# Clinically Isolated Syndrome of Early Onset Multiple Sclerosis in a Sample of Iraqi Patients

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## ABSTRACT:

**BACKGROUND:**

The first acute demyelinating event without encephalopathy, 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. It is becoming increasingly recognized that MS affects children and adolescents, with many of these patients receiving the diagnosis and initiating therapy prior to their 18th birthday[2].

**OBJECTIVE:**

To evaluate the clinically isolated syndrome in individuals with early onset of multiple sclerosis.

**MATERIALS AND METHOD:**

The records of the multiple sclerosis centers in Baghdad teaching hospital have been surveyed. The study enrolled 77 patients who had early multiple sclerosis (onset before age of 18 years), their clinically isolated syndrome data have been analyzed.

**RESULTS:**

Two thirds of the patients were female (a female/male ratio of 1.6:1). Forty eight of the patient where female (62.3%) and twenty nine patients where males (37.7 %). Mean age at onset was 14.95 years. Seven patients where children (age below 10years) (9.1%) and seventeen patients where adolescents (age 10 to 18 years) (90.9%) at onset. The most common presenting clinically isolated syndrome was optic neuritis (35.8%) followed by brain stem lesion. Fifty nine patients had monofocal presentation (76.6%) and eighteen had polyfocal presentation (23.4%). forty seven patients had complete improvement of the clinically isolated syndrome (61.0%), the rest had partial or no improvement.

**CONCLUSION:**

The most common clinically isolated syndrome of early onset Multiple sclerosis is optic neuritis. monofocal clinically isolated syndrome more than polyfocal. Complete improvement is high.


***KEY WORDS*:** multiple sclerosis and clinically isolated syndrome

## INTRODUCTION:

While it is thought that multiple sclerosis (MS) onset in childhood occurs in a small percentage of patients, unique characteristics of children may lead to under diagnosis of the disease in this population[1].

Although MS was originally believed to be a disease of young adults, with a mean age of onset of 30 years, it is becoming increasingly recognized that MS affects children and adolescents, with many of these patients receiving the diagnosis and initiating therapy prior to their 18th birthday[2]. In this age group, MS presents almost exclusively as a relapsing-remitting disease and most recover from the initial attacks[3].

The first acute demyelinating event without encephalopathy, termed a clinically isolated syndrome (CIS)[4],(i.e., isolated in time)[5].

CIS can manifest with signs and symptoms caused by a single lesion (monofocal clinically isolated syndrome) or with polyfocal features, implicating multiple lesions[5].

Some patients with CIS will go on to develop relapsing-remitting MS and suffer from multiple attacks, whereas others will have no further evidence of demyelinating disease. It is difficult to predict whether a given individual will develop MS following symptom onset; however, natural history studies show that the risk of having a

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second attack after 14 years of follow-up is 88% if any lesions are present on the initial brain MRI and only 19% if the brain MRI is normal[6].

The aim of the study is to evaluate the clinically isolated syndrome in individuals with early onset of multiple sclerosis.

## PATIENTS 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. The clinic was established in 2000 at medical city teaching hospital, which is geographically accessible by most of the population in Baghdad as well as from the rest of Iraq[7].

The records of 1125 MS patients from 2000 to 2010 were reviewed. Patient included must first be diagnosed to have MS according to the revised McDonald`s diagnostic criteria[8] for multiple sclerosis. The onset of disease must be before the 18th birthday. 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)[5]

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 gathered: age, sex, date of onset, date of diagnosis, date of second attack, presenting symptom.

To define CIS as multifocal if the clinical features could be attributed to more than one CNS site and monofocal if the clinical symptoms could be attributed to a single CNS lesion. These distinctions are based solely on clinical findings. The term multifocal cannot be applied to a clinically monofocal presentation in which the MRI shows multiple asymptomatic lesions[5].

The statistical package of social sciences (SPSS) version 15 was used for data input and analysis, where Mann Whitney test was used to test the significance of difference between two means, Z test to test the significance of difference between two proportions, chi square test to test the significant association between discrete variables and Pearson correlation to test the relation between two continuous variables. $P<0.05$ was considered as statistically significant.

## RESULTS:

Of the 1125 patients record surveyed for the research, 77 patients were eligible for the study, with the diagnosis of MS and onset of disease before the 18th birthday, A prevalence of 6.8%. 48 of patient where female (62.3%) and 29 patients where males (37.7 %), F: M ratio 1.6:1. Mean age to diagnosis of MS was 18.9±5.9 with lag time to diagnosis 3.9 years

Mean age at onset (calculated as the time difference between date of birth and date of onset of the first attack ) was 14.95 years (minimum 5, maximum 18, SD 3.2 years) seven patients where children (age below 10 years ) (9.1%) and 70 patients where adolescents (age 10 to 18 years) (90.9%) at onset (table 1).

