The course of early-onset multiple sclerosis in Iraqi children

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Background: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that is increasingly recognized worldwide in children and adolescents. The current study aimed at identifying the clinical characteristics of MS with onset under 18 years of age.

Methods: This cross-sectional study was conducted in the Multiple Sclerosis Center archive system in Baghdad Teaching Hospital during the period from March 1 to May 15, 2008. The records of 1125 MS patients from 2000 to 2008 were reviewed. Among them 77 patients had the onset of MS under 18 years of age.

Results: Two thirds of the patients were female (a female/male ratio of 1.6:1). The mean age of the patients at the onset of the disease was 14.95±3.21 years, and the mean time between the first and second attacks was 3.06±4.09 years. Seventy patients (90.9%) had an initial course of relapse remitting MS. Among them 9 (12.9%) progressed to secondary progressive MS after a mean duration of 9.87±4.14 years. The remaining 7 patients had primary progressive MS associated with optic neuritis and brain stem lesion. Fifty-nine (76.6%) patients had monofocal signs and 18 (23.4%) had polyfocal signs. The mean extended disability status scale score was 4.15±2.17 and the mean progression index was 1.44±2.31. There was a strong inversed correlation between the progression index and interval between the first and second attacks (*P*=0.0001).

Conclusions: The results of the present study show that the course of MS in Iraqi children and adolescents is more aggressive than in children from other countries. This finding needs to be evaluated by further studies.

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Introduction

Pediatric multiple sclerosis (MS) has been increasingly recognized in the past 2 decades. This is, in part, due to the advent of MRI, which has made sensitive detection of white matter abnormalities possible. Approximately 3%-10% of patients with MS show the onset before the age of 18 years.[1-4] The disorder presents almost exclusively as a relapse-remitting disease in children, and most of the children recover from the initial attack. The accumulation of disabilities and the development of secondary progressive MS are commonly seen more than 15 years after the first attack.[5]

The prognostic factors in early onset of MS have been evaluated in few studies with various methodologic approaches, and the discussion about the existence of clinical courses different from that of adult-onset MS is still open.[4] Based on these assumptions, this study was conducted to analyze a hospital-based historical cohort of MS patients from Iraq characterized by young age at clinical onset to assess their clinical and demographic features.

Methods

This cross-sectional study was conducted in the Multiple Sclerosis Center (MSC) in Baghdad Teaching Hospital in the Medical City in Baghdad during the period of March 1 to May 15, 2008 using the records (from the archive system) of patients attending this center from all over Iraq since its establishment till January 1, 2008 referred by neurologists, ophthalmologists, neurosurgeons, and other specialists.

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Their final diagnosis was reviewed by a committee of three neurologists in most cases.

The MSC was established in 2000 at Baghdad Teaching Hospital, which is geographically accessible by most of the population in Baghdad as well as from all over Iraq.[6]

Inclusion criteria

Patients included were first diagnosed to have MS according to the revised McDonald's diagnostic criteria for multiple sclerosis. The onset of MS must be before the 18th birthday.

For each patient the following information was gathered: age, sex, date of onset, date of diagnosis, date of second attack, presenting symptoms, degree of recovery from the first attack (complete, partial, or none), the course of the disease (relapse-remitting MS or primary progressive MS), secondary progression and its date, cognitive function test, extended disability status scale (EDSS) and its duration.

The age limit was based on the WHO definition of "children" (under the age of 10) and "adolescents" (aged 10 and above but prior to the 18th birthday).[7] Relapse-remitting MS and progressive MS were defined according to the established criteria.[8-11]

Neurological disability was assessed according to the Kurtzke EDSS score, a seven functional systems score, that includes motor, sensory, cerebellar, brain stem, visual, mental and sphincter systems. The score ranged from normal examination (0) to death from MS (10), with a score of 6 representing moderate disability that needs assistance in walking a distance of 100 m.[12]

The progression index (PI) was calculated for each patient according to the following formula (PI = EDSS / disease duration), and PI<0.5 was considered a good prognostic indicator.[12]

Statistical analysis

The statistical package of social sciences (SPSS) version 15 was used for data entry and analysis, where Student's t test was made to test the significance of difference between two means, the Chi-square test to test the significant association between discrete variables and Pearson's correlation coefficient analysis to test the relation between two continuous variables whenever applicable. Also the Kaplan-Meier method was used to estimate the time to secondary progression and the time between the first and second attacks. $P<0.05$ was considered as statistically significant.

