architecture. These closely related receptors and their cognate ligand compounds play a key role in homeostasis, reproduction, growth, and development. Despite their biological significance, their evolution and diversification remains to be elucidated. SNPs and mutations are characterized by the permanent alteration of the nucleotide sequence in the genome of an organism. These alterations can be used as biomarkers of genetic variation within a population. Genetic variation is of extreme importance in the evolutionary process, since it may lead to both structural and functional differentiation in gene products.

Objective and Hypotheses: To update in-depth the phylogenetic tree of the full Nuclear Receptor family across all species in the tree of life, in an effort to identify molecular and evolutionary traits specific to the glucocorticoid sub-family. To study mutations and SNPs as Nuclear Receptor points of interest, directly associated with the structure and function of this specific protein family.

Methods and Results: Combinations of key terms were employed in order to identify relative NR and GR protein sequences on both primary and tertiary/quaternary structural levels. Sequence data were collected from the NCBI Database. Two distinct datasets were prepared for the purposes of this study. The first dataset comprised of all NRs, which involved 117080 (308 GR) entries across all known receptor sub-classes. In the second dataset, 400 entries were collected containing 3D structures of the NR ligand binding domain and clustered in groups, using both evolutionary and structural features. Both datasets were aligned using progressive methods. Phylogenetic analyses were conducted using the UPGMA distance method while the distance matrix in the structural tree was estimated using a hybrid function. Finally, 29 natural occurring mutations and 10 SNPS were chosen and studied on a human GR predicted 3D model. The selection made was based on their impact on the receptor's structure and function.

Conclusions: Based on our comprehensive evolutionary study in nuclear receptors, a reliable phylogeny "map" was constructed for NRs with more emphasis in GRs. It allowed to pinpoint evolutionary and structurally invariant patches on both the 1D and 3D level of the NR/GR, which led to the identification of structural 'hotspots' directly related to function, that are of great interest as novel pharmacological targets. A strong case can be presented for both natural occurring mutations and SNPs being used as structural 'hotspots'.

LB-P5

Association Between the Use of Antenatal Steroids for Lung Maturation and Hypoglycemia in Newborns Between 26 and 34 6/7 Weeks of Gestation

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Objective: The aim of this study was to evaluate the difference between the incidence of hypoglycemia in those preterm newborns who were exposed to steroids and those who were not.

Methodology: This is a prospective cohort study of preterm infants born between 2017 and 2018 at a gestational age of 26 to 34 6/7 weeks in the *Hospital Universitario de Santander- HUS- in Bucaramanga, Colombia.*

Results: 128 preterm infants were evaluated. 111 (86.7%) had been exposed to antenatal steroids. The median maternal age was between 23 and 24 years of age for both those who were exposed and those who were not (p=0.190). The exposed vs unexposed maternal comorbidities were: preterm labor (70.6 % vs. 52.3; p=0.157), premature rupture of membranes (29.4% vs. 27.9%; p=0.921), gestational diabetes (5.9% vs 7.2%; p=0.842), urinary tract infection (29.4% vs 18.0; p=0.270) and chorioamnionitis (11.8% vs 9.0%; p=0.717). Female sex patients were 47.1% vs 45.1% (p=0.927) respectively. The median gestational age was 33 weeks for both

groups (p=0.216) and birth weight was 1640 vs 1945 g (p=0.190) respectively. The proportion of Apgar scores under seven at 5 minutes was 11,8% vs 5,4% (p=313). Median metabolic flux was similar among the two groups (6.17 vs 6.19 mg/kg/min, p=0.365). The incidence proportion of hypoglycemia during the first 48 hours of life was 29.4% in unexposed vs 24,3% in exposed (RR 0,827, IC95% 0.371-1.851; p=0.652), while incidence density of hypoglycemia was 8.80 and 6.30 cases per 1000 person-hour (HR 8,859m IC95% 0,380-1,912; p=0,468), respectively.

Conclusion: there was no significant difference in the incidence of hypoglycemia among those who were exposed to antenatal corticosteroid for lung maturity and those who were not.

LB-P6

Sex Hormone Levels in Young Children: A Pilot Study of the Japan Environment and Children's Study

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Background: Information on sex hormone levels in young children is currently lacking, because those levels are generally below the lower limit of quantitation of conventional immunoassay methods. We investigated sex differences in serum levels of sex hormones in relation to upstream hormones and other background factors in young children, using liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Methods: This cross-sectional study enrolled 151 children (80 boys and 71 girls) aged around 6 years, who participated in a pilot study of the Japan Environment and Children's Study (JECS). Serum levels of estradiol (E2), testosterone (T), and dehydroepiandrosterone sulfate (DHEA-S) were measured by LC-MS/MS, and serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were measured by chemiluminescent enzyme immunoassay. A gender-stratified multiple linear regression model with sex hormones as the outcome variable and upstream hormone levels and background factors (height, abdominal girth, and specimen-collection time) as explanatory variables was generated.

