Lethal Very Long-Chain Acyl-Coa Dehydrogenase Deficiency with a Novel Mutation

Yeni Mutasyon Saptanan Ölümcül Çok Uzun Zincirli Açil-Coa Dehidrogenaz Eksikliği Olgusu

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ABSTRACT

Very long chain acyl-CoA dehydrogenase deficiency is an autosomal recessive genetic disorder in which the first step in the mitochondrial β-oxidation of fatty acids for 14-20 carbons is defective. Clinical presentation is heterogeneous ranging from the severe neonatal form presenting with hypo-ketotic hypoglycemia, liver dysfunction and rapidly fatal cardiomyopathy with episodes of hypo-ketotic hypoglycemia in infants. Herein we report a patient with novel homozygous missense mutation c.1391C>A in exon 14 with a severe neonatal onset type who presented with hypoketotic hypoglycemia, cardiomyopathy and hepatomegaly.

Key Words: Very long chain acyl-CoA dehydrogenase deficiency, children, hypoglycemia, cardiomyopathy.

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ÖZET

Çok uzun zincirli açil-KoAdehidrogenaz eksikliği, yağ asitlerinin mitokondriyal beta-oksidasyonunda ilk basamak olan 14-20 karbonlu yağ asit oksidasyonunun defektif olduğu otozomal resesif geçiş gösteren genetik bir hastalıktır. Klinik başvuru şekli hipoketotik hipoglisemi, karaciğer yetmezliği ve hızlı seyirli fatal kardiyomyopatinin eşlik ettiği form ile hafif hipoketotik hipoliseminin eşlik ettiği infant form arasında heterojendir. Burada, hipoketotik hipoglisemi, hepatomegali ve kardiyomyopati ile başvuran, exon 14'de c.1391C>A yeni tanımlanmış homozigot missense mutasyon saptanan, ciddi yenidoğan başlangıçlı bir çok uzun zincirli açil-KoA eksikliği vakası sunulmaktadır.

Anahtar Sözcükler: Çok uzun zincirli açil-KoA dehidrogenaz eksikliği; çocuk; hipolisemi; kardiyomyopati

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INTRODUCTION

Very long chain acyl-CoA dehydrogenase deficiency (VLCADD) was first described in 1993. It is an autosomal recessive genetic disorder in which the first step in the mitochondrial β-oxidation spiral of fatty acids for 14-20 carbons is defective (1). The phenotype is heterogeneous ranging from thesevere neonatal form presenting with hypo-ketotic hypoglycemia, liver dysfunction and rapidly fatal cardiomyopathy overthe infantile formwith episodes of hypo-ketotic hypoglycemia and liver dysfunction to the adult myopathicform (2).VLCADD is implemented in newborn screening in the US and several European countries (3). In view of the emerging genotype-phenotype correlation in this disorder genetic confirmation may be helpful in designing the appropriate therapeutic regime for these patients. Here we report a patient with novel homozygous missense mutationc.1391C>A in exon 14with a severe neonatal onset type who presented withhypoketotichypoglycemia, cardiomyopathy and hepatomegaly.

CASE REPORT

The patient was bornat 40 weeks of gestation by spontaneous delivery afteran uncomplicated pregnancyas fourth child from consanguineous parents. There was one sibling with SIDS at 3 months of age. Apart from a single hypoglycemia atthe first day of life our patient had an uncomplicated neonatal adaptationand was discharged home at three days. At age 4 months, he presented with vomiting and diarrhea to a local emergency and had to be admitted to the pediatric ICU because of dehydration, metabolic acidosis, and hypoglycemia. Physical examination revealed tachycardia, hepatomegaly and muscular hypotonia. The liver was 7 cm below the right costal margin. Abdominal ultrasonography confirmed thehepatomegaly and revealed a steatosis. Echocardiography showed left ventricular hypertrophy.

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Laboratory investigations revealed elevated creatine kinase level of 1844 U/L (normal range, 60-305 U/L) and a borderline blood glucose level of 2.38 mmol/l (43 mg/dl) with negativeurine ketone, lactate 11.1mmol/l (100 mg/dl), uric acid level of 482umol/l (8.1 mg/dl), AST level of 162 U/L and ALT level of 91 U/L and triglyceride level of 818 mg/dl. Plasma acylcarnitine profile demonstrated elevations in multiple long chain acylcarnitine species (C14:1 level of 1.25 µmol/L (normal value <0.6), C14 level of 1.68 µmol/L (nv<0.8), C14: 2 level of 0.28 µmol/L (<0.18), C16:1 level of 1.32 µmol/L (nv: <1.04), C18:1 3.86 µmol/L (nv: <3.53)free carnitine level was low 2.25 µmol/L (nv:3.8-50 µmol/L). Organic acid profile showed marked dicarboxlicaciduria indicating VLCADD. DNA sequencing of *ACADVL*, revealed a yet unreported homozygous missense mutation (c.1391C>A) in exon 14. Family studies confirmed the disease causing mutation. The treatment with a medium chain triglyceride-rich diet and frequent feeding was started. However the patient died unexpectedly one month after the diagnosis, supposedly fromcardiac dysrhythmia secondary to hypertrophy in left ventricle.