Results

Of the 1125 patients since the establishment of the center in 2000 surveyed, 77 patients were eligible for the study, with the diagnosis of MS before the 18th birthday, giving a rate of 6.84%. Among the patients 48 (62.3%) were female and 29 (37.7%) were male, giving a female/male ratio of 1.66:1. The mean age at onset of the disease was 14.95±3.21 years (calculated as the time difference between date of birth and date of the first attack) ranging between 5 and 18 years and only 7 (9.1%) patients were children (aged below 10 years) at onset of the disease. No significant association was found between the gender of the patients and the age at onset of the disease (P=0.704).

The mean age of the patients at diagnosis was 18.90±5.98 years (calculated as the time difference between date of birth and date of diagnosis), ranging between 7.27 and 41.29 years. The mean lag time to diagnosis was 3.95 years (calculated as the time difference between date of onset and date of diagnosis), ranging between 0 and 23.29 years.

Regarding the course of the disease, 70 patients (90.9%) had an initial course of relapse-remitting MS (RRMS). Among them 9 (12.9%) patients progressed to secondary progressive MS (SPMS) after a mean duration of 9.87±4.14 years. The remaining 7 patients (9.1%) had primary progressive MS (PPMS) as an initial course. Of the 77 patients, 59 (76.6%) had monofocal signs while 18 (23.4%) presented with polyfocal signs with more than one clinical feature. The most presented lesion was optic neuritis in 29 patients (37.66%), followed by brain stem lesion in 20 patients (25.97%) (Table 1). Complete improvement of the first attack happened in 47 patients (61.0%), partial improvement in 15 (19.5%), no improvement in 10 (13%), and unknown improvement in 5 (6.5%).

The mean time between the first and second attacks was 3.06±4.09 years (range: 0.03 to 23.04 years). For each group of clinical onset the mean time between the first and second attacks was 1.91 years in those with sensory symptoms, 0.46 years in those with other symptoms, and 4.52 years in those with transverse myelitis (Table 2).

Regarding disability, the mean EDSS score was 4.15±2.17 with a minimum score of 1 and a maximum score of 9. The duration between time of disease onset and last EDSS score (duration of disease) was 7.73±6.35 years.

The mean PI was 1.44±2.31 (range: 0.08-14.05). An inverse correlation was also found between PI and interval between the first and second attacks (the shorter the interval the higher the PI) (P=0.0001). But no significant difference was found when PI was compared between those with SPMS and those who did not progress to SPMS, between those with RRMS and those with PPMS at onset, between those with monofocal

Table 1. Distribution of all patients according to their course of illness and clinical presentations

Variables	*n*	Percentage
Initial course		
RRMS	70	90.9
SPMS	9	12.9
PPMS	7	9.1
Monofocal	59	76.6
Polyfocal	18	23.4
Clinical presentations		
Optic neuritis	29	37.66
Brainstem	20	25.97
Pyramidal	16	20.78
Sensory	14	18.18
Transverse myelitis	11	14.29
Cerebellar	5	6.49
Sphincter disturbance	2	2.59

RRMS: relapsing remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis.

Table 2. Interval between the first and second attacks calculated for each clinical presentations

Clinical presentations	*n*	Minimum	Maximum	Mean	SD
Monofocal	59	0.03	23.04	2.99	4.27
Polyfocal	18	0.14	21.36	3.32	5.65
Transverse myelitis	11	0.25	23.04	4.52	6.73
Optic neuritis	29	0.17	21.36	3.53	4.87
Brainstem	20	0.11	15.25	2.83	3.79
Cerebellar	5	1.29	4.00	2.47	1.26
Pyramidal	16	0.08	12.00	2.28	3.95
Sensory	14	0.03	12.00	1.91	3.07
Sphincter disturbance	2	0.14	0.77	0.46	0.45

SD: standard deviation.