Results: There were no significant gender-related differences in levels of T and DHEA-S, but serum levels of E2 and FSH were significantly higher in girls than boys. Median (interquartile range) levels of E2 in girls and boys were 1.02 (0.65–1.58) and 0.10 (0.06–0.16) pg/mL, respectively (Welch's *t*-test; $p<0.001$). The Wald test suggested that T levels in both boys and girls were associated with DHEA-S levels (both $p<0.001$) and were higher in the morning ($p=0.007$ and 0.006, respectively). Furthermore, E2 levels in boys were significantly associated with T levels (=0.018), while E2 levels in girls were significantly associated with both T and FSH levels ($p<0.001$ and 0.010, respectively).

Conclusion: Obvious gender differences in E2 levels exist even in young children. Furthermore, E2 levels in pre-pubertal girls are associated with both DHEA-S and FSH.

LB-P7

Mutational Analysis of *SRD5A2* and *AR* Genes in Indian Children with 46 XY Disorders of Sex Development

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Aim: To study the mutation spectrum in *SRD5A2* and *AR* genes among Indian children with 46 XY disorders of sex development (DSD).

Methods: This work is part of an ongoing study at Department of Pediatrics, AIIMS, Delhi, approved by the ethics committee of the Institute. Children with 46 XY DSD in whom endocrine investigations were suggestive of either 5α reductase deficiency or androgen insensitivity syndrome were enrolled for mutational analysis of *SRD5A2* (steroid 5-alpha reductase 2) and *AR* (androgen receptor) genes after obtaining voluntary informed consent from the parents, and assent from children older than 12 years. Endocrine investigations including HCG stimulated testosterone and dihydrotestosterone levels were done. Bidirectional sequencing was undertaken for all 5 exons of *SRD5A2* gene in 66 children. Sequencing for all 8 exons of *AR* gene was done in 36 of those children in whom no mutation was identified in *SRD5A2*.

Results: We identified mutations in 24 children (36.4%) for *SRD5A2* gene, the commonest being homozygous missense mutation p.R246Q in exon 5 (in 15 children). Mutations were noted in 8 children (22.2%) for *AR* gene (hemizygous, as *AR* is located on the X chromosome), of which 2 were novel mutations not reported in HGMD, ensembl and 1000 genome data base. The clinical and endocrine parameters of the children with mutations are summarized in Table 1.

Conclusion: Mutations were identified in nearly half of the patients (32 of 66) with suspected 5α reductase deficiency or androgen insensitivity syndrome. Clinical and endocrine parameters were similar in those with mutations in either *SRD5A2* or *AR* gene,

Table 1. (for Abstract no LB-P7)

Parameter	SRD5A2 Homozygous (N=19)	sRD5A2 Compound heterozygous (N=4)	SRD5A2 Heterozygous (N=1)	AR Hemizygous (N=8)
Age (years)	5.5 (0.5 – 18)	8 (3.6 – 20)	1.6	3 (1.4 –10.5)
External masculinization score (range 0-12)	6 (2 – 9)	3 (2 – 6)	1	4 (0 – 8)
LH (miu/ml)	0.14 (0.01 – 4.90)	0.13 (0.06 – 17.82)	2.68	0.25 (0.06 – 7.87)
FSH (miu/ml)	0.95 (0.09 – 3.45)	1.09 (0.15 – 28.75)	3.5	3.4 (0.79 – 51.42)
Basal testosterone (ng/dl)	2.9 (0 – 149)	10.3 (4 – 846)	264	3.5 (1.44 – 25)
HCG stimulated testosterone (ng/dl)	354 (71 – 974)	900 (142 -1388)	971	519 (200 – 758)
Testosterone : Dihydrotestosterone (T: DHT) ratio	26.53 (22.3 – 68.8)	30 (18.9 – 42)	32.5	35.5 (25.5 – 59)

indicating that genetic analysis is important for correct diagnosis. p.R246Q in exon 5 was a hotspot for mutations in *SRD5A2* in Indian patients.

LB-P8

Pharmacokinetics of Diazoxide Choline Controlled-Release Tablets, a Once Daily Treatment Being Evaluation in Patients with Prader Willi Syndrome

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Diazoxide Choline Controlled Release Tablet (DCCR) is under development for the treatment of Prader-Willi syndrome (PWS). The objective of this research was to characterize single dose and steady state pharmacokinetics, dose linearity and food effects of DCCR across 5 clinical studies.

