Early onset multiple sclerosis

A longitudinal study

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Abstract—*Objective:* To evaluate the clinical course of MS in individuals with onset of MS before age 16. *Methods:* Patients with onset of MS before age 16 (n = 116) with complete clinical information on the clinical course from the MS Clinic at The University of British Columbia (UBC) Site Hospital computerized database (MS-COSTAR) were included in this study. The data were compared to those from the Canadian natural history study for MS clinic attendees, regardless of age at onset. *Results:* The mean duration of observation was 19.76 ± 0.90 years; the mean age at MS onset was 12.73 ± 0.25 years. Only three cases (2.6%) had a primary progressive (PP) MS course. To date, 60 (53.1%) of 113 subjects have developed secondary progressive (SP) MS. The 50% probability for SPMS was reached 23 years after onset. For patients with relapsing remitting (RR) or SPMS the mean disease duration from onset to the time of confirmed Expanded Disability Status Scale (EDSS) 3.0 was 16.03 ± 1.17 years (at mean age 28.47 ± 1.14); mean duration from onset to the time of EDSS 6.0 was 19.39 ± 1.43 years (at mean age 32.32 ± 1.44). Annual relapse rate was 0.54 ± 0.05 per year. The correlation between the number of relapses during the first year of disease and the course of the disease was also significant. *Conclusions:* The prevalence of early onset MS (3.6%) in our study confirms the previous findings on early onset MS. A RR course was seen in the majority of cases of early onset MS. A high frequency of relapses, early age at permanent disability, and the presence of malignant cases raise the question of possible early use of disease-modifying therapy in patients with early onset MS.

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MS is a chronic disease of the CNS with the onset of symptoms usually occurring between the ages of 20 and 40. Prior studies have shown that early onset MS (EOMS) (onset before age 16) occurs in 3 to 5% of all MS cases.[1-5] Less than 1% of all MS cases have an onset earlier than 10 years.[4-8] In the past, MS was often not considered in the differential diagnosis when a young patient presented with neurologic signs and symptoms.[5,8] Current diagnostic techniques allow neurologists to evaluate very young patients for this disease and adult diagnostic criteria for MS may be applicable to the pediatric population.[9]

The literature on EOMS is largely based on small groups of patients or on individual case reports.[11-19] Study groups of over 100 patients are rare.[1,4] Information about the natural history of EOMS is not uniform. As potentially disease-modifying therapies evolve in the management of this disease, it becomes even more important to better understand the natural history of MS in such cases.[19-21] The current study is a longitudinal follow-up of individuals seen at the University of British Columbia (UBC) MS Clinic who had their onset of MS before age 16.

Subjects and methods. Subjects were ascertained from the UBC MS Clinic's computerized database (MS-COSTAR).[22] Inclusion criteria for this study were 1) diagnosis of clinically definite (CD) MS[23]; 2) clinical onset (first documented sign or symptom) before age 16; and 3) longitudinal follow-up at the UBC MS Clinic for at least 1 year. The studies based on MS-COSTAR are frequently reported as population-based. It may potentially be under-representative of patients with very malignant MS and older individuals with EOMS who had already been in residential facilities owing to severe disability prior to the UBC MS Clinic's inception in September 1980. Nevertheless, as confirmed by a recent study on the onset of childhood MS after hepatitis B vaccination,[24] the UBC MS Clinic is the major referral center for children in British Columbia who are suspected to have MS and who survive the initial bout.

In addition to the age at onset, prospective longitudinal information on individuals seen at the UBC MS Clinic includes clinical course (e.g., primary progressive [PP], secondary progressive [SP]), relapse history (date, duration, and severity), type of MS (e.g., spinal, brainstem), and Expanded Disability Status Scale (EDSS) score.[25] Thus this database provides an excellent, and perhaps unique, opportunity to study MS using defined parameters such as duration of disease from the onset to EDSS 3.0 (mild disability) or to EDSS 6.0 (use of a cane), or to switch to a SP course.

The data were analyzed using the standard statistical software package (SPSS, Chicago, IL). Results were compared to the findings of a Canadian natural history study for MS clinic attendees, regardless of age at onset (hereaf-

*See the Appendix on page 1010 for a list of the UBC MS Clinic Neurologists.

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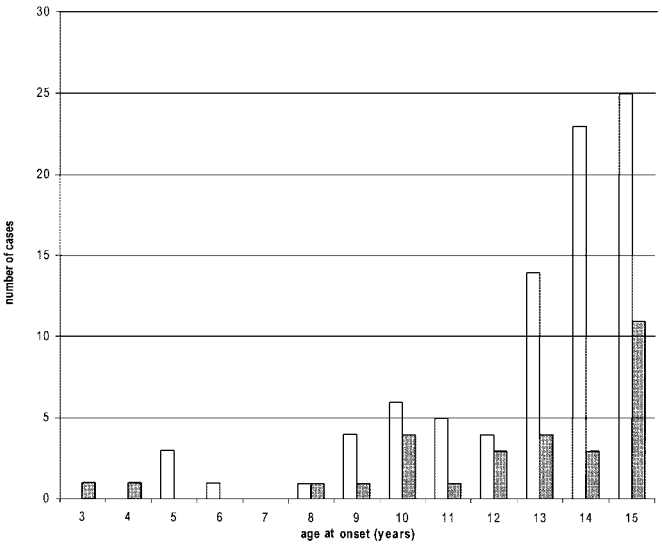

Figure 1. Distribution of patients with early onset MS according to age at onset and sex. White bars = girls; gray bars = boys.

ter referred to as the "adult group").[26] These data were obtained from 1,099 cases of a predominantly adult-onset MS cohort in the same geographical area.

Results. A total of 129 individuals were identified as having onset of MS before age 16. This number represents 3.6% of the entire UBC MS Clinic caseload with CDMS[24] during the study period (September 1980 until September 1999). Of these, 13 cases (10.1%) were excluded from the study as there was insufficient information (e.g., EDSS scores) or they were lost to clