Multiple Sclerosis 2002; **8**: 115–118
www.multiplesclerosisjournal.com

Prospective study of multiple sclerosis with early onset

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Fifty-four subjects (36 females and 18 males) affected by clinically definite multiple sclerosis (MS) and with onset of the disease at 15 years of age or before were prospectively studied in five Italian MS centres. Female/male ratio was 4.7 in subjects with age ≥12 years, suggesting a role of hormonal changes in triggering MS onset. The mean follow-up duration was 10.9–5.6 years. The functional systems more frequently involved at onset were the pyramidal and brainstem (both in 28% of cases). The onset was monosymptomatic in 31 subjects (57%). The course was relapsing-remitting in 39 subjects (72%) and relapsing-progressive in 15 (28%). Disability was assessed by the Expanded Disability Status Scale (EDSS): the mean score after 8 years of follow up was 3.5 (–2.5). The score was <4 in 68% of cases, between 4 and 6 in 8% of cases, >6 in 24% of cases. Disability after 8 years was highly predicted by disability in the first year (p=0.008). There was a tendency to a worse prognosis in relation to the number of relapses in the first 2 years (p=0.08). The outcome was not influenced by the characteristics of symptoms at onset, age and gender.

Multiple Sclerosis *(2002)* **8,** 115–118

Key words: *childhood; multiple sclerosis; prognosis*

Introduction

Multiple sclerosis (MS) usually occurs between the ages of 20 and 40 years, and is rare in childhood. Assuming the limit of 15 years, the frequency of early onset multiple sclerosis (EOMS) ranges from 2.7% to 5%.[1,2] A recent retrospective study of an Italian population reported the figure of 4.4% for MS onset at 15 years or less.[3] The most relevant clinical findings of this study were: the preponderance of females affected, specially between 12 and 15 years, the preponderance of symptoms of brainstem dysfunction at onset, the rarity of the progressive course.

The prognosis of EOMS does not seem to differ significantly compared to the adult onset MS (AOMS),[3,4] although there is no agreement on this issue: both the malignant[5,6] as well as the benign course[1,2,7,8] has been found to be more frequent in EOMS than in AOMS.

The diagnosis of MS in a young subject can exert a strong psychological impact on the family because of the unpredictable course of the disease, its tendency to progression and to cumulate disability over years. With a few exceptions[1,3] most studies on EOMS are based on a small number of cases and do not allow obtaining exhaustive information on its prognosis.[2,5,7–10] Only the studies of Cole *et al*[7] (14 subjects) and Dale *et al*[10] (13 subjects) were prospectively performed.

In this prospective study we describe the clinical characteristics and the evolution of EOMS in a large series of cases observed since the initial manifestation of the disease and followed up for a long time, in order to better define the features of MS with onset in childhood or adolescence in comparison to a previous retrospective study.[3]

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Received 21 February 2001; revised 18 September 2001; accepted 25 September 2001

Subjects and methods

Five Italian MS centres participated to this prospective study and collected 78 patients affected by clinically definite MS (according to Poser's criteria[11]) with a disease onset at 15 years of age or before. In order to have a precise assessment of the disease and an appropriate follow-up, the study was restricted to subjects seen at onset or not later than 1 year since onset, provided that a complete clinical neurological evaluation was available, and to subjects who had a follow up of at least 4 years. Fifty-four subjects fulfilled these criteria and were included in the study. In each patient, at least a yearly clinical examination was available.

For each patient the following findings were sought: sex, age of onset, initial symptoms, interval between first and second and between second and third attack, total number of relapses and number of relapses in the first 2 years, clinical course, (classified as relapsing-remitting, RR; relapsing-progressive, RP; primary progressive, PP),[3] duration of the disease. Neurological examination was scored using Kurtzke's Functional System (FS) and Expanded Disability Status Scale (EDSS):[12] if a patient was seen during an acute relapse, the EDSS was confirmed after 3 months. If available at the time of the first attack, the results at brain magnetic resonance imaging (MRI), (classified according to Paty's criteria[13]), CSF examination, and evoked potentials were recorded.

10.1191/1352458502ms786oa

Results

Age and symptoms at onset

Fifty-four subjects (36 females and 18 males) were collected, with a mean age of 12.6± 2.1 (median 13) years and a mean follow-up duration of 10.9± 5.6 (median 9.5) years. Most of them were seen at MS onset, three cases within the first year. The distribution of cases in relation to age of onset is reported in Figure 1: MS was less frequent in females than in males before the age of 12 years (8 versus 12, f/m ratio=0.7) on the contrary MS was greatly more frequent in females than in males with age ≥12 years (28 versus 6, f/m ratio 4.7; chi-square test: $p=0.04$).

