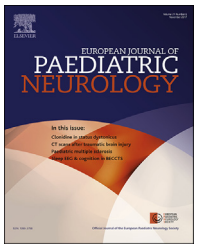
Official Journal of the European Paediatric Neurology Society



Original article

Characteristics of pediatric multiple sclerosis: The Turkish pediatric multiple sclerosis database

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ARTICLE INFO

Article history:
Received 29 June 2016
Received in revised form
26 May 2017
Accepted 20 June 2017

Keywords:
Pediatric
Multiple sclerosis
Relapse
Magnetic resonance
Imaging
Vitamin D
Visual evoked potentials

ABSTRACT

Objective: To document the clinical and paraclinical features of pediatric multiple sclerosis (MS) in Turkey.
Methods: Data of MS patients with onset before age 18 years (n = 193) were collected from 27 pediatric neurology centers throughout Turkey. Earlier-onset (<12 years) and later-onset (≥12 years) groups were compared.
Results: There were 123 (63.7%) girls and 70 (36.3%) boys aged 4–17 years, median 14 years at disease onset. Family history of MS was 6.5%. The first presentation was polysymptomatic in 55.4% of patients, with brainstem syndromes (50.3%), sensory disturbances (44%), motor symptoms (33.2%), and optic neuritis (26.4%) as common initial manifestations. Nineteen children had facial paralysis and 10 had epileptic seizures at first attack; 21 (11%) were initially diagnosed with acute disseminated encephalomyelitis (ADEM). Oligoclonal bands were identified in 68% of patients. Magnetic resonance imaging revealed periventricular (96%), cortical/juxtacortical (64.2%), brainstem (63%), cerebellum (51.4%), and spinal cord (67%) involvement. Visual evoked potentials (VEP) were abnormal in 52%; serum 25-hydroxyvitamin D levels were low in 68.5% of patients. The earlier-onset group had a higher rate of infection/vaccination preceding initial attack, initial diagnosis of ADEM, longer interval between first 2 attacks, and more disability accumulating in the first 3 years of the disease.
Conclusion: Brainstem and cerebellum are common sites of clinical and radiological involvement in pediatric-onset MS. VEP abnormalities are frequent even in patients without history of optic neuropathy. Vitamin D status does not appear to affect the course in early disease. MS beginning before 12 years of age has certain characteristics in history and course.

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http://dx.doi.org/10.1016/j.ejpn.2017.06.004

1. Introduction

Multiple sclerosis (MS) manifests before 18 years of age in 2–10% of patients, which is defined as pediatric MS.[1–9] Early diagnosis and optimal management of pediatric MS are important because significant disability is attained at earlier age in this age group compared to adults[3,5,10] and early intervention with disease-modifying drugs may slow this progression.[11] On the other hand, pediatric cases may remain underdiagnosed or misdiagnosed, mainly due to difficulties in distinguishing from other white matter diseases prevalent in children, particularly acute disseminated encephalomyelitis (ADEM) and metabolic disorders.[8,12–15] MS starting before puberty is even more complicated because clinical, radiological, and cerebrospinal fluid (CSF) examination findings may differ from those in adolescents.[15–19] Pediatric MS has been associated with higher incidence of visual, motor, sensory and brainstem symptoms at onset and lower prevalence of progressive disease compared to adult MS.[5,8,17] Genetic and environmental factors including viral exposure and vitamin D deficiency may contribute to the development of pediatric MS.[5,17,20] In this multicentric retrospective study, we reviewed the demographic, clinical and paraclinical features of pediatric MS in Turkey.

2. Methods

Demographic, clinical, and paraclinical data of MS patients with onset before 18 years old were collected from 27 child neurology centers accross 15 cities in Turkey. Data were entered into the SPSS data editor by one of the study participants who had either evaluated the patient or reviewed the medical record. Institutional Ethical Committee approved the study (IRB No: 2016/05-05). Children with clinically isolated syndrome, recurrent ADEM, or neuromyelitis optica were excluded.