No significant difference was found regarding distribution of gender in each age group (table 1). Also no significant difference was found when age at onset was compared between males and females (Male = 14.705 ± 3.134, Female = 15.105 ± 3.265).

Regarding the clinical presentation 29 patients presented with optic neuritis (35.8%), 20 patients (24.7%) with symptoms referred to a brainstem lesion,16 patients (19.8%) with pyramidal, 14 (17.3%) with sensory symptoms, 11 patients (13.6%) with transverse myelitis ,5 patients (6.2%) with cerebellar lesion and 2 patients (1.5%) had Sphincter disturbance. 59 patients had monofocal presentation (76.6%) and 18 had polyfocal presentation (23.4%)(Table 2).

Although optic neuritis was not the most common presenting symptom in children (under the age of 10) there is no statistical significance difference was found between children and adolescents regarding the presenting symptom and mode of onset (table 2).

No significant difference was found between the two genders regarding the presenting symptom and mode of onset (table 3).

Regarding resolution of the first attack 47 patients had complete improvement (61.0%), 20 had partial improvement (26%), in 10 patients there was no improvement (13%).

**Table1: Distribution of patients according to their age at onset and gender.**

| AGE / Gender | Under 10 years | | From 10 to 18 years | | P |
|---|---|---|---|---|---|
| | Number | Percent | Number | percent | |
| Male | 2 | 28.6 | 27 | 38.6 | |
| Female | 5 | 71.4 | 43 | 61.7 | 0.704 |
| Total | 7 | 100 | 70 | 100 | |

**Table 3: Distribution of patients according to their gender and presentation**

| Gender | Male | | Female | | P |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Optic Neuritis | 9 | 31 | 30 | 41.7 | 0.486 |
| Brainstem | 9 | 31 | 11 | 22.9 | 0.604 |
| Sensory | 4 | 13.8 | 10 | 20.8 | 0.640 |
| Pyramidal | 7 | 24.1 | 9 | 18.8 | 0.790 |
| Transverse Myelitis | 4 | 13.8 | 7 | 14.6 | 0.811 |
| Sphincter disturbance | 0 | 0 | 2 | 4.2 | 0.702 |
| Cerebellar | 4 | 13.8 | 1 | 2.1 | 0.123 |
| | | | | | |
| Monofocal | 24 | 82.8 | 35 | 72.9 | 0.323 |
| Polyfocal | 5 | 17.2 | 13 | 27.1 | |

**Table 2: Distribution of patients according to their age and presentation**

| | Under 10 years | | From 10 to 18 years | | P | Number (out of 77 patients) |
|---|---|---|---|---|---|---|
| | Number (out seven chilren) | Percent (out of all under 10) | Number (out of 77 child) | Percent (out of all ≥10) | | |
| Optic Neuritis | 1 | 14.3 | 28 | 40 | 0.172 | 29 |
| Brainstem | 2 | 28.6 | 18 | 25.7 | 0.387 | 20 |
| Pyramidal | 2 | 28.6 | 14 | 20 | 0.481 | 16 |
| Sensory | 1 | 14.3 | 13 | 18.6 | 0.408 | 14 |
| Transverse Myelitis | 2 | 28.6 | 9 | 12.9 | 0.286 | 11 |
| Cerebellar | 0 | 0 | 5 | 7.1 | 0.364 | 5 |
| Sphincter disturbance | 0 | 0 | 2 | 2.9 | 0.134 | 2 |
| | | | | | | |
| Monofocal | 5 | 71.4 | 54 | 77.1 | 0.704 | 59 |
| Polyfocal | 2 | 28.6 | 16 | 22.9 | | 18 |

## DISCUSSION:

The study enrolled 77 patients who had the onset of MS before the age of 18 years, this represent 6.8% of the 1125 patients involved in the MS clinic in Baghdad teaching hospital. This result were close to the figure given by the review of Chintnis[2] but it is highly different from that of Pinhas-Hamiel, et al[9] which estimates 72 (17%) of 418 patients with MS fulfilled the criteria for early onset MS[9]. Although the difference may be due to different environment, it could be due to the different criteria of inclusion in his study, poser's criteria for diagnosis of MS and age at onset below 21 years, while in this study we relied on revised McDonald criteria[8] for diagnosis and age at onset up to18 years. also in our study we calculated the ratio to that of the total number of patients in the MS clinic which is representative of patients referred for the diagnosis of MS and is not population-based study. Diagnosis of MS in children can be more difficult than in adults[10]. The majority of children will recover from the first attack or left with mild residual disability[11]which make the referral system different from population-based study.