In 31 cases only one FS was involved at onset, with a preponderance of brainstem FS involvement, in 18 cases two FSs were involved, in 5 cases three FSs or more (Figure 2).

Course and disability

The course was RR in 39 cases, RP in 15, whereas the primary progressive course was not represented.

The mean EDSS at onset was 2.2± 1.0 (<3.5 in 49 cases). Changes of EDSS during the course of the disease are reported in Figure 3. The distribution of EDSS scores after 8 years, in the 37 cases that reached this follow up, is reported in Figure 4: the EDSS was <4 in 67.7% of cases, between 4 and 6 in 8.3% of cases, >6 in 25.0% of cases and the mean score was 3.5± 2.5: After 10 years the percentages were, respectively, 59.1%, 9.1%, 31.8%, and 18.2% had a score ≥7.

Correlations between EDSS and clinical or demographic data were performed at 8 years of follow up as the number of patients was reduced to 22 after 10 years. Disability was predicted by the EDSS at 1 year (Figure 5, $p=0.008$) and was more severe in subjects with RP course (6.0± 2.0) than in those with RR course (1.8± 1.0) ($p<0.001$). There was a trend towards association between number of relapses in the first 2 years and disability, but not at a significant level ($p=0.08$). Correlations with gender, age, mono/polysymptomatic onset, symptoms at onset did not give significant results.

A second attack occurred after a mean time of 24.9 months (median 12 months), and a third attack occurred after 11.7 months (median 7 months). The relapse rate was 0.87± 0.62 (median 0.7): it was higher than this value in 22 and lower in 32 subjects.

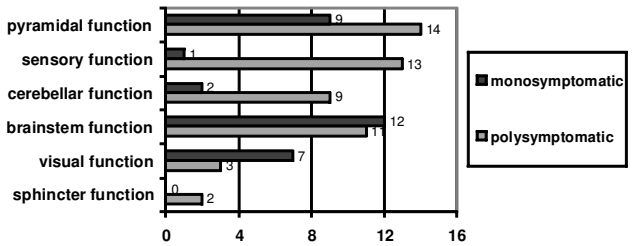

Figure 2 *Frequency of initial symptoms, alone or combined*

Paraclinical tests

Diagnostic tests were performed during the first attack in most cases. Brain MRI showed lesions within the white matter in all cases (39 subjects), fulfilling the criteria of lesions strongly suggestive/suggestive of MS.[13] CSF exam was performed in 47 cases and showed an intrathecal IgG synthesis in 41 of them (87.2%): the EDSS at 8 years was not influenced by CSF results (3.3 in CSF− versus 3.6 in CSF+). Visual-evoked potentials were abnormally delayed in 36/41 cases (87.8%), in 28/41 (68.3%) with no detectable optic nerve involvement. Brainstem auditory-evoked potentials were abnormal in 19/25 cases (76%), in 10/25 (40%) with no detectable brainstem involvement. Somatosensory evoked potentials were abnormal in 16/27 cases (59.2%), in 13/27 (48.1%) with no sensory involvement.

Discussion

MS in childhood commonly begins with the usual symptoms observed in adult patients, but the encephalomyelitic onset, with headache, fever, confusion, epilepsy, nausea and vomiting,[2,14] as well as atypical presentations are described (acute myelitis, Devic's disease, pure idiopatic neuritis, central and peripheral nervous system involvement).[15–18] There is no agreement about the frequency of initial characteristics of EOMS: sensory disturbances were reported as prominent by Duquette *et al*,[1] optic neuritis by Hanefeld[5] and Sindern *et al*,[2] ataxia by Selcen *et al*.[8] In this prospective study, we confirmed the high frequency of brainstem and motor involvement at onset observed in the retrospective one. Results of the two studies are compared in Figure 6.

