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Unfavorable outcome of pediatric onset multiple sclerosis: Follow-up in the pediatric and adult neurology departments of one referral center, in Turkey

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ABSTRACT

Background:: The prevalence of MS starting under 18 years of age ranges between 2–10% of the total MS population.
Objective:: We aimed to examine the clinical and long term follow-up data of pediatric-onset cases in our institutional MS database.
Method:: We evaluated the clinical data from the MS database of the Departments of Neurology and Pediatric Neurology of Hacettepe University Hospital.
Results:: The clinical features of 74 patients who had experienced the first attack before age 18 years comprised 3.9% of our MS population. Median age at onset was 15 (3, 5–17, IQR=3.63) years, and female: male ratio was 2.4. The most frequent symptom at onset was brainstem/cerebellar dysfunction (32.4%). Seventy two patients (97.3%) initially had relapsing remitting course and in the follow-up, 17 (23%) of them developed secondary progressive (SP) course. The median interval to develop SPMS course was 10 (5–21, IQR=8) years. At the last visit, median disease duration was 6.67 (0.83–25, IQR=9.06) years, 41 (55.4%) of them had EDSS of ≥ 4.
Conclusion:: These findings illustrate the profile of our pediatric MS patients: almost all are relapsing-remitting initially; about one fourth become secondarily progressive in 10 years, and about half acquire disability EDSS ≥ 4 in mean 8 years.

1. Introduction

Multiple sclerosis (MS) is a chronic demyelinating disorder that usually affects young adults. The prevalence of MS starting under 18 years of age ranges between 2–10% of the total MS population (Waldman et al., 2014). Information about this disorder increased considerably through multicentric studies in the last decades (Chitnis et al., 2009; Renoux et al., 2007; Ghezzi et al., 2002). Despite the diagnostic criteria for acquired demyelinating diseases in childhood, diagnosis of MS remains more problematic in this group compared to adults (Krupp et al., 2007, 2013). Pediatric MS appears as a more heterogeneous disorder in terms of clinical, radiological features and outcome, possibly due to different stages of development in the immune and nervous systems and ongoing myelination in children (Waldman et al., 2014; Banwell et al., 2007). In this study we examined the clinical and long term follow-up data of pediatric-onset cases in our institutional MS database.

2. Materials and methods

We evaluated the clinical data from the MS database of the Departments of Neurology and Pediatric Neurology of Hacettepe University Hospital, between 1995 and 2014, a tertiary referral center in Turkey. The patients who experienced their first attack of MS before 18 years of age and who meet the recent diagnostic criteria were identified (Krupp et al., 2013). We recorded the gender, age of onset, family history of MS, symptoms at onset, clinical course, interval between first two attacks, final expanded disability status scale (EDSS) score and cognitive state, duration of

Abbreviations: ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; IQR, interquartile range; MS, multiple sclerosis; PP, primary progressive; RR, relapsing remitting; SP, secondary progressive

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follow-up, and cerebrospinal fluid (CSF) features, from the database and patients notes of the University.

We compared the onset symptoms and EDSS score at the last visit according to disease duration with adult onset MS patients who were registered in MS database of the same clinics.

3. Statistical analysis

Data from the study were imported into SPSS 11.0 (SPSS Inc., Chicago, IL) for analysis. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. Categorical variables were expressed as frequencies and percentages. Mean values and standard deviations were calculated for continuous variables for normally distributed data, otherwise as median (minimum-maximum) and interquartile range (IQR). Chi square and Fisher's exact tests were used to compare categorical variables. Student's *t* test and Mann-Whitney *U* test for continuous variables. Bonferonni correction used to adjust for multiple comparisons if necessary. Significance was considered as $p \leq 0.05$.

4. Results

Of the 1872 MS patients registered in the MS database of our hospital, 74 (3.9%) had experienced their first attack before age of 18 and had been followed-up in the pediatric neurology department until that age. Their median age at onset was 15 (3.5–17, IQR=3,63) years. The majority of them (n=52, 70.3%) were female, with a female/male ratio of 2.4/1. Five patients, 3 boys and 2 girls, had experienced their first clinical event before age of 10. Nine (12.2%) patients had a family history of MS.

The most frequent initial symptom was brainstem/cerebellar dysfunction (32.4%). There were three (4%) patients with atypical clinical presentation suggesting acute disseminated encephalomyelitis (ADEM). The symptoms of onset are summarized in the Fig. 1.

Initial presentation was monosymptomatic in 58 (78.4%) and polysymptomatic in 16 (21.6%) patients. The median interval between the first and second attack was 1 (0.08–10; IQR=1.67) year. In 43 (58%) patients the second attack occurred within 1 year.

Initially, the course of the disease was relapsing remitting (RR) in 72 (97.3%) and primary progressive (PP) in 2 (2.7%) patients. During follow-up, 55 (74.3%) patients remained in RRMS course while 17 (23%) developed secondary progressive (SP) course. The median time to develop SPMS course was 10 (5–21; IQR=8) years.

