Original Article

# Clinical prognostic factors after the first attack of early onset multiple sclerosis in Iraq

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*Abstract:*

Background: Paediatric-onset multiple sclerosis (MS) has been a focus of great interest in recent years. 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

Objectives: to evaluate effect of the clinical factors after the first attack of central nervous system inflammatory demyelination in individuals with onset of multiple sclerosis before age 18 on the outcome of the disease.

Materials and Method: A record based study was conducted in multiple sclerosis center in the medical city in baghdad The records of 1125 multiple sclerosis patients from 2000 to 2009 in have been surveyed. 77 patients had onset of multiple sclerosis below 18 years their first episode of central nervous system inflammatory demyelination data have been analyzed.

Results: 48 of the patient where female (62.3%) and 29 patients where males (37.7 %) F: M ratio 1.6:1. Mean age at onset was 14.95 years. Seven patients where children (age below 10years) (9.1%) and 70 patients where adolescents (age 10 to 18 years) (90.9%) at onset. The most common presenting symptom was optic neuritis (35.8%) followed by brain stem lesion. 59 patients had monofocal presentation (76.6%) and 18 had polyfocal presentation (23.4%). 47 patients had complete improvement of the first attack (61.0%), the rest had partial or no improvement. 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).

Conclusion: The prognosis of MS in paediatric age group after the first attack depend on the degree of recovery and the degree of residual disability. The initial site of insult is a predictor of the duration of further attacks. No significance to the age of onset and gender as a prognostic factors, and polyfocal first attack is independent predictor of outcome in MS.

Key worlds: Multiple sclerosis and Prognosis

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## Introduction:

Paediatric-onset multiple sclerosis (MS) has been a focus of great interest in recent years.(1,2)

The first acute demyelinating event, termed a clinically isolated syndrome, can manifest with signs and symptoms caused by a single lesion (monofocal clinically isolated syndrome) or with polyfocal features, implicating multiple lesions. There are published clinical definitions for these various clinical demyelinating presentations. The term CIS is applied to the first clinical demyelinating event (i.e., isolated in time)(3)

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.

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## Patient and Methods:

The study was a record based study. The sampling technique was convenience sampling. The study was conducted in multiple sclerosis center archive system in the medical city in Baghdad. Patients attended MS center in Baghdad from all over Iraq referred by neurologist, ophthalmologist, neurosurgeons and other specialists. The diagnosis is reviewed by a committee of five neurologists in most cases. The clinic was established in 2000 at medical city teaching hospital, which is geographically accessible by most of the population in Baghdad and from the rest of Iraq (5). The records of 1125 MS patients from 2000 to 2009 were reviewed.

The tool of data collection was a questionnaire form that was administered and filled by the researcher through reviewing all the records (1125) since the establishment of the centre on 2000. For each patient the following information were collected: age, sex, date of onset, date of diagnosis, date of second attack, presenting symptom.

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 collected: 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), 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 before to the 18th birthday).(3) 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.(6)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.(6)

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 with its onset 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 and 41 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). 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%) of them presented with polyfocal signs with more than one clinical feature. The most common presenting lesion was optic neuritis in 29 patients (37.66%), followed by brain stem lesion in 20 patients (25.97%) (Table1). Complete improvement of the first attack happened in 47 patients (61.0%), partial improvement in 20 (26%), no improvement in 10 (13%). The mean time between the first and second attack 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 attack was 1.91 years in those with sensory symptoms, and 4.52 years in those with transverse myelitis (Table 2).

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) (Fig.1). But no significant difference was found when PI was compared between those with monofocal 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 compared between children and adolescents patients, a shift to younger age was observed. The time estimated was 9.15±6.04 in children and 15.11±1.23 in adolescents (P=0.019) (Fig.2). 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.

**Table 1: Distribution of all patients according to clinical presentation.**

| Variable | Number | Percent |
|---|---|---|
| Clinical Presentation | | |
| - Optic Neuritis | 29 | 29.9 |
| - Brainstem | 20 | 20.6 |
| - Pyramidal | 16 | 16.5 |
| - Sensory | 14 | 14.4 |
| - Transverse Myelitis | 11 | 11.3 |
| - Cerebellar | 5 | 5.2 |
| Monofocal | 59 | 76.6 |
| Polyfocal | 18 | 23.4 |
| Total | 77 | 100 |

**Table 2: Interval between the first and second attack calculated for each clinical presentation**

| Clinical Presentation | No. of patients | Minimum | Maximum | Mean | Stand. Dev. |
|---|---|---|---|---|---|
| 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 |

**Table 3: Mean and standard deviation of Progression Index at different conditions**

| Progression Index | Mean ± SD | Significance |
|---|---|---|
| For the whole sample | 1.436 ± 2.3 | |
| Focal lesions:<br>Monofocal<br>Polyfocal | 1.37 ± 2.8<br>1.64 ± 2.4 | P=0.404 |
| Initial course RRMS<br>PP<br>MS | 1.46 ± 0.29<br>1.16 ± 0.34 | P=0.404 |
| Gender:<br>Male<br>Female | 1.51 ± 3.0<br>1.39 ± 1.77 | P=0.136 |

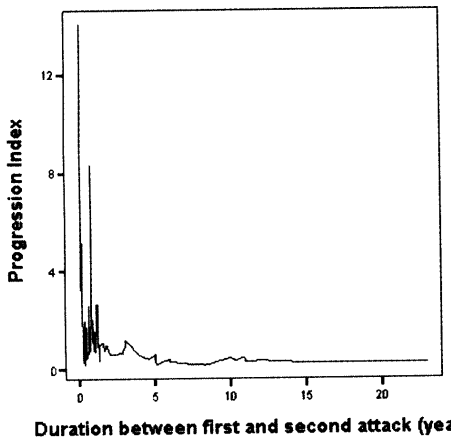


**Figure 1: Distribution of patients according to their progression index and the duration between first and second attack of Multiple Sclerosis.**

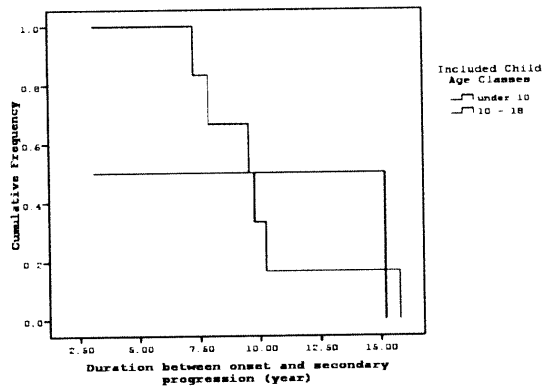


**Figure 2: Kaplan–Meier Estimates of the Time to secondary progression compared between children and adolescents**

**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 that is close to the other studies (12-13.7 years)(7) 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 the mean age to diagnosis was 18.9±5.9 years with lag time to diagnosis of 4 years, which was consistent with the finding of Pinhas-Hamiel et al.(6) The mean age at diagnosis was 18.5±2.5 years (range: 12-21 years) and the mean lag time to diagnosis was 4.7 years.(6) 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.(8) 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.

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.(9) 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 polysymptomatic 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.(9) Renoux et al. (7) and Simone et al(4) but they were consistent with the findings of Visudhiphan et al(10)and Mikaeloff et al(8) that optic neuritis was commonly the first sign in Asia. It is also consistent with the figure given by Stephen(11) for MS in the general population. Also 20.6% of our patients had brainstem symptoms that are close to the frequency reported:(12,13,14)11.3% of our patients had transverse myelitis as a presenting symptom, consistent with less than 10% in Mikaeloff et al.(8)Sindern et al.(15)and Duquette et al(16) studies. Mikaeloff et al show that optic neuritis is one of the predictors for a second attack in MS and decreased risk of MS was found in patients who presented with myelitis or altered mental status(8).

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(17) 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.

PI was 1.43 that is much higher than 0.27 reported by Pinhas-Hamiel et al.(6) but the age at the onset of the disease was not correlated with neurological disability. Moreover, PI used to quantify progression was less than 0.5, indicating a favourable prognosis. These findings suggest that early onset does not cause aggressive course and the age at the onset of the disease did not contribute to disability per se, but longer disease duration resulted in increased disability. This is not the situation in this study.

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 may indicate the aggressiveness of the course of MS in Iraqi children and adolescents, which needs to be assessed in further studies.

In conclusions the prognosis of MS in paediatric age group after the first attack depends on the degree of recovery and degree of residual disability. Initial site of insult is a predictor of the duration of further attacks. Insignificant was to the age of onset and gender as a prognostic factors, and polyfocal first attack is independent predictor of outcome in MS.

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