We found mean age at onset of CIS to be 14.9±3.2 years similar to the figures given by other studies (12-13.7years) [12] also 62.3% of

our patients were females close to the figure given by Renoux et al [12] and Guilhoto et al [13].
The early age at onset in our study is 5 years and the earliest age reported in the literatures was10 months[14] suggesting that the number of early onset MS cases may have been underestimated, may be because the adult-based MRI lesion distribution criteria are not as sensitive to the MRI appearance of MS in this age group[15]. This may be due to inherent age-related differences in disease pathology, including limited time for accrual of clinically silent white matter lesions, age-related influences on regional proclivity for lesion distribution, or an enhanced reparative capacity in children limiting residual lesion burden[16]. In addition, the current literature on pediatric demyelinating diseases is difficult to interpret because of the variability in terms and definitions used.
No significant difference in age at onset between male and female patients was noted (Male = 14.705 ± 3.134, Female = 15.105 ± 3.265), although in male patients a shift to younger age was observed despite younger age at puberty in female. The female preponderance was highest for subjects with disease onset at ages 13 (18 cases, female/male ratio 3.5:1) and 14 (26 cases, female/male ratio 7.67:1). Although numbers are small, these data support the theory that hormonal changes related to puberty, especially sex hormones, may play an important role in MS onset[17].
Mean age to diagnosis was 18.9±5.9 with lag time to diagnosis 3.9 years which was consistent with Pinhas-Hamiel et al (The mean age at diagnosis was 18.5 ± 2.5 years (range 12 to 21 years, the mean lag time to diagnosis was 4.7 years.),[9]. With the new advance in treatment of MS early diagnosis is of outmost important. Thus a high index of suspicion is required to make a diagnosis at first attack especially if the remission after first attack is complete[1].
Of our patients 76.6% had monofocal versus 23.4% had polyfocal presentation while in by Banwell, Brenda. et al [3] 50 –70% of patients had polyfocal or polysymptomatic presentation and 30-50% had monofocal or monosymptomatic presentation. The difference may be because of the terminology, that is, the terms monosymptomatic and polysymptomatic have been used, so no direct comparison could be made with these figures as many of our patients who has polysymptomatic presentation that could be attributed to single lesion clinically, have been considered to have monofocal presentation. Any combination of symptoms that had a reasonable possibility of being explained on single lesion base was considered monofocal despite the fact that the presentation is polysymptomatic and also not be applied to a clinically monofocal presentation in which the MRI shows multiple asymptomatic lesions.
When CIS were analyzed 35.8% of our patients presented with optic neuritis (unilateral or bilateral) compared to only 10-22% given by Banwell et al [3] and Renoux et al [12] who described 30% to have motor dysfunction but consistent with Visudhiphan et al[18]. where optic neuritis were common in Asia it is also consistent with the figure given in Hauser and Goodin [19] for the first presentations of MS in general population, also in our study, the brainstem symptoms (24.7%) of our patients was higher than the figures given by Renoux et al [12], 13.6% of our patients had Transverse Myelitis as CIS compared to less than 10% in Mikaeloff et al [20], Sindern et al [21], Duquette et al. [22]. Renoux et al [12]states that isolated optic neuritis and isolated brain-stem dysfunction were more frequent, and isolated dysfunction of long tracts was less frequent, in patients with childhood-onset multiple sclerosis than in patients with adult-onset multiple sclerosis (23.4%, 16.8%, and 37.8%, respectively, vs. 17.9%, 8.5%, and 52.9%, respectively; P<0.001). One potential source of bias is that the presence of optic neuritis might be more likely to lead to a diagnosis of multiple sclerosis than would the presence of other neurologic symptoms. Even so, the presence of CIS other than optic neuritis would probably only delay the time to the diagnosis of multiple sclerosis and not reduce the probability of the diagnosis itself.
Regarding resolution of the CIS, 47 patients had complete improvement (61%), 20 had partial improvement (26%), in 10 patients there was no improvement (13%). This is consistent with Godath [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.

## CONCLUSION:

The most common clinically isolated syndrome of early onset Multiple sclerosis is optic neuritis. monofocal presentation of CIS more than polyfocal. Complete improvement is high.

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