

Original Article

Childhood-Onset Multiple Sclerosis: Report of 82 Patients from Isfahan, Iran

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Background: Although multiple sclerosis is considered as an inflammatory demyelinating disease of young adults, nearly 3% of patients manifest it under the age of 16 years. The aim of this study was to highlight the clinical and demographic features of early-onset multiple sclerosis in Isfahan, Iran.

Methods: This prospective study concerned multiple sclerosis patients in whom the disease started before the age of 16 years and who were referred to the only clinic of multiple sclerosis in Isfahan from October 1997 through February 2003. All early-onset multiple sclerosis patients underwent magnetic resonance imaging. Magnetic resonance imaging findings were analyzed according to the Barkhof's criteria. All early-onset multiple sclerosis patients were followed for a mean period of 4.7 years.

Results: Among 1,238 multiple sclerosis patients, 82 early-onset multiple sclerosis patients were identified. The female to male ratio was 4.5:1. The mean age of onset was 14.1 (range: 5 to 16) years. In 53 (65%) patients, the onset was monosymptomatic; in the remaining 29 (35%), it was polysymptomatic. Sixty-four (78%) patients presented a relapsing-remitting course, 14 (17%) had a secondary-progressive and 4 (5%) had a primary-progressive course. At the last evaluation, the expanded disability status scale score was ≥ 6 in only 8 (10%) patients. According to Barkhof's criteria, the characteristic magnetic resonance imaging findings were observed in 80 (98%) of early-onset multiple sclerosis patients.

Conclusion: In our study, a high rate of childhood multiple sclerosis was observed that may be because of geographical or ethnic differences. Our study also showed that Barkhof's criteria, which is mostly used in adult patients, could be also applied to early-onset multiple sclerosis cases.

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Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system, which predominantly involves young adults.¹ It is characterized by neurologic deficits, which are disseminated in time and space, corroborated by

magnetic resonance imaging (MRI).²

Early-onset MS (EOMS) is defined as the first presentation of symptoms before the age of 16 years and occurs nearly in 0.4 – 5.6% of patients.^{3–7} Eichhorst described the first autopsy-proven case of childhood MS in an 8-year-old boy in 1896.⁸ From 1950s, childhood MS was recognized and subsequently well-characterized⁴ and affected individuals, as young as 10 months has been reported.^{4,9} Childhood MS, compared to adult MS, tends to present with an acute onset leading to rapid hospitalization manifesting as headache, fever, seizure, vomiting, unconsciousness, encephalopathy mimicking acute disseminated encephalomyelitis (ADEM), prominent cerebellar-brainstem disorders, etc.^{3,4,7} Onset with extensive

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spinal cord and brainstem involvement may indicate a poor prognosis.¹⁰ Sometimes childhood MS is diagnosed and treated after a delay of two to five years, because of unusual presentations, which mislead physicians to consider different metabolic or degenerative disorders, leukodystrophies, and especially ADEM other than MS.^{4, 9} Furthermore, in the differential diagnosis of this disease, abnormalities such as subacute sclerosing panencephalitis (SSPE), embolic events, vasculitis, moyamoya, migraine, neurosyphilis, Lyme disease, cerebral toxoplasmosis, Mollaret meningitis, mitochondrial disorders, syringomyelia, lymphoma, and chronic intoxication with barbiturates and phenytoin should be considered.^{6, 7}

In 40 – 60% of EOMS cases, the relapse after the first attack occurs within a year and in general, children are more prone to relapse than adults.^{3-5, 8,}

^{10 - 12} Despite rapid and often dramatic presentations of MS during early childhood and excess of relapses, the majority of these cases recover from the first attack and after a period of 8 – 10 years, the expanded disability status scale (EDSS) score of ≥ 6 is observed in only 16 – 20% of them. Thus, the severe form of the disease occurs in about one-fifth of EOMS patients, which is the same as adult-onset MS.^{5, 6}

There is scarce epidemiological data on EOMS in the Middle East and Iran. The objective of this survey was to highlight the clinical and demographic features of EOMS in Isfahan, Iran.

Patients and Methods

Our study was performed in Isfahan, a large province, 107,003 km² wide, located in central part of Iran, between latitudes 30 and 34 degrees North of the equator and longitude 49 to 55 degrees East, with a population of more than four million. The population structure and socioeconomic status of Isfahan are similar to the rest of the country.

This prospective study concerned MS patients diagnosed according to the Poser's criteria,¹³ in whom MS started before the age of 16 years (EOMS), who were referred to the only clinic of MS in Isfahan from October 1997 through February 2003. We did our best to collect all MS patients in Isfahan Province, yet there may be a possibility of missing cases.