The diagnosis of MS was based on the 2010 Revised McDonald criteria.[9,21] Because age of puberty varies between boys and girls, and because of the International Pediatric Multiple Sclerosis Study Group's application of the 2010 Revised McDonald MRI criteria after age 12 years,[9] we selected this age as cut-off for defining earlier-onset (<12 years) and later-onset (≥12 years) pediatric MS groups.

Analyzed variables included sex, age at first attack, interval between the first and second attacks, number of attacks during the first year of disease, total number of relapses during follow-up, clinical course (relapsing-remitting or progressive), family history of MS (at least one first or second-degree relative with MS), history of breastfeeding, parental smoking, infection within one month or vaccination within two months preceding clinical onset, initial diagnosis of ADEM, functional sites involved during the first attack and follow-up, disability, treatments and adverse effects, CSF analyses, serum 25-hydroxyvitamin D concentrations, MRI and visual evoked potential (VEP) results. A clinical attack was defined as new neurological deficit lasting more than 24 h. Major adverse events were defined as any effects leading to discontinuation of treatment. Onset was considered mono- or poly-symptomatic depending on clinical features' compatibility with one or more CNS lesions, respectively. According to the proposed 2012 IPMSSG criteria, we defined ADEM as a first polysymptomatic presentation associated with encephalopathy in the form of alteration in consciousness or behavioral change that cannot be explained by fever.[9] We included patients with an initial diagnosis of ADEM only if they experienced a nonencephalopathic clinical event three or more months after symptom onset that was associated with new MRI lesions that fulfill 2010 Revised McDonald DIS criteria. Transverse myelitis was defined as sensory level with motor disturbance with/without bladder or bowel dysfunction. Neurologic disability was scored by the mean expanded disability status scale (EDSS) score, which was calculated at least 30 days after a clinical attack and recorded yearly.

The latest brain and spinal cord MRI findings were reviewed by the radiologists of each center. The results of CSF oligoclonal bands (OCB) and IgG index, VEP and serum 25-hydroxyvitamin D levels were recorded whenever available. For the purpose of this study VEP was defined as abnormal when the P100 wave was absent or delayed. In patients who had more than one CSF and VEP investigations, any positive result was recorded.

Data were described as mean ± standard deviation for continuous variables. Groups were compared by Pearson's chi-square or Fisher's exact tests for categorical variables and t test or Mann Whitney U test for continuous ones. The EDSS scores at different times of the study (baseline and the 1st, 2nd, and 3rd years) were evaluated by the Friedman test with a Bonferroni post hoc correction. Missing data were excluded from analysis for that particular case. Significance was set at $p < 0.05$ (SPSS for Windows, version 20.0, Chicago, IL).

3. Results

The study group consisted of 123 (63.7%) girls and 70 (36.3%) boys, age of onset 4–17 years, median 14 years, earlier-onset (<12 years) and later-onset (≥12 years) consisting of $n = 45$ and $n = 148$, respectively. General demographics and clinical features are presented in Table 1.

MRI findings and the results of OCB, IgG index, VEP and serum 25-hydroxyvitamin D levels are presented in Table 2.

Data regarding medications and side effects are shown in Table 3. While 27.4% of patients experienced one or more side effects, only two patients, both receiving interferon beta 1-a, discontinued treatment due to elevation of liver transaminases. The mean EDSS score was 0.37 after the first clinical attack and increased to 1.04 at the end of the third year: EDSS increase at 3 years was significant in children with earlier-onset MS, but not in the later-onset group (Table 4).

4. Discussion

This is one of the largest series of pediatric MS. Our database covering the majority of child neurology referral centers from all geographical regions in Turkey may represent the general characteristics of the disease in this country.

Table 1 – Clinical and demographic characteristics of patients with pediatric multiple sclerosis.