Single dose pharmacokinetics of DCCR were compared to diazoxide oral suspension (Proglycem®) in a study in obese subjects (PK001). Steady state pharmacokinetics were evaluated for DCCR in 4 studies in healthy normal weight, obese, and obese PWS patients (PK008, PK015, TR002, and PC025). Food effects and pharmacokinetics of the major metabolite were each evaluated in healthy volunteers (PK008 and PK015, respectively). Trough circulating drug levels at steady state were characterized in 11 PWS subjects treated with a range of doses of DCCR (PC025).

Diazoxide choline rapidly hydrolyses to diazoxide. Diazoxide is readily and extensively absorbed from Proglycem® oral suspension and DCCR. On single dose administration, T_{max} was 6.5 hours for Proglycem vs. 22 hours for DCCR. Proglycem® C_{max} was 47% higher than C_{max} for DCCR (13.32 vs. 9.07µg/mL), while the $AUC_{0-\infty}$ was only 15% higher (678.01 vs. 588.34µg*hr/mL). The terminal half-life of the products was comparable (29.2hr. vs. 32.4hr. for DCCR). DCCR steady state was reached after 7 days of dosing. There was no significant food effect on any pharmacokinetic parameter suggesting that the drug can be dosed with or without food. Over the DCCR dose range of 217.5 to 507.5mg administered once daily to obese subjects, steady state peak and trough circulating drug levels increased linearly with dose ($R^2 > 0.997$ for both). The major metabolite of diazoxide reached steady state at 10 days and the metabolite-to-parent ratio was 8.6% for both $C_{max(ss)}$ and $AUC_{0-\tau(ss)}$. Dose-related circulating drug levels were similar in PWS and comparably obese non-PWS subjects, suggesting that the pharmacokinetic data generated in non-PWS subjects is relevant and applicable to the use of DCCR in PWS patients.

The pharmacokinetics of DCCR are well characterized across the series of 5 studies reported here. DCCR was well tolerated and suitable for once-daily dosing in patients with PWS. Given the lower C_{max} for a similar AUC, DCCR may lower the likelihood and severity of C_{max} related adverse events compared to Proglycem®. The constant intraday circulating drug level that follows from the continual absorption of drug from DCCR likely results in a consistent therapeutic response in treated PWS patients.

LB-P9

Two Siblings with Autosomal Recessive Syndromic Hypopituitarism Caused by Mutations in *TBC1D32*

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Patients who suffer from congenital hypopituitarism display a wide spectrum of phenotypes including pituitary hormone deficiencies and, in some cases, additional extrapituitary manifestations depending on the causative gene. A group of genes underlying hypopituitarism has been identified, yet several of them remain unknown. Here, we identified compound heterozygous variants in the *TBC1D32* gene, c.1165_1166dupGT, p.(Gln390Phefs*32) and c.2151delA, p.(Lys717Asnfs*29) in two affected siblings with congenital hypopituitarism by analyzing whole-genome seguencing (WGS) data and confirming the findings by Sanger sequencing. The c.1165_1166insGT p.(Gln390Phefs*32) (rs546631812) variant had a frequency of 0.009348 in the Finnish population and

was carried by the father and healthy brother. The c.2151delA p.(Lys717Asnfs*29) variant was absent in databases and was carried by the mother. *TBC1D32* has previously been implicated in Sonic hedgehog (Shh) signaling, which is crucial in the development of craniofacial features and causes ciliopathies when disrupted. Mutations in *TBC1D32* have previously been found in an oro-facio-digital syndrome type IX patient who displayed an overlapping phenotype with those of our patients. Our results suggest that *TBC1D32* mutations should be considered as potential causes of ciliopathy-like syndromic hypopituitarism.

LB-P10

The Influence of Oil-Soluble Iodinated Contrast Medium (Lipiodol) on Child's Thyroid Function in Mice

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Introduction: Hysterosalpingography using oil-soluble iodinated contrast medium (ethiodized oil; Lipiodol) is a common examination for patients with infertility. Lipiodol remains in the body long after the examination, and there are some reports suggesting that Lipiodol induces thyroid dysfunction not only to the mother but also the fetus and the newborn. However, since there are no known mouse models of Lipiodol-induced thyroid dysfunction, we examined the influence of Lipiodol on child's thyroid function in mice by administering Lipiodol to its mother.