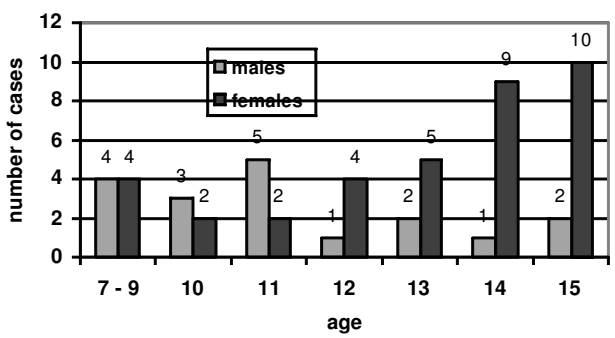

Figure 1 *Distribution of subjects in relation to gender and age at onset*

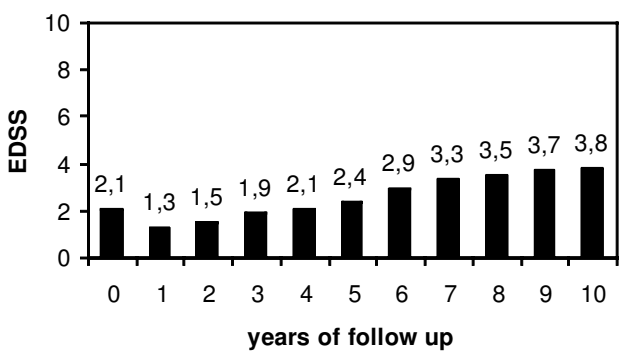

Figure 3 *Changes of mean EDSS during the follow up*

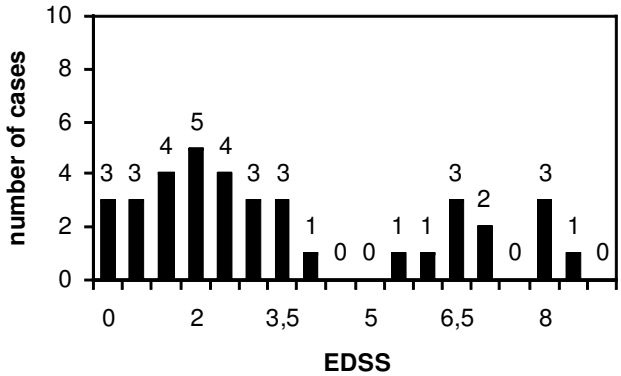

Figure 4 *Distribution of cases in relation to EDSS at onset*

A peculiar aspect of EOMS is the overrepresentation of females from 12 to 15 years of age (f/m ratio=4.7). On the contrary the sex ratio was inverted for age <12 years (=0.7) (p=0.004). In agreement with our previous retrospective study, we confirmed the predominance of females affected, particularly for ages from 12 to 15 years. A similar result was observed by Duquette *et al*,[1] who reported a sex ratio of 3 in a series of 125 subjects with MS onset before age 16 years, and by Ruggieri *et al*[6] who reported a lower f/m ratio for cases under 6 years of age, as observed in our younger cases. These ratios are quite different compared to the usual value of 3/2 of the general MS population, suggesting that hormonal changes during puberty may play a role in triggering MS onset.[19,20]

The mean interval between the first and second attack lasted 24.9 months, and in 30 subjects the second attack occurred within 12 months: this frequency was slightly higher than the retrospective study, due to the more accurate prospective method.

The course was relapsing-remitting in most cases (about 3/4) and relapsing-progressive in the remaining, whereas no subject showed the primary progressive course, which was also rare in the retrospective study (5.4%).[3] As a whole, these findings are consistent with literature data.[1,6,8,9]

Disability increased slightly with time: the mean EDSS was 2.3 at onset, decreased to 1.3 in the first year and

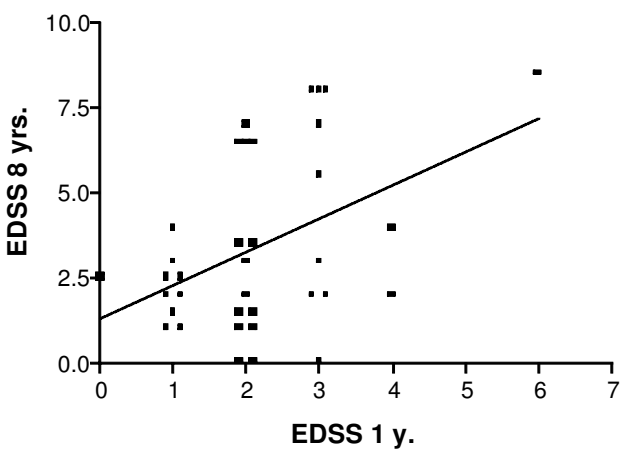

Figure 5 *Relationship between EDSS at 1 year and disability after 8 years*

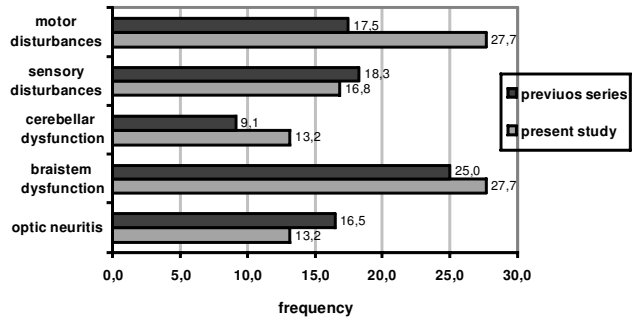

Figure 6 *Frequency of symptoms at onset of the present study compared with our previous, retrospective study*