Sixty (81.1%) patients were treated with any disease modifying treatment (DMT) at least six months in the course of the disease and 81.8% of RRMS, 82.4% of SPMS and 50% of the PPMS had

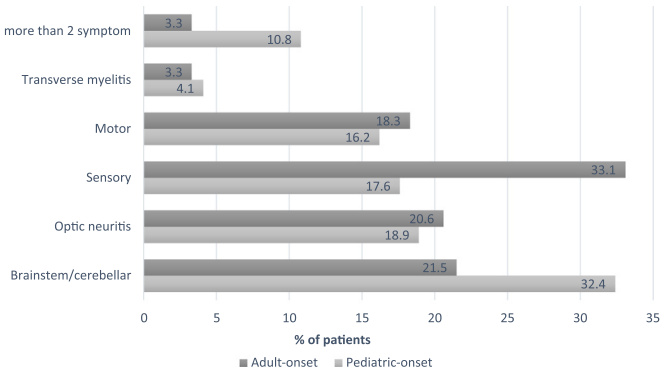

Fig. 1. Symptoms at onset in pediatric and adult MS.

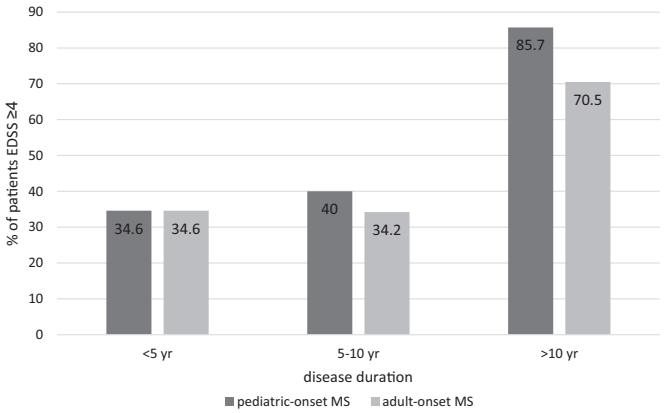

Fig. 2. Rates of EDSS score ≥ 4 in pediatric and adult onset MS patients with regard to disease duration.

received any DMT in follow-up. Frequency of DMT between different disease course showed no significance ($p=0.602$).

Median disease duration at the last visit was 6.67 (0.83–25; IQR: 9.06) years. It was less than 5 years in 26 (35.1%) patients, 5–10 years in 20 (27.1%), and >10 years in 28 (37.8%) patients. EDSS score (sustained for at least 6 months) at the last visit was <4 in 33 (44.6%) and ≥ 4 in 41 (55.4%) patients. EDSS scores increased with prolonged follow-up: a score ≥ 4 was found in 34.6% of patients who had a follow-up <5 years whereas 85.7% of patients who had follow-up periods >10 years. (Fig. 2).

Interval between the first and second attack were not different between the EDSS <4 vs EDSS ≥ 4 groups (median 0.58 (0.08–10, IQR=0.83) vs 1 (0.08–6, IQR=2.08) years, respectively; $p=0.114$) and gender groups ($p=0.446$). Patients with EDSS ≥ 4 had longer disease compared to the EDSS <4 group (median 10.17 (0.83–25, IQR=3.92) vs 4.5 (1.25–15, IQR=7.84) years, $p=0.001$); they were older when disease started (median 16 (8.5–17, IQR=3) vs. 15 years (3.5–17, IQR=2), $p=0.002$) and at their last visit (median 26 (10–42, IQR=10) vs. 20 (6–29, IQR=4) years, $<p=0.001$).

Distribution of the initial symptom and age at onset were similar ($p=0.427$, $p=0.072$ respectively) between SPMS and RRMS patients. SPMS patients had a longer disease duration (median 13.67 (2.5–25, IQR=9.42) vs 5.67 (0.83–19.92, IQR=6) years; $<p=0.001$) and the age at the last visit was older than RRMS patients (median 30 (15–42, IQR=7) vs 20 (6–35, IQR=6); $<p=0.001$). The interval between the first two attacks was longer in SPMS patients (median 2 (0.25–6, IQR=4) vs 0.58 (0.08–10, IQR=1.25) years; $p=0.007$). The gender ($p=0.530$), family history ($p=0.916$), usage of any DMT ($p=0.960$) were not different between patients.

Epileptic seizures occurred in seven (9.5%) patients during the course of MS. Cognitive impairment as detected from history and routine neurological evaluation was observed in five (6.8%) patients, four of whom also having epileptic seizures. One child died in the second year of a highly active disease because of cardiac arrest following an epileptic seizure.

Cerebrospinal fluid was examined in 29 (41.9%) of the 74 patients: 19 of them had (66%) oligoclonal bands.

Comparison of pediatric-onset and adult-onset MS patients showed significant difference in the distribution of symptoms at onset ($p=0.003$) (Fig. 1). Sensorial dysfunction was more common in adult-onset ($<p=0.001$) whereas multiple symptoms suggesting polyfocal localization were more common in pediatric-onset MS patients ($<p=0.001$). Also brainstem/cerebellar dysfunction was more common in pediatric-onset disease but the difference was not statistically significant ($p=0.77$). Also The rate of EDSS score ≥ 4 according to disease duration was not different (<5 yrs, $p=0.086$; 5–10 yrs, $p=0.613$; >10 yrs, $p=0.094$) (Fig. 2).