Materials and methods: 12 week-old ICR female mice were intraperitoneally administered with Lipiodol once before mating or during pregnancy or after delivery, and the thyroid uptake rate of I-131 (74 kBq / mouse) in their newborn mice was examined 24 hours after oral administration of I-131. The dose of Lipiodol used was either equivalent to that used in humans (0.2 μL/g BW, iodine amount=96 μg/g BW) or its 1/2 or 1/10 amount. Lipiodol was diluted with corn oil, and all were set to a total of 10 μL/g BW. The same volume of corn oil was used as a control. When the offspring mice reached 4 weeks of age, serum TSH and FT4 were measured by ELISA method. The number of mice in each experiment was 6 or more.

Results and discussion: When 0.2 μL/g BW Lipiodol or its 1/2, 1/10 amount were administered intraperitoneally before pregnancy (5 days before gestation), thyroid uptake rate of I-131 in 5 day old infants was decreased to 24.4%, 24.0% and 58.7% compared to control, respectively. When 0.2 μL/g BW of Lipiodol was administered to mice during pregnancy (10th gestation) or immediately after birth, thyroid uptake rate of I-131 in 5 day old infant was decreased to 5.8% and 2.4% compared to control, respectively. There was no change in TSH level in infant mice at 4 weeks of age, but a significant decrease in FT4 was observed.

This result suggests that the amount of Lipiodol used in examinations such as hysterosalpingography should be kept as little as possible, and that thyroid function in children born after examinations using Lipiodol needs to be carefully observed.

LB-P11

Metabolic Profile in Survivors of Pediatric Hematopoietic Stem Cells Transplantation After Chemotherapy-only Conditioning

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Background: Metabolic syndrome (MS) is a long-term complication of pediatric haematopoietic stem cell transplantation (HSCT) and it was described more often in patients who were exposed to total body irradiation (TBI). Since previous studies reported discrepancy in the presence of metabolic complications in HSCT survivors who underwent chemotherapy-only conditioning, we investigated the frequency of MS in our HSCT-treated children for various disorders without being exposed to TBI in the conditioning regimen.

Material and method: 29 pediatric HSCT survivors after chemotherapy-only conditioning were compared with 16 healthy subjects matched for age and sex. MS was defined according to the criteria of Ferranti et al. Total body fat and android/gynoid (A/G) ratio were assessed by dual-energy X-ray absorptiometry (DXA) in 22 HSCT recipients.

Results: We identified only 2 patients (6.9%) who met at least 3 criteria for MS in our study, another 5 patients (17.2%) presented 1 criterion of MS while 3 patients (10.3%) met two criteria for MS. A waist circumference (WC) higher than percentile 75 was present in 20.7% (n=6) of HSCT survivors, high blood pressure (BP) in 4 patients (13.8%), glucose metabolism disorders in 1 patient (3.4%), while 27.5% of recipients TCSH (n=8) were diagnosed with dyslipidemia. A total of 63.63% of HSCT recipients (n=14) had an A/G ratio adjusted for age and sex higher than normal (66% of girls and 60% boys). HSCT survivors were more likely to develop high BP compared to controls (17.39% vs 0%, p=0.047). HSCT survivors who fulfilled at least 1 criteria of MS had higher mean BMI (0.13±1.54 kg/m² vs -1.33±1.06kg/m², p=0.009), higher mean WC (77.90±14.57cm vs 63.78±10.29 cm, p=0.006) and higher mean WC/height (0.5±0.07 vs 0.44±0.04, p=0.029) compared to the HSCT recipients with none of the MS criteria. Mean A/G ratio and total body fat were similar in autologous and allogeneic HSCT recipients.

Conclusion: This study demonstrates that pediatric HSCT survivors who underwent chemotherapy-only conditioning are also associated with an unfavorable metabolic profile, one third of them presenting at least one MS component.

LB-P12

Disrupting the Norm: The Experience of Young People with DSD

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The experiences of older adults with Variations in Sex Characteristics (VSC or Differences/Disorders in Sex Development/DSD) are well documented. However there has been a gap in the literature with respect to representing the voices of younger people. This qualitative research study has been conducted in collaboration with Intersex Trust Aotearoa New Zealand. Ten young people with VSC were recruited via health professionals, intersex advocates, support groups and social media platforms throughout Aotearoa/New Zealand.

Interviews were in-depth and semi-structured, digitally recorded and transcribed. Braun and Clarke's (2006) Thematic Analysis was used to identify key themes regarding the young persons' experiences of the health system, including their own decision-making process or their experience of decisions made for them by their parents and or health professionals involved in their care.

A variety of experiences were reported, some very positive. Negative experiences highlighted were communication issues, bias, and lack of understanding of diversity in relation to interactions with health professionals. All these factors had a direct impact on young people's decision making. The complexities of identity, gender, bodily autonomy, acceptance of difference and peer support were identified as issues and explored by the young people.