Table 3. Mean and standard deviation of progression index at different conditions

Progression index		Mean ± SD	*P* value
The whole sample		1.44 ± 2.33	
Course	SPMS	0.73 ± 0.41	0.858
	No SPMS	1.53 ± 1.43	
Focal lesions	Monofocal	1.37 ± 2.82	0.404
	Polyfocal	1.64 ± 2.41	
Initial course	RRMS	1.46 ± 0.29	0.359
	PPMS	1.16 ± 0.34	
Gender	Male	1.51 ± 3.03	0.136
	Female	1.39 ± 1.77	

SPMS: secondary progressive multiple sclerosis; RRMS: relapse-remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis.
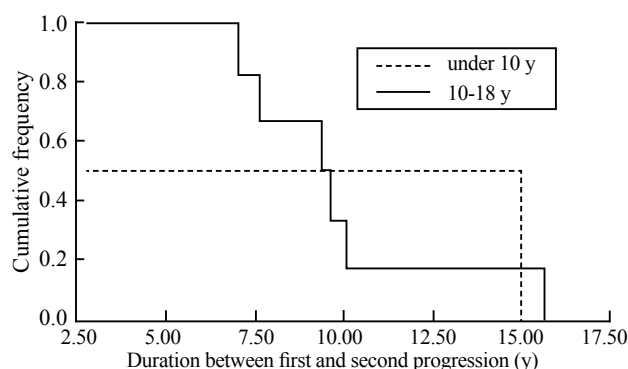

Fig. Kaplan-Meier estimates of the time to secondary progression compared between children and adolescents.

signs and those with polyfocal signs at onset, and also between male and female patients (Table 3).

By using the Kaplan-Meier method the time to the secondary progression was estimated and a comparison was made between children and adolescents. The time estimated was 9.15±6.04 in children and 15.11±1.23 in adolescents (*P*=0.019) (Fig.). But no significant difference was found when the time between the first and second attacks was estimated between children and adolescents as well as between males and females.

Discussion

Seventy-seven patients had the onset of MS before the age of 18 years. The patients represented 6.8% of all 1125 patients recorded in the MS clinics in Baghdad. The mean age of the patients at onset was 14.9±3.2 years, which is close to the ages reported by other studies (12-13.7 years),[8,13] also 62.3% of our patients were females close to 65.1% reported by Simone et al.[4] No significant association was noted in the age at onset of the disease

between male and female patients, although in male patients a shift to younger age was observed.

The mean age of the patients at diagnosis was 18.9±5.9 years with lag time of diagnosis for 4 years, which was consistent with the finding of Pinhas-Hamiel et al [The mean age at diagnosis was 18.5±2.5 years (range: 12-21 years) and the mean lag time for diagnosis was 4.7 years].[12] With the advance in treatment of MS early diagnosis is of utmost importance and thus a high index of suspicion is required to make a diagnosis at the first attack.

The time from the initial acute attack to the second reported by different studies is highly varied. Younger children tend to have a longer interval from the first to second attack (median: 6 years), in contrast to adolescent patients who often have their second attack within 12 months.[14] The mean time between the first and second attacks was 3.06 years (in one case it was up to 23 years). This difference may be due to the size of sample or different methods of statistical analysis.

More than 90% of our patients had an initial course of RRMS and 9.1% had an initial course of PPMS. The same finding (90% for RRMS and 2.3%-7% for PPMS)

was reported by Ness et al[15] and that is consistent with 93% for RRMS and 7% for PPMS reported by Pinhas-Hamiel et al,[12] 97.7% for RRMS and 2.3% for PPMS by Renoux et al,[8] 96% for RRMS and 3.7% for PPMS by Banwell et al[5] and 100% for RRMS by Guilhoto et al.[16] Of the patients with RRMS 12.9% evolved into SPMS after a median period of 9.58 years [shorter median in children (3.1 years) compared to adolescents (9.5 years)]. Both figures differ from those reported by Renoux et al, i.e., 28.6% developed SPMS after observation for 28.1 years; this difference may be due to the longer observation period.[8] According to Stephen[17] SPMS always begins as RRMS at some time points, however the clinical course of RRMS is changed so that the patient exhibits a steady deterioration in function unassociated with acute attacks. Also SPMS produces a greater amount of fixed neurological disability than RRMS. Approximately 50% of patients with RRMS will develop SPMS after 15 years and longer follow-up indicates that the great majority of cases of RRMS ultimately evolve into SPMS cases. Thus, SPMS appears to represent a late-stage of the same underlying illness as RRMS.