reached the mean value of 3.8 after 10 years. After 10 years this score was <4 in the 59.1% of cases, between 4 and 6 in 9.1% of cases, >6 in 31.8% of cases (of these, 18.2% had a score ≥7). After 8 years, the number of subjects under study was higher, and the percentages were, respectively, 67.7%, 8.3% and 25.0%, according to the usual bimodal distribution of cases.[21] Results are compared with data of the retrospective study in Figure 7. Duquette *et al*[1] found quite similar results: 60% of EOMS had a score <3, 24% a score from 3 to 6.5, 16% a score ≥7. In our cases, disability was predicted by the EDSS score in the first year and was slightly correlated to interattack length. It was higher in subjects with RP than in those with RR course. Similar findings have been observed in the general population.[21,22]

Among diagnostic tests, brain MRI was confirmed as the most sensitive test, showing white matter lesions in all patients with the pattern of lesions strongly suggestive/suggestive of MS.[13] The demonstration of oligoclonal bands was also frequent in our (87.2%) as well as in other reports.[4,8,23–26] Evoked potentials can also substantiate the diagnosis, showing asymptomatic lesions in several cases: in our series the frequency of subclinical lesions ranged from 40%, for brainstem auditory evoked potentials, to 68.3%, for visual evoked potentials.

Although MS is rare in adolescence and childhood, its diagnosis can be defined accurately in suspected cases by means of MRI, CSF and EP, provided that a better explanation is excluded. Cases are described with abrupt onset and characteristics similar to ADEM: in these cases a follow up is necessary, monitoring the clinical evolution and the MRI pattern: the appearance of new MRI lesions is suggestive

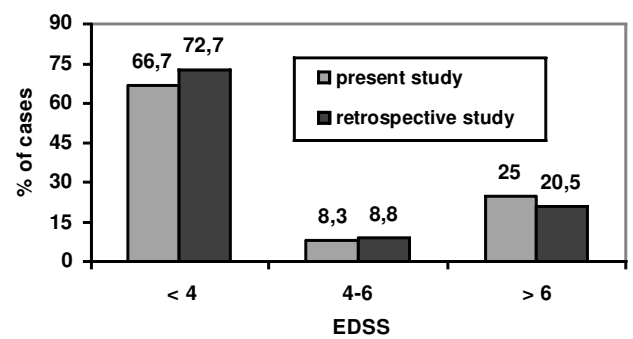

Figure 7 *Distribution of cases in relation to disability in the present study compared with our previous, retrospective study (follow up > 8 years)*

of MS whereas in ADEM MRI lesions disappear completely or partially.[10] On a clinical ground infections before the onset of the disease, a polysymptomatic presentation, pyramidal signs, bilateral involvement of the optic nerve, seizures are more frequent in ADEM than in MS patients, helping to differentiate the two diseases.[10] After diagnosis is properly defined, the question of treatment raises: there is a general consensus that the acute phase of the disease should be treated with high dose corticosteroids, and this schedule was adopted in most of our cases. Disease-modifying drugs, namely interferon-beta and glatiramer acetate, are now available, with a clear effect in reducing relapse rate, MRI correlates of disease activity and, partially, in preventing disease progression. At present data are not available for subjects with age <16 years and no patient of our series was treated with these drugs. An effect in reducing relapses was observed by Adams *et al*[27] in a single male MS patient 7 years old treated with Interferon-Beta.

Our results show that EOMS frequently develops with relapses, with recovery in three-fourths of cases and progression in one-fourth of cases. The relapse rate was variable but generally high, next to 1 per year. The EDSS was > 6 in 1/4 after 8 years of follow up. In other words, there are cases with an active form of the disease, with frequent relapses and tendency to progression, especially if the initial relapse rate and the initial level of disability are high. There is no reason to believe that interferon-beta and glatiramer acetate cannot be equally useful in EOMS as in subjects with typical age of onset. It will be interesting to evaluate their safety and their impact in EOMS, reducing relapse rate and disease progression. This topic will be the object of our future studies.

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