Challenging the concept of "the Norm" was a major theme for young people. They reported that this concept was revisited and changed over time with self-reflection, ultimately creating a path towards self-acceptance and a sense of belonging. Support for both young people and those who care for them was identified as crucial. The need for collaboration and opportunities for having and holding difficult discussions around the possibilities of care within the health system were also raised.

Implications of the findings include the need for: (i) better support systems (especially peer support from others with a variation in sex characteristics, and the development of caring communities); (ii) a need for additional training for health professionals in this area around communication skills and identifying and managing bias.

LB-P13

Clinical and Endocrine Characteristics and Genetic Analysis of Korean Children with McCune–Albright Syndrome

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McCune-Albright syndrome(MAS) is a rare disease defined by the triad of precocious puberty(PP), café au lait spots, and fibrous dysplasia(FD). There are only a few patients with MAS in Korean because of the rarity of this disease. We reported the various clinical and endocrine manifestations and genetic analysis of 14 patients with MAS in Korea.

It is a retrospective cohort study of patients' clinical data including about peripheral PP, FD. Also, treatment experiences of letrozole in five patients with peripheral PP were described. Mutant enrichment with 3'-modified oligonucleotides – polymerase chain reaction (MEMO-PCR) was performed on 8 patients to detect mutation in *GNAS* using blood.

The median age at diagnosis was 5 years 2 months. (18months to 16 years) there were 11 female and 3 male. 13 patients showed FD. All female patients showed peripheral PP at onset, 3 patients subsequently developed central PP. there was a significant decrease in estradiol levels after 2 years of letrozole treatment, but the bone age was advanced in 4 patients. 2 patients had clinical hyperthyroidism, and 2 patients had growth hormone(GH) excess with pituitary microadenoma. c.602G>A(p.Arg201His) in *GNAS* was detected in 2 patients in blood, and c.601C>T(p.Arg201Cys) in *GNAS* was detected in one patient in pituitary adenoma.

This study described the various clinical manifestations of 14 patients with MAS in a single center in Korea. This study first applied MEMO-PCR on MAS patients to detect *GNAS* mutation. Because a broad spectrum of endocrine manifestations could be found in MAS, multiple endocrinopathies should be monitored in MAS patients. Better treatment options for peripheral PP with MAS are needed.

LB-P14

Beta-Cell Function in Chinese Youngsters with Type 1 Diabetes and Assessment of Surrogate Markers of Severe Insulin Deficiency

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Objective: We assessed whether beta-cell function progressively decreases over time with greater type 1 diabetes mellitus(T1DM) duration using a mixed-meal tolerance test (MMTT). We also assessed simpler and more practical surrogate parameters for clinical use.

Methods: We studied 57 children and adolescents with T1DM in Hangzhou (China), mean age at diagnosis was 8.3 years (range 2.3 to 15.3 years), with an average diabetes duration of 2.5 years (range 2 weeks to 8 years). A 120-minute MMTT was performed with plasma C-peptide measurements taken every 30 minutes. Urine C-peptide and creatinine levels were measured at 0 and 120 minutes. Severe insulin deficiency (SID) was defined as a C-peptide peak from the MMTT <0.2 nmol/l.

Results: Every one-year increase in diabetes duration was associated with a 37% decrease in C-peptide AUC ($p<0.001$). The rate of SID steadily increased over time, being particularly marked after two years when the rate increased from 13% to 67%. In addition, every one-year decrease in age at T1DM diagnosis was associated with a 20% decrease in C-peptide AUC ($p=0.005$). There was a consequent decline in the rate of SID with increasing age at diabetes diagnosis, with a 86% prevalence among children under 5 years of age compared to virtually no cases among children aged 11 years or older. Fasting C-peptide levels were perfectly corrected with both C-peptide peak and AUC.The C-peptide peaks at any time point had 100% sensitivity and thus were able to detect all cases of SID (n=25). However, the peak at 0-120 min was the only one with 100% specificity, with no false positives. Fasting C-peptide was somewhat accurate to detect cases of SID, missing just one case (sensitivity 96%) and with no false positives (100% specificity). Urine C-peptide/creatinine at 120 minutes had 100% sensitivity, but poor specificity at 63% with 11 false positives (out of 30 negatives). Urine C-peptide peak had nearly perfect sensitivity at 96%, and its specificity was considerable better than that of the ratio at 87%.

Conclusions: There seems to be a steady decrease in beta-cell function with increasing duration of T1DM. In addition, children diagnosed at a younger age tend to have a much more marked loss in beta-cell function. Importantly, we showed that surrogate makers can be used in a routine clinical setting to detect SID in Chinese children and adolescents, particularly fasting C-peptide levels and a 120-minute urine C-peptide peak.