	All patients	Onset at <12 Yr	Onset at 12–18 Yr	P
Number	193	45 (23.3)	148 (76.7)	
Sex ratio, F:M	1.76	1.25	1.96	0.193
Female	123 (63.7)	25 (55.6)	98 (66.2)	
Male	70 (36.3)	20 (44.4)	50 (33.8)	
Age at first attack, years	13.47 ± 2.88 (4–17), median:14	9.12 ± 2.0 (4–11), median:10	14.8 ± 1.43 (12–17), median:15	**<0.001**
Interval between the first two attacks in months, n = 122	10.29 ± 10.85 (1–60) median: 6	15.20 ± 14.38 (1–60) median:11	8.39 ± 8.49 (1–39) median:6	**0.006**
Number of attacks during the first year, n = 153	1.80 ± 0.86, median:2 (1–5)	1.50 ± 0.81, median:1 (1–4)	1.91 ± 0.86, median:2 (1–5)	**0.002**
Family history of MS, n = 185	12 (6.5)	3 (6.8)	9 (6.4)	0.918
Breastfeeding, n = 79	77 (93.4)	15 (93.8)	62 (98.4)	0.366
1–6 months	21 (26.6)	5 (31.3)	16 (25.4)	
6–12 months	22 (27.8)	4 (25.0)	18 (28.6)	
>12 months	34 (43.0)	6 (37.5)	28 (44.4)	
Smoking at home, n = 86	48 (55.8)	9 (52.9)	39 (56.5)	0.790
Infection/vaccination preceding initial episode, n = 192	30 (15.7)	14 (31.8)	16 (10.8)	**0.001**
Disease course				
Relapsing-remitting	191 (99.0)	45 (100)	146 (98.6)	
Primary progressive	2 (1.0)	0	2 (1.4)	
Initial diagnosis of ADEM, n = 191	21 (11.0)	15 (33.3)	6 (4.1)	**<0.001**
Presenting clinical phenotype				0.482
Monofocal	86 (44.6)	18 (40.0)	68 (45.9)	
Polyfocal	107 (55.4)	27 (60.0)	80 (54.1)	
Functional systems involved during initial attack				
Brainstem	97 (50.3)	24 (53.3)	73 (49.3)	0.638
Cerebellar	57 (29.5)	17 (37.8)	40 (27.0)	0.166
Diplopia	52 (26.9)	10 (22.2)	42 (28.4)	0.415
Facial palsy	19 (9.8)	5 (11.1)	14 (9.5)	0.777
Sensory	85 (44.0)	10 (22.2)	75 (50.7)	**0.001**
Motor	64 (33.2)	13 (28.9)	51 (34.5)	0.487
Optic neuritis	51 (26.4)	15 (33.3)	36 (24.3)	0.230
Transverse myelitis	4 (2.1)	1 (2.2)	3 (2.0)	
Urinary/fecal incontinance	8 (4.1)	2 (4.4)	6 (4.1)	
Seizure	10 (5.2)	4 (8.9)	6 (4.1)	0.246
Functional systems involved during follow-up				
Brain stem	125 (64.8)	33 (73.3)	92 (62.2)	0.170
Cerebellar	88 (45.6)	29 (64.4)	59 (39.9)	**0.004**
Diplopia	67 (34.7)	13 (28.9)	54 (36.5)	0.349
Facial paralysis	32 (16.6)	13 (28.9)	19 (12.8)	**0.011**
Sensory	125 (64.8)	25 (55.6)	100 (67.6)	0.140
Motor	97 (50.3)	27 (60.0)	70 (47.3)	0.136
Optic neuritis	74 (38.3)	19 (42.2)	55 (37.2)	0.541
Transverse myelitis	14 (7.3)	5 (11.1)	9 (6.1)	0.322
Bladder-bowel incontinance	15 (7.8)	4 (8.9)	11 (7.4)	0.754
Seizure	11 (5.7)	4 (8.9)	7 (4.7)	0.286

Data are number (%) or mean ± SD (range), unless otherwise specified.
S.D: Standard deviation, ADEM: acute disseminated encephalomyelitis.
"n" on the first column is the number of subjects who have data for the specific parameter on that line.
Bold values indicate P value < 0.05.