In our patients 76.6% had monofocal signs versus 23.4% had polyfocal signs in contrast to 50%-70% of patients had polyfocal or polysymptomatic signs and 30%-50% had monofocal or monosymptomatic signs in the literature.[5] However, it is worth mentioning that in many studies the terms monosymptomatic and polysymptomatic have been used and polysymptomatic signs could be attributed to the single lesion that can be considered to have monofocal signs and any combination of symptoms that had a reasonable possibility of being explained based on the single lesion. The lesion was considered monofocal despite the fact that the signs are poly symptomatic and so no direct comparison could be made with these findings. When the presenting symptoms were analyzed 29% of our patients presented with optic neuritis (unilateral or bilateral) compared to only 10%-23% reported by Banwell et al,[5] Renoux et al,[8] and Simone et al[4] but they were consistent with the findings of Visudhiphan et al[18] and Mikaeloff et al[14] that optic neuritis was commonly the first sign in Asia. It is also consistent with the figure given by Stephen[17] for MS in the general population. Also 20.6% of our patients had brainstem symptoms that are close to the frequency reported;[19,20,21] 11.3% of our patients had transverse myelitis as a presenting symptom, consistent with less than 10% in Mikaeloff et al,[14] Sindern et al,[22] and Duquette et al[3] studies. One potential source of bias in the presenting symptoms of early onset MS is that the presence of optic neuritis might be more likely to lead to a diagnosis of MS than the presence of other

neurological symptoms. However, even if a diagnosis of MS is more likely in patients with childhood-onset MS presenting with optic neuritis, the presence of symptoms other than optic neuritis at onset would probably delay the time to the diagnosis of MS and not reduce the probability of the diagnosis itself.

Recovery of the first attack was complete in 61% of our patients and partial in 19.5% of them. This agrees with Gadoth[23] who states that the majority of children will recover from the first attack or left with mild residual disability; however, some children may be left with considerable disability.

Severe disease outcome was defined by the occurrence of a third attack or by an EDSS score greater than 4 (persisting for more than 12 months).[19] In the present study the mean EDSS score was 4.15 after a mean follow-up of 7.7 years (The short follow up period in most cases is related to the infrequent recording of EDSS that is one of the limitations of this record based study). This score is higher than what is reported by Ghezzi et al[19] and Pinhas-Hamiel et al,[12] in which the mean EDSS score was 3.7±3.0 (range: 0-9) after a mean disease duration of 13.9±7.1 years. In this study PI was 1.43 that is much higher than 0.27 reported by Pinhas-Hamiel et al,[12] but the age at the onset of the diesease was not correlated with neurological disability. Moreover, PI used to quantify progression was less than 0.5, indicating a favorable prognosis. These findings suggest that early onset does not cause aggressive course and that the age at the onset of the disease does not contribute to disability per se, but longer disease duration results in increased handicapping. This is not the situation in the present study.

Renoux et al[8] reported the estimated median times from the onset of MS to the assignment of EDSS scores of 4, 6, and 7 were 20.0 years (95% CI, 19.0 to 22.4), 28.9 years (95% CI, 27.0 to 33.0), and 37.0 years (95% CI, 34.0 to 42.2), respectively. In comparison to adult findings the estimated median times to assignment of EDSS scores of 4, 6, and 7 were approximately 10 years longer in patients with childhood-onset MS than in those with adult-onset MS ($P<0.001$ for all comparisons). Despite a slower development of irreversible disability, patients with childhood onset MS reach secondary progression and disability milestones at ages approximately 10 years younger than those with adult-onset disease. In the present study the PI and time between the first and second attacks was shorter than other studies and the time between the first and second attacks was inversely correlated with PI (the shorter the duration the higher the PI). This higher rate of PPMS may indicate the aggressiveness of the course of MS in Iraqi children and adolescents, which needs to be assessed in further studies.

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