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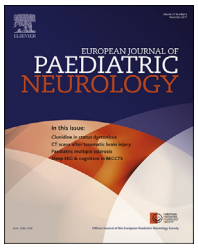

Original article

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

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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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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.