Mean age of onset was 13.5 years, 23% were younger than 12 years: this is comparable to most pediatric MS series where mean age of onset is 8–14 years, and the young age group (<10 or 12 years) comprises 15–20% of the cohorts.[8] The age distribution affects other variables described in cohorts: for instance, the female/male ratio is reported as 0.8/1 below 6 years, 1.6/1 between 6 and 10 years, but varying between 0.79 and 2.9/1 after age 11 years, suggesting higher influence of pubertal status rather than chronological age in this period.[3,5,6,13,17,22,23] Indeed the relapse rate and therefore likelihood of manifestation is increased around menarche.[24] In the present study, the female/male ratio increased from 1.25 in prepuberty to 1.96 in adolescence. Gender distribution is also affected by environmental factors as shown by a female/male ratio of 0.86/1 in American Hispanic compared to 2.8/1 in European children.[5,23] This is supported by a recent study showing a marked increase in MS incidence and a major shift in sex distribution (F/M 0.9 in 1980; and 2.1 in 2008) in a genetically stable population with transition from rural to urban living over 3 decades, implicating environmental

Table 2 – Paraclinical characteristics of patients with pediatric multiple sclerosis.

	All patients	Onset at <12 Yr	Onset at 12–18 Yr	P
MRI characteristics				
Supratentorial white matter, n = 191	187 (97.9)	44 (97.8)	143 (97.9)	0.662
Periventricular white matter, n = 181	174 (96.1)	41 (97.6)	133 (95.7)	0.488
Cortical/Juxtacortical, n = 176	113 (64.2)	30 (75.0)	83 (61.0)	0.105
Brainstem, n = 187	118 (63.1)	33 (75.0)	85 (59.4)	0.061
Cerebellar, n = 183	94 (51.4)	28 (62.2)	66 (47.8)	0.093
Spinal cord, n = 185	124 (67.0)	28 (65.1)	96 (67.6)	0.761
VEP latency abnormalities, n = 156	81 (51.9)	20 (64.5)	61 (48.8)	0.117
Patients with a history of ON, n = 66	52 (78.8)	12 (63.2)	40 (72.7)	0.896
Patients without a history of ON, n = 90	29 (32.2)	8 (30.8)	21 (22.6)	0.093
Cerebrospinal fluid				
OCB present in CSF, n = 169	115 (68.0)	25 (67.6)	90 (68.2)	0.944
Elevated IgG index, n = 154	96 (62.3)	20 (54.1)	76 (65.0)	0.233
Positive OCB and/or elevated IgG index, n = 169	132 (78.1)	28 (75.7)	104 (78.8)	0.686
Serum				
Low serum levels of 25-hydroxyvitaminD, n = 111	76 (68.5)	17 (68.0)	59 (68.6)	0.954

Data are number (%).
CSF: cerebrospinal fluid, OCB: oligoclonal band, ON: Optic neuritis.
"n" on the first column is the number of subjects who have data for the specific parameter on that line.

factors affected by urbanization including nutrition and vitamin intake, smoking, alcohol and childhood rubella, chickenpox, and herpes simplex virus infections.[25] Among environmental factors, vitamin D insufficiency, viral infections, and exposure to cigarette smoke have been implicated in susceptibility of children to MS.[15,17,26,27]

Genetic factors' role in the development of MS is supported by family studies. A nationwide study from Denmark demonstrated 7-fold increased risk of MS in relatives of adult MS patients.[28] The rate of a positive family history varies between 6 and 22% in the pediatric MS population, possibly because certain studies include first-degree, but others, more distant relatives.[3,5,6,13,18] We included 1st and 2nd-degree relatives; the rate of positive family history was 6.5%, comparable to,[3,17,18] but lower than some previously reported rates.[5,19,29]

Having been breastfed for at least 4 months might lower the risk of MS.[30] A recent study found a significant association between MS and short/no exposure to breastfeeding in Italy and only in men in Norway. History of breastfeeding ≥4 months was present in 65.4% of MS patients from Norway and 48.9% in MS patients from Italy.[31] In contrast, the rate of at least 6-month-long breastfeeding in our study was higher than the Turkish average (71 vs. 38%)[32] and does not support a protective effect. Well-designed case–control studies are needed to investigate the role of breastfeeding in MS.