DISCUSSION

VLCADD is an autosomal recessive disorder of fatty acid oxidation. VLCAD catalyzes the initial step of mitochondrial β-oxidation of long chain fatty acids with a chain length of 14 to 18 carbons. Heart, liver, and skeletal muscle, all requiring high amounts of ATP, are the most affected organs (1,2). Early diagnosis and treatment is essential to prevent cardiomyopathy, arrhythmia, hypoketotic hypoglycemia, rhabdomyolysis and death. Neonatal screening programs for VLCADD have been implemented recently in various countries (3). Mildly elevated C14:1 carnitine on third day of newborn strongly suggests VLCADD. Patients with VLCADD detected thorough newborn screening are usually asymptomatic during the well state but they are at risk for metabolic decompensation during catabolic episodes such as intercurrent infections or other episodes of fasting (2,3).Genetic an enzymatic confirmation is of importance due to the wide variety of clinical presentations ranging from severe neonatal to mild adult myopathic variants. Implementation of newborn screening usually leads to an increasing incidence of VLCADD due a great number of asymptomatic patients with a good outcome after timely diagnosis (4-7). But overall the severe neonatal form is the most common type and presents with cardiomyopathy and hepatopathy and has the highest mortality thus justifying neonatal screening.The presentation of our patient with hypoketotic hypoglycemia, acute liver steatosis with hepatomegaly,cardiomyopathy, and rhabdomyolysis and the history of unexplained death of a sibling were very suggestive a beta oxidation disorder (7-10). In countries where newborn screening is not available for these disorders, diagnosiscan be reached with acylcarnitine, organic acid analysis and VLCAD enzymatic analysis (10-11).In view of the emerging genotype-phenotype correlation in this disorder, with low residual activity-associated deletions and nonsense mutations and variable disease-associated missense mutations. Genetic confirmation and enzymatic analysis is helpful in designing the appropriate follow-up and therapeutic regime for these patients. The mainstay of therapy is the prevention of recurrent attacks by an anti-catabolic therapy during surgery, prolonged fasting, perioperative stress to minimize fasting stress (12-13).

In summary we present a new missense mutation(c.1391C>A)associated with a severe neonatal VLCADD phenotype.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. Schiff M, Mohsen AW, Karunanidhi A, McCracken E, Yeasted R, Vockley J. Molecular and cellular pathology of very-long-chain acyl-Co Adehydrogenase deficiency. Mol Genet Metab. 2013;109(1):21-7.
2. Spiekerkoetter U, Mueller M, Sturm M, Hofmann M, Schneider DT. Lethal Undiagnosed Very Long-ChainAcyl-CoA Dehydrogenase Deficiency with Mild C14-Acylcarnitine Abnormalities on Newborn Screening. JIMD Rep. 2012;6:113-5.
3. Siu WK, Mak CM, Siu SL, Siu TS, Pang CY, Lam CW, Kwong NS, Chan AY. Molecular diagnosis for a fatal case of very long-chain acyl-CoA dehydrogenase deficiency in Hong Kong Chinese with a novel mutation: a preventable death by newbornscreening. Diagn Mol Pathol. 2012;21(3):184-7.
4. Pervaiz MA, Kendal F, Hegde M, Singh RH. MCT oil-based diet reverses hypertrophic cardiomyopathy in a patient with very long chain acyl-coA dehydrogenase deficiency. Indian J Hum Genet. 2011;17(1):29-32.
5. Eminoglu TF, Tumer L, Okur I, Ezgu FS, Biberoglu G, Hasanoglu A. Verylong-chain acyl CoA dehydrogenase deficiency which was accepted as infanticide. Forensic Sci Int. 2011;210(1-3):e1-3.
6. McGoey RR, Marble M. Positive newborn screen in a normal infant of a mother with asymptomatic verylong-chainAcyl-CoA dehydrogenase deficiency. J Pediatr. 2011;158(6):1031-2.
7. Vellekoop P, Diekman EF, vanTuijl I, de Vries MM, vanHasselt PM, VisserG. Perioperative measures in very long chain acyl-CoA dehydrogenase deficiency. Mol Genet Metab. 2011;103(1):96-7.
8. Mendez-Figueroa H, Shchelochkov OA, Shaibani A, Aagaard-Tillery K, ShinawiMS. Clinical and biochemical improvement of very long-chain acyl-CoA dehydrogenase deficiency in pregnancy. J Perinatol. 2010;30(8):558-62.
9. Coughlin CR 2nd, Ficicioglu C. Genotype-phenotype correlations: sudden death in an infant with very-long-chain acyl-CoAdehydrogenase deficiency. J Inherit Metab Dis. 2010;33 Suppl 3:S129-31. Ficicioglu C, Coughlin CR 2nd, Bennett MJ, Yudkoff M. Verylong-chain acyl-CoA dehydrogenas edeficiency in a patient with normal newborn screening by tandem mass spectrometry. J Pediatr. 2010;156(3):492-4.
10. Aliefendioğlu D, Dursun A, Coşkun T, Akçören Z, Wanders RJ, Waterham HR. A newborn with VLCAD deficiency. Clinical, biochemical, and histopathological findings. Eur J Pediatr. 2007;166(10):1077-80.
11. Merinero B, Alcaide P, Martín-Hernández E, Morais A, García-Silva MT,Quijada-Fraile P, Pedrón-Giner C, Dulin E, Yahyaoui R, Egea JM, Belanger-Quintana A, Blasco-Alonso J, FernandezRuano ML, Besga B, Ferrer-López I, Leal F, Ugarte M, Ruiz-Sala P, Pérez B, Pérez-Cerdá C. FourYears' Experience in the Diagnosis of Very Long-ChainAcyl-CoA Dehydrogenase Deficiency in Infants Detected in Three Spanish Newborn Screening Centers. JIMD Rep. 2018;39:63-74.
12. Katz S, Landau Y, Pode-Shakked B, Pessach IM, Rubinshtein M, Anikster Y, Salem Y, Paret G. Cardiac failure in very long chain acyl-CoA dehydrogenase deficiency requiring extracorporeal membrane oxygenation (ECMO) treatment: A case report and review of the literature. Mol Genet Metab Rep. 2016;10:5-7.