LB-P15

A Novel Compound Heterozygous Mutation of the *CYP17A1* Gene Is Associated with Rhabdomyolysis: Demonstration of Combining 17α-Hydroxylase/17,20-Lyase Deficiency

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Objective: To investigate the clinical and molecular characteristics of a girl with 17α hydroxylase/17,20-lyase deficiency, of which, onset was as rhabdomyolysis and hypokalemia. And then we identified the functional consequences of two novel CYP17A1 mutations.

Materials and Methods: A 11 years old girl, 46, XX karyotypes, presented with rhabdomyolysis, hypokalemia and hypertension. She had elevated levels of plasma adrenocorticotropic hormone, serum gonadotropin and progesterone, and reduced cortisol, testosterone, dehydroepiandrosterone sulfate (DHEA-S) and plasma renin activity (PRA). All coding exons sequences of CYP17A1 were directly sequenced using genomic DNA. Wild-type and mutant CYP17A1 cDNAs were inserted into the pcDNA3.1(+) vector, and transiently expressed in HEK-293T cells. This was followed by an assessment of 17α-hydroxylase and 17,20-lyase activities by measuring the conversions of progesterone to 17-hydroxyprogesterone and 17-hydroxypregnenolone to DHEA.

Results: The mutation analysis identified one patient with compound heterozygosity [c.1304T>C/p.F435S;c.1228delG/p.D410Ifs*9]. An in vitro functional analysis of both novel p.P435S and p.D410Ifs*9 mutations revealed a complete loss of 17α-hydroxylase/17, 20-lyase activities.

Conclusion: We present a case of combined deficiency of 17a-hydroxylase/17,20-lyase caused by compound heterozygosity for two novel mutations in the CYP17A1 gene. Rhabdomyolysis may be a complication of 17OHD or its initial performance. In such cases, it is mandatory to assess the perform hormonal and molecular genetic studies.

LB-P16

Successful Treatment of Alopecia Totalis with Calcitriol and Paricalcitol in Two Girls Aged 3 and 7-years

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Backgound: Alopecia areata (AA) or Alopecia Totalis (AT) is an autoimmune disease directed at the hair follicle, either limited to patchy hair loss over the scalp (focalis), or as total loss of scalp hair (totalis) or as total loss of both scalp and body hair (universalis). Management can be challenging, and despite multiple treatment modalities, no therapy still stands. While localized AA may respond well to topical corticosteroids, many patients require more aggressive second-line therapy. Pediatric age and more extensive disease with resistance to initial therapies may sometimes benefit from a cocktail of established therapies, with the likelihood of complete regrowth spontaneously with AT/AU being <10%, but even then, relapses are common and frustrating. The functions of vitamin-D, far beyond calcium metabolism, related to autoimmune diseases are under continual investigation, because of the significant anti-inflammatory and immunomodulatory properties of this powerful nuclear receptor-activating hormone.

Cases: We report two girls with AT, who experienced sudden and total hair loss at the age of 1 and 5yrs and consulted in our pediatric endocrine unit at the age of 3 and 7 years respectively. For 2yrs, all available treatments local and systemic including oral methotrexate had been tried from pediatric and adult experienced dermatology clinics with no result. Having published on the negativation of Type 1 associated autoantibodies with oral calcitriol (J Diabetes. 2013 PMID: 23302101) and recently on the cure of severe atopic dermatitis with calcitriol and it's analog paricalcitol (Case Reports in Pediatrics. 2018, https://doi.org/10.1155/2018/9643543) we tried to induce immunomodulation by oral calcitriol at the dose of 0.5-0.5 x 3 mcg/day. With 0.5 mcg/day the 7-year-old girl grew hair within 6m (except from a region no longer visible at the rear of the scalp) and the result is maintained for 3yrs now with normal calcium metabolism. With 0.5 mcg x 3/day p.o. the 3-year-old girl developed asymptomatic hypercalcemia 14 mg/dl at 3m and was switched to the equivalent and slightly higher dose of paricalcitol 2 mcg x 3/day p.o. Calcium metabolism normalized, and complete hair regrowth was achieved by 6m.

Conclusions: The active hormone calcitriol has immunomodulating properties that may even cure autoimmune diseases like AT, while it's analog paricalcitol is a safe and effective alternative. Randomized controlled studies are required to prove the effectiveness and safety of this therapeutic approach, especially to establish the optimal dosage and type of Vit D administration.

LB-P17

Protein-Induced Hypoglycemia Secondary to Hyperinsulinism-Hyperammonemia (HI/HA) Syndrome: A GLUD1 Gene Mutation

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Introduction: Hyperinsulinism-Hyperammonemia (HI/HA) syndrome is a rare autosomal disease characterized by episodes of hypoglycemia related to consumption of high-protein containing foods or fasting with associated hyperammonemia secondary to an activating mutation in the GLUD1 gene. It often remains unrecognized until later in childhood because symptomatic episodes can be misinterpreted as epilepsy if patterns of hypoglycemia with fasting and protein-rich meals are not identified.

Case: The patient is a male infant born at 37 weeks to a 25 year old G6P2 mother, who presented to the ED at 9 months of life with seizure-like activity in the setting of hypoglycemia. His past medical history is pertinent for failure to thrive. Evaluation in the OSH ED noted POC glucose 33 mg/dl and otherwise clinically stable. His blood sugar increased to 53 mg/dl after administration of apple juice and to 81 mg/dl with IV D10 water at 25 ml/h. Patient transferred to our PICU where he was found well appearing with a glucose of 59 mg/dl. Stable vital signs on admission. He was admitted with IV dextrose to keep blood sugar greater than 50 mg/dl, which was eventually discontinued. Patient was placed NPO to induce hypoglycemia. Patient maintained BG greater than 50 mg/dl for ~10 hours. Patient was fed a protein rich meal, two hours after which he became hypoglycemic to 40s. Critical sample drawn when POC glucose measured at 42 mg/dl, with verified serum glucose of 31 mg/dl, insulin 5.6 uIU/ml, negative ketones, cortisol 1.8 ug/dl. On next episode of hypoglycemia, cortisol was found to be 12.6 ug/dl, ACTH 48 pg/ml and ammonia 178 ug/DL (high). Patient restricted to formula feeds, with stable glucoses. Glucose sensor placed with meal times recorded, which noted hypoglycemia with high protein content foods (milk, chicken). Genetic testing heterozygous in the GLUD1 gene for variant designated c.965>A (p.Arg322His), pathogenic for the HI/HA syndrome. Patient was started on Diazoxide 15mg PO TID (5.2mg/kg/d) with improvement of hypoglycemic episodes.

Conclusion: HI/HA syndrome should be considered in patients with unexplained hypoglycemia, particularly if associated with hyperammonemia outside of the newborn period. A thorough clinical history, including the timing of hypoglycemia in relationship to meals and the type of foods consumed by the patient, is important in defining a pattern for hypoglycemic episodes and diagnosing more rare causes of hypoglycemia.

LB-P18

The Efficacy of GnRHa Alone or in Combination with rhGH for the Treatment of Idiopathic Central Precocious Puberty or Early and Fast Puberty in Chinese Girls

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Object: To assess the efficacy and impact factors of treatment with GnRHa alone or in combination with rhGH in idiopathic central precocious puberty(CPP) or early and fast puberty(EFP) in Chinese girls.

Methods: We conducted a retrospective analysis on 20 years of data obtained from 11 medical centers from January 1998 to March 2017, and 393 girls with CPP (n=302) or EFP (n=91), who untreated or received GnRHa alone or in Combination with rhGH therapy for more than six months and reached their adult height were enrolled. Another group of 55 patients is from our hospital, and their medical records were reviewed as an independent dataset, including 31 CPP and 24 EFP patients.We evaluated age, height, weight, and bone age (BA) before and after treatment,the final adult height was recorded for each patient. During treatment, the dosage of medication was recorded.

Results: we calculated the difference between height gain (FAH-PAH1) [GnRHa+rhGH&GnRHa&control group:(9.51±0.53)&(8.07±0.37)&(6.44±0.91),P<0.05], the difference between delta genetic height (FAH-genetic height)[GnRHa+rhGH&GnRHa&control group:(4±0.5)&(2±0.27)&(0±0.61),p<0.01], and the difference of predictive adult heights before and after treatment (PAH2-PAH1). In GnRHa group, the ROC curve analysis of each parameter indicated that five different ones (PAHSDS, PAH1, Height1/BH1, HA/BA1, and PAH2-PAH1) had excellent performance of diagnosing patients whether they received good therapeutic results from GnRHa treatment or not.In GnRHa+rhGH group,the ROC curve analysis and identified another five clinical parameters(PAH2-PAH1, Height1/BH1, PAH1, PAHSDS, HA/BA1) had excellent performance of diagnosing patients whether they may receive good therapeutic results.

Conclusions: Therapy to CPP or EFP girls can effectively improve the height gain(FAH-PAH1), especially in the GnRHa+rhGH treatment.HA/BA is an important factor affecting the long-term efficacy of CPP/EFP. Clinicians should pay attention to it.

LB-P19

Characterization and Clinical Course of Prolactinoma in Korean Adolescents

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Prolactinoma is most common functioning pituitary adenoma (50%). However, there have been limited studies for prolactinoma in adolescents. Pituitary adenomas are uncommon in childhood and adolescence (<3% of childhood supratentorial tumors, 3-6% of all surgically treated adenomas). The aim of this study is to assess the characteristics of Korean adolescents with prolactinoma and their clinical course.

This study is retrospective cohort study. Patients diagnosed with prolactinoma (age < 19years) in Samsung Medical Center during a 13-year period (2005-2017). Study subjects are (1) Total 25 patients (20 female/5male), (2) Median age is 16.9, ranged from 10.1 to 18.5, (3) divided into two groups according to tumor size, (4) 11 microadenomas and 14 macroadenomas, (5) factors related to tumor size were evaluated. (6) Surgery group (n=14) and non-surgery group (n=11).

The results are presented as the mean (SD) or mean change (SD). The relationship of each risk factor with macroprolactinoma was defined by logistic regression analysis. Correlations between macroprolactinoma and other variables were determined by Spearman rank order correlation. All statistical analysis was performed using SPSS Statistics 24 (IBM Corporation, USA).

The most common clinical manifestations are galactorrhea(40%), amenorrhea(36%), visual field defect(16%), and headache(12%). Patients are diagnosed by 11 microadenomas and 14 macroadenomas. Prolactin level at diagnosis was significantly higher in macroadenoma group (516 vs 114.2 ng/mL, $p < 0.001$). Patient diagnosed to panhypopituitarism is 1(9%) in microadenoma patients, 10(71%) in macroadenoma patients($p = 0.008$). Male gender, Prolactin level at diagnosis, and immediate postoperative PRL level were positively correlated with maximal tumor diameter (r=0.443, p=0.026; r=0.710, p<0.001; r=0.623, p=0.001). Maximal tumor diameter and PRL level at diagnosis were significantly higher in surgery group in comparison with non-surgery group (p=0.001, p=0.013, respectively).

Macroprolactinoma is more prevalent in adolescents than adults. In adolescents with prolactinoma, girl is more prevalent, boys usually present with mass effect symptoms from macroprolactinoma. Male gender is in higher risk for macroadenoma more than female in adolescents with prolactinoma. Macroprolactinoma usually presents with panhypopituitarism. Given that diagnosis and prognosis may vary depending on the gender, we need to consider a more aggressive treatment in males. In addition, cocktail test for adolescents with prolactinoma is essential and adjustive hormone replacement is important to improve their quality of life.

LB-P20

The Efficacy and Safety of Octreotide Treatment for Diazoxide-unresponsive Congenital Hyperinsulinism in China

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Backgrounds: The treatment of diazoxide-unresponsive congenital hyperinsulinism (CHI) is a big challenge in clinical practice. Octreotide is an off-lable medicine for CHI but widely used nowadays. However, the efficacy and adverse effects have been reported varied in centers.

Objective: To evaluate the efficacy and safety of the subcutaneous octreotide injection for diazoxide-unresponsive CHI in China.

Subjects and methods: Diazoxide-unresponsive CHI children treated with subcutaneous octreotide injection at an adjusted dosage of up to 50μg/kg/day were involved in the study. Octreotide is ineffective when blood glucose(BG) <2.8mmol/L or is completely effective if BG > 3.3mmoll/L over 48 hours by every 2 hours check after wean-off iv dextrose. BG between the above means partial effectiveness. We also test CHI genes by next generation sequencing.

Results: Twenty-five Chinese (15 males) children were enrolled in the study. Their median onset age was 1 day (range1-150 days), the median diagnosis age was 7.5 weeks (range 1-24 wk), the mean age of last visit was (1.6±0.9) (maximum 3.3) years. The effective median dose of octreotide required was 10.0 (range 1.2~20.0) μg/kg/d and the BG stabilized at (7.3±2.0) days, the mean duration was (8.9±6.3) months (range 1.5-25 mo). Eighty-eight percent (22/25) were confirmed with ATP sensitive potassium channel gene mutation (19*ABCC8*, 3*KCNJ11*). The octreotide was completely effective, partly effective in 12, 9 patients respectively and ineffective in 4 (16%). The effectiveness (included complete and partial effectiveness) of octreotide was not different between gene-positive and -negative group. The dose of octreotide was not different between monoalliec and biallelic ATP sensitive potassium channel mutation. Transient elevation of liver enzymes occurred in 20% patients, asymptomatic gallbladder pathology occurred in 1 patient. The growth charts of this cohort patients were in normal range (mean height SDS was 0.3±1.5 at the last follow-up).

Conclusions: The octreotide was well tolerated, effective therapy for diazoxide unresponsive CHI cases. It could be a choice for diazoxide-unresponsive patients.

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