Smoking and MS have been associated, but few data are available on the role of passive smoke exposure, particularly

Table 3 – Treatment in patients with pediatric multiple sclerosis.

	All patients	Onset at <12 Yr	Onset at 12–18 Yr	P
Number of patients on immunomodulatory treatment n = 165	128 (66.3)	27 (60.0)	101 (68.2)	0.306
Interferon beta-1a (Rebif)	58 (35.1)	13 (28.9)	45 (35.2)	
Interferon beta-1a (Avonex)	50 (30.3)	7 (18.9)	43 (33.6)	
Interferon beta-1b (Betaferon)	8 (4.8)	2 (5.4)	6 (4.7)	
Glatiramer acetate (Copaxone)	2 (1.2)	2 (5.4)	0	
Azathioprine	6 (3.6)	3 (8.1)	3 (2.3)	
Mitoxantrone	1 (0.6)	0	1 (0.8)	
Other	3 (1.8)	0	3 (2.3)	
Duration of treatment, months, n = 107	18.95 ± 16.6, median 13 (1–79)	20.83 ± 21.34, median 13 (1–79)	18.41 ± 15.09, median 13 (1–72)	0.878
Effectiveness of the first immunomodulatory drug, n = 128	110 (85.9)	22 (81.5)	88 (87.1)	0.533
Adverse effects, n = 73	20 (27.4)	7 (15.6)	13 (8.8)	0.119
Major, n = 70	2 (2.9)	1 (6.2)	1 (1.9)	
Minor, n = 65	18 (27.7)	6 (13.3)	12 (24.0)	

Data are number (%) or mean ± SD (range), unless otherwise specified.
S.D: Standard deviation.
"n" on the first column is the number of subjects who have data for the specific parameter on that line.

Table 4 – Change in EDSS over three years.

	Baseline n = 105	First year of follow-up n = 71	Second year of follow-up n = 36	Third year of follow-up n = 24	P Value
All patients	0.37 ± 0.72, Median 0 (0–4)	0.38 ± 0.88, Median 0 (0–4.5)	0.65 ± 1.41, Median 0 (0–6)	1.04 ± 1.75, Median 0 (0–6)	**0.001**
Onset at <12 Yr	0.27 ± 0.51, Median 0 (0–2)	0.58 ± 1.14, Median 0 (0–4.5)	0.93 ± 1.79, Median 0 (0–6)	1.36 ± 2.15, Median 0 (0–6)	**0.012**
Onset at 12–18 Yr	0.41 ± 0.79, Median 0 (0–4)	0.28 ± 0.72, Median 0 (0–4)	0.45 ± 1.07, Median 0 (0–4)	0.76 ± 1.36, Median 0 (0–4)	0.121

Data are mean ± SD (range), unless otherwise specified.
EDSS: Expanded Disability Status Scale, S.D: Standard deviation.
Bold values indicate P value < 0.05.

in children.[26,33] A population-based, case–control study has found that the risk of MS attack was twice in children exposed to parental smoking compared to children with non-smoking parents, and was even higher with exposure of 10 years or more.[26] In our series, exposure to current or past parental smoking was 55.8%, a rate similar or lower than the previously reported prevalence rates of passive smoking in Turkey (59.9%–81.5%).[34] This argues against a role of smoke exposure as a risk factor in our population.