A clinical reporting form was designed for every patient, and was used in the course of follow-up. Two neurologists were incorporated in

the full course of follow-up for evaluating and recording patients' data such as clinical course, EDSS,¹⁴ MRI findings, etc. Certain laboratory tests such as measurement of serum antinuclear antibodies (ANA), antineutrophil cytoplasmic antibodies (ANCA), antiphospholipids and anticardiolipin IgG and IgM antibodies, angiotensin-converting enzyme inhibitors (ACEIs), and HIV serology were performed, if needed, to rule out common differential diagnosis of MS. All EOMS patients were followed for a mean period of 4.7 (range: 1 – 7) years. For each patient we considered gender, age of onset, symptoms at onset, seizure frequency, clinical course, outcome, family history, and MRI findings. All patients underwent central nervous system MRI at first, and then whenever recommended in the course of follow-up in two different MRI centers in Isfahan with field strengths of 1.0 and 1.5 Tesla superconductive system. Axial, sagittal, and coronal; T1-weighted (without and with gadolinium); T2-weighted; fluid attenuated inversion recovery (FLAIR), and proton density sequence imaging were performed. The Barkhof's criteria was used for analyzing the MRI findings.¹⁵ Visual evoked potential (VEP) test was used as a paraclinical criterion for the diagnosis of MS.

All data were registered in certain reporting forms in the course of follow-up. Chi-square was used for analyzing categorical data. All tests were two-tailed and a *P* value of <0.05 was considered statistically significant. Data were analyzed by SPSS version 11.5 (SPSS[®] Inc.).

Results

Among 1,238 MS patients (932 females and 306 males) referred to our center, 91 had EOMS. Of these 91 patients, seven were excluded because they did not complete the course of the study; additionally, two more patients were excluded because they had paraclinical evidences of systemic lupus erythematosus. In the remaining 82 patients (6.6%; CI95%: 5.4 – 8.1%), according to Poser's criteria,¹³ 77 (94%) presented with clinically definite MS and the remaining five patients (6%) were clinically probable MS. VEP, as a paraclinical criterion for the diagnosis of MS, was abnormal in 45 (55%) patients who underwent this test. Detailed information on EOMS subgroups (under and above 10 years of age) can be seen in Table 1.

Table 1. Clinical characteristics of true childhood MS (<10) and juvenile MS (>10).

Age	N	Sex		PS	Monosymptomatic				SF	Course			EDSS		PFH
		F	M		ON	BC	M	S		RR	SP	PP	<6	≥6	
≤10 yr	7	7	—	2	2	1	2	—	1	7	—	—	7	—	—
>10 yr	75	60	15	27	21	11	8	8	12	57	14	4	67	8	7
Total	82	67	15	29	23	12	10	8	13	64	14	4	74	8	7

PS = polysymptomatic, ON = optic neuritis, BC = brainstem-cerebellar, SF = seizure frequency, M = motor, S = sensory, PFH = positive family history.

Gender

Our patients with childhood-onset MS consisted of 67 girls (82%) and 15 boys (18%); the female to male ratio was 4.5:1. The total MS population of 1,238 patients included 932 females and 306 males with a female to male ratio of 3:1.

Age at onset

In EOMS group, the mean \pm SD age at onset was 14.1 ± 2 (range: 5 – 16) years. In 7 (9%) patients, MS begun under the age of 10 years (true childhood-onset MS); in the remaining 75 (91%) patients, the age at onset was between 10 and 16 years (juvenile-onset MS). In juvenile MS subgroup, 64 (78%) patients developed MS between the ages of 14 and 16 years. Distribution of EOMS patients by age at onset is depicted in Figure 1.

Onset of symptoms

Onset presentation in 29 (35%) patients was polysymptomatic, whereas in the remaining 53 (65%) patients it was monosymptomatic. In monosymptomatic group, optic neuritis was observed in 23 (28%) patients, brainstem-cerebellar disorders in 12 (15%) (diplopia in six, ataxia in four, and vertigo and dysarthria each in one), motor disturbances in 10 (12%) (hemiparesis, monoparesis in lower extremities and monoparesis

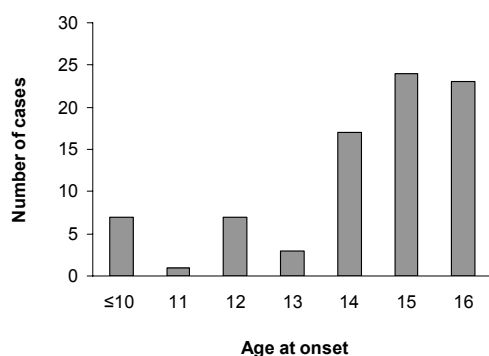


Figure 1. Distribution of EOMS patients by age at onset

in upper extremities each in three, and paraparesis in one), and finally sensory symptoms in 8 (10%) (limb paresthesia in seven and facial paresthesia in one) patients.

Seizure frequency

Seizure was observed in the course of MS in 13 (16%) EOMS patients, and most frequently in those with a polysymptomatic onset (24% of polysymptomatic vs. 11% of monosymptomatic patients).

Clinical course and outcome

Over a mean follow-up period of 4.7 years, 64 (78%) patients were characterized as relapsing-remitting MS (RRMS), 14 (17%) as secondary progressive MS (SPMS), and 4 (5%) as primary progressive MS (PPMS). At the last evaluation, the EDSS score was <6 in 74 (90%) patients and ≥6 in only 8 (10%) patients. The mean \pm SD EDSS of the group was 3.1 ± 1.2 .

MRI findings

The characteristic MRI findings for MS according to Barkhof's criteria, were observed in 80 (98%) EOMS patients. The most common site of demyelination was in periventricular white matter in 73 (89%) patients, followed by spinal lesions in 12 (15%), brainstem lesions in 10 (12%) and cerebellar plaques in 8 (10%) patients.

Family history

Among our EOMS patients, 7 (9%) had a positive family history of MS, of whom 4 (5%) had first-degree affected relatives and 3 (3%) patients had second-degree affected relatives.

Other findings

We observed the following abnormalities occasionally in the course of MS: facial palsy in 5 (6%); myokymia in 4 (5%); choreoathetosis and dystonia in 3 (3%); and posterior uveitis, hypoglossal palsys and sensorineural hearing loss each in one patient.

Discussion

It has been reported that 0.4 – 5.6% of all MS patients manifest the disease before the age of 16 years.^{3–7} Childhood MS is divided into the “true childhood-onset MS” presenting under the age of 10 years and accounting for 0.2 – 1% of all MS patients,^{4, 6, 7, 16} and “juvenile-onset MS” when MS begins between the ages of 10 and 16 years which consists 80% of childhood MS cases and 4 – 5% of all MS patients.^{4, 6} In our study, 6.6% of our MS population manifested MS before the age of 16 years, which is higher than other reports. This higher rate may be either as a result of ethnic or geographic differences. In addition, true childhood-onset MS consisted of 0.6% of our MS population (7 of 1,238 patients), while juvenile-onset MS consisted of 6% (75 of 1,238 patients) of our MS patients. Although the small number of patients involved in the true childhood-onset MS makes comparison difficult, it seems that differences in the frequency of relapsing-remitting course and the sex ratio may be important, compared to juvenile MS subgroup.

The over-representation of female patients in EOMS patients compared to adult patients is well-known.^{17, 18} The female to male ratio in adulthood MS is reported to be between 1.6:1 to 2.1:1, and in EOMS patients between 2.2:1 to 3:1.^{4, 9} In our study, this ratio was 4.5:1, which is higher than that reported in the literature. However, keeping with other studies,^{4, 9} the female preponderance in our EOMS group was higher than adult MS patients (4.5:1 vs. 3.0:1).

A review of neurology literature reveals that polysymptomatic onset is more frequent in EOMS patients than adult MS patients (48.9% vs. 12%). Moreover, monosymptomatic onset in EOMS patients is more frequent than polysymptomatic onset (49 – 62% vs. 48.9%).^{1, 3, 5, 7, 9, 11, 12, 19–25} In our study, like previous reports, polysymptomatic onset (35%) was common in children; monosymptomatic onset (65%) occurred more frequently than polysymptomatic onset (35%). In the monosymptomatic group of our patients, in contrast to previous studies in which brainstem syndromes or cerebellar ataxia were the most common initial presentations,^{5, 9} optic neuritis was the most frequent initial presentation (28%). Nonetheless, like other studies on childhood-onset MS,^{3, 5, 9, 12, 19, 22, 24, 25} brainstem syndromes,

cerebellar involvement, and optic neuritis were among the most common symptoms in our study.

Some authors believe that seizure is more frequent in EOMS patients and is associated with a more aggressive course.⁹ It is observed in 22% of MS patients under six years of age.⁹ In our study, the seizure was observed in 16% of EOMS patients, which was more frequent than the rate (5%) reported in adulthood-onset MS.^{7, 21} Positive family history of MS was reported in 0 – 21% of EOMS group;^{1, 3, 4, 9, 20, 24} in the current study, 9% of patients had another MS patient among their relatives.

In our study, RRMS was the most frequent (78%) form of presentation followed by SPMS (17%) and PPMS (5%). This finding was similar to other reports, which revealed that RRMS is the most common form (32 – 84%, mean: 67%), followed by SPMS (7 – 61%, mean: 24.4%) and PPMS (5 – 15%, mean: 8.6%).^{3, 5–7, 9, 12, 22}

In the present study, EDSS score of ≥ 6 (severe disability) was recorded in only 8 (10%) patients, which is lower than that reported previously. In other studies, after 8 – 10 years of follow-up, an EDSS score of ≥ 6 was found in 16 – 20% of patients.^{5, 9} This lower rate is perhaps due to our shorter follow-up period.

Ninety-eight percent of EOMS patients fulfilled Barkhof's criteria for the characteristic MRI findings in MS, which is mostly applied to adult patients.¹⁵ Therefore, MRI can be regarded as a very valuable and sensitive diagnostic tool in children as well as in adults, and the same criteria could be applied even for EOMS patients.

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