Serum 25-hydroxyvitamin D levels were associated with certain parameters in adult MS: relapse rate, risk of new T2 lesions, risk of gadolinium-enhancing lesion, and subsequent disability.[35,36] High 25-hydroxyvitamin D levels during the years preceding disease onset reduces the risk of MS, as recently shown in a study on stored blood samples.[27] Vitamin D deficiency is also prevalent in pediatric-onset MS and lower serum 25-hydroxyvitamin D levels are associated with increased relapse rate.[37] In our series, low vitamin D levels were found in 68.5%, more frequent than reported prevalences of vitamin D deficiency and insufficiency in Turkish children (<20 ng/mL in 8% and 20–29 ng/mL in 25.5%).[38] However, the relapse rates were not different between children with low or normal vitamin D levels. Indeed, a systematic review of randomized, double-blind, placebo-controlled trials examining the clinical efficacy of vitamin D in adults with MS showed that 4/5 trials reported no beneficial effect of vitamin D on any outcome measures while one reported fewer T1 enhancing lesions on brain MRI. These observations do not support a critical role for oral vitamin D supplementation in prevention or treatment of MS in children, at least in the short term.[39]

4.1. *Clinical presentation*

Reported frequencies of presenting symptoms in pediatric MS vary widely.[6,8,15] A review of four prospective studies reported cerebellar presentation in 28%, sensorial in 27%, motor in 27%, brainstem in 22%, and ON in 20% of patients.[15] In agreement with these reports, the most common initial symptoms in our series were cerebellar-brainstem, followed by sensorial, motor, optic nerve, and spinal cord symptoms. Sensorial symptoms at onset were more frequent in later-onset compared to earlier-onset patients, possibly due to more limited verbal expression and cooperation in young children. Comparison between studies is complicated because certain are based on symptoms while others rely on examination findings.

Polysymptomatic presentation is common in children with MS and even more so in younger children compared to adolescents.[13,15,18,40] In our series it was 55%, and tended to be more frequent in the younger group. Studies reporting low rates of polysymptomatic presentation in pediatric MS are mostly from Canada, USA and South America.[6,8,23] Banwell et al. reported monofocal first attacks were more frequent in European patients than in North and South America.[17] This could suggest the influence of genetic, geographic and/or environmental factors on the presentation of pediatric MS.

An initial diagnosis of ADEM may be the first episode of pediatric MS especially in younger patients, as in our series.[5,16–18,23,40,41] A combined analysis of four prospective studies has demonstrated 16% of children with MS had

encephalopathy at the initial attack.[15] From the other angle, between 6% and 29% of children diagnosed with ADEM later received the diagnosis of MS.[42–44] Genetic background may have a strong influence on encephalopathy at presentation: only 2.7% of American Hispanic children with MS had an initial diagnosis of ADEM.[23] There has been increasing interest in the role of myelin oligodendrocyte glycoprotein (MOG) antibody response in demyelinating diseases. MOG-IgG seropositivity has been reported to plead against a diagnosis of MS.[45–47] Our series could possibly contain certain anti-MOG-positive cases because testing for these antibodies became available only recently. However the imaging features of relapsing disease associated with MOG antibodies differs from MS, and the diagnosis of MS was clinically and radiologically defined in our cases by examination of their latest MR images.

Cerebellar and brain stem involvement were reported in about 50% of patients in some studies,[3,19] similar to rate in our series, but lower in others.[6,16,17] The reason for variability is unclear but may depend on the accuracy of young children's expression of symptoms like vertigo or diplopia, initial examination being carried out in an emergency room or in a pediatric neurology clinic, or definition being inconsistent between studies, some including both clinical and MRI involvement.[48] Isolated spinal involvement is infrequent in pediatric MS series, including ours: transverse myelitis was the initial clinical finding in only 2.1% of our patients.[1,3,4,8,18] However, myelopathy as the presenting symptom is frequent (18%) in Hispanic children with MS.[23] Indeed myelopathy is the second most common presenting symptoms after ON in Hispanic children and adults with MS.[23]

Epileptic seizures can occur in 5–10% of children with MS during the course of disease, and in 22% of children <6 years old.[13,41,49] A recent study from Turkey calculated the prevalence of epileptic seizures as 1.5% among 2300 definite MS patients: 22% of MS patients with seizures were under the age 16 years, compared to 6% without seizures, although mean age at first MS attack was not significantly different between MS patients with and without epileptic seizures.[50] In our series, the frequency of epileptic seizures at the first clinical attack was high, 5.7%, and not different between earlier and later-onset MS patients.

Although fatigue is one of the most common and disabling symptoms affecting up to 76% of children and adolescents with MS,[51] it remained an under-recognized symptom in pediatric MS until recently. We did not find any recording of fatigue in our patients. This may be due to difficulties in verbalization of fatigue by patients and parents, and also lack of awareness of this symptom by the treating physicians. In a recent study, children with MS described fatigue physically as a complete loss of energy and heaviness that felt *"like wearing a giant sandbag"*, and cognitively, as *"like looking through a haze"*.[52] Thus, awareness and specific questioning should be advised to physicians who treat children with MS.

4.2. *Disease course and outcome*

The annualized relapse rate in pediatric-onset MS is higher than the rate in adult-onset MS; a tendency that persists during the first 6 years of disease suggesting an active, inflammatory nature of the disease.[53,54] The first inter-attack interval in pediatric MS varies between age groups, median interval being reported between 11 and 71 months.[3–5,17,18,48] In our series, interval between the first two attacks was longer in patients with earlier-onset MS than later-onset MS (15 vs. 8 months), but still shorter than some figures above.[3,5,18] Mean interval was 10.3, and median interval, 6 months in our study: because of extreme or outlying figures there is a large variability which diminishes the value of these parameters as outcome or follow-up measures. It can be speculated that some prepubertal patients follow an active, aggressive disease with frequent attacks and early accumulation of disability in early years. In contrast, some others in the same age group might have a much more benign course with a long interval between first 2 attacks. Because the number of patients in this age group is small, the results obtained from different series vary considerably.

Even though relapses during the first year were less frequent in children with earlier-onset MS in our study, mean EDSS scores increased significantly only in children with earlier-onset pediatric MS after 3-year-follow-up. A previous study reported on the frequency of severe and incompletely recovering first attacks in patients with disease onset before age 11 than those with onset between age 14–16 years.[40] On the other hand, complete recovery after the first episode is expected to occur in most children.[5,17,29] Disability accumulates slower in pediatric MS than in adult MS.[3,23,29] Increased relapse rates in a multiethnic pediatric cohort compared to adult-onset MS was reported; however, the pediatric group did not have the same degree of disability as adults.[54] In another study, permanent physical disability (EDSS $\geq$ 4.0) developed in only 15% of pediatric patients within 5 years.[17] Likewise, the EDSS scores remained low during 3-year follow-up in our study. Significant disability can still accumulate by early adulthood.[5]

Primary progressive course is very rare in pediatric-onset MS while secondary progression can begin in median 28 years of disease, at the median age of 41 years.[5,17,48] Our study did not collect such long-term follow-up data, but another study from Turkey showed secondary progression in pediatric-onset cases starting after median disease duration of 10 years and at a median age of 26 years.[10] This is much earlier than described above, and may be due to our patients' young age of onset. In consistence with previous reports, primary progressive course was rare (1%) in our series.

4.3. *Paraclinical features*

The incidence of OCB varies between series.[8] Oligoclonal bands and elevated IgG index were observed at lower rates in earlier-onset than those in later-onset children (43% vs. 63% and 35% vs. 68% respectively).[16] Most laboratories currently use isoelectric focusing which is a valid and reliable method: therefore differences are likely to originate not from methodology but from the time of sampling: lumbar puncture at first attack vs. later in the disease, or whenever diagnosis is uncertain. The rate of positivity may be as low as 45% at first attack to increase as patients get older, but still remain around 55% in 13–16 year olds.[18] We included any positive OCB results including second or later attacks, thus accounting for our higher rate.

The recent McDonald MRI criteria can be used to meet the requirement for dissemination in time and space at first clinical attack, enabling an early diagnosis of pediatric MS.[9,21] Children with MS can have a high lesion burden on initial MRI scan, especially in the brainstem and cerebellum.[55] In our series, MRI revealed supratentorial lesions in more than 90%, and brainstem and spinal cord lesions in about two-third of patients. Cortical/juxtacortical lesions were seen in 64% in our study, 57% in Mikaeloff's.[18] The frequency of infratentorial and spinal cord lesions were particularly high in young children in our series, similar to rates reported in some studies,[19,29] but higher than others.[18] The indication for spinal imaging, usually not emphasized in guidelines, may affect the rate of finding. In our study it was most probably related to clinical suspicion. In the light of a recent study demonstrating the persistence and enlargement of lesions in ADEM in the first three months, the timing of MRI follow-up in childhood demyelinating disease appears important.[56]

Approximately one-third of children with MS present with optic neuritis and a higher proportion have subclinical abnormalities of the visual pathway. Abnormal VEPs were detected in 56% of the children before a second clinical attack, only 40% of whom having had prior visual disturbances.[8,57] Likewise, 79% of patients with, and 32% of patients without a history of ON had VEP abnormalities in our series. This finding supports the inclusion of the presence of a lesion in the optic nerve shown not only with clinical features of optic neuritis (visual impairment, scotoma, red–green desaturation, and pain with ocular movement) or MRI evidence of optic nerve inflammation (increased T2 signal, gadolinium enhancement, and optic nerve swelling), but also with neurophysiological abnormalities (especially delayed visual evoked potentials) to the criteria for dissemination in space as an additional CNS area for the diagnosis of multiple sclerosis.[58] VEP testing appears helpful in detecting subclinical abnormalities of the visual pathway at onset of pediatric MS.

4.4. *Treatment*

Currently, 13 disease-modifying medications including intramuscular glatiramer acetate, intramuscular and subcutaneous interferon (IFN)-β1a, subcutaneous IFN-β1b, and three oral agents: teriflunomide, dimethyl fumarate, and fingolimod are approved by the FDA for use in relapsing forms of MS in the adult population. No randomized controlled trials, but data accumulated from small retrospective and observational studies in children suggest IFN-β1 and glatiramer acetate have similar safety and efficacy rates to adult population.[12,15] According to the International Pediatric MS Study Group, IFN-β or glatiramer acetate should be considered as first-line therapy in all patients with active relapsing-remitting disease.[59] This was done in 66% in our series. Lack of effect prompted switching to other immunomodulatory or immunosuppressive drugs in 14% of patients. Adverse or side effects are uncommon reasons for altering treatment.[15] Consistently, while 27% patients experienced undesired effects, only 2 patients who received IFN-β1a discontinued treatment because of elevated transaminases in our series.

In conclusion, the present study confirms well-known characteristics of pediatric MS such as predominantly relapsing-remitting disease course and frequent presentation with brainstem-cerebellar dysfunction. In addition, it underlines several distinctive features of pediatric MS, including a high incidence of initial presentation resembling ADEM, facial paralysis, and seizure; a high rate of vitamin D deficiency; and a high rate of subclinical VEP abnormalities. Children with earlier-onset MS are more likely to have an initial diagnosis of ADEM; a history of infection or vaccination preceding the initial attack; a longer first inter-attack interval; lower incidence of sensorial symptoms at onset; more frequent cerebellar signs and facial palsy during the course of disease; and faster accumulation of disability when compared to later-onset patients. On the other hand, the frequency of breastfeeding or smoke exposure among children with pediatric MS do not seem to differ from the rates of general population in Turkey.

Conflict of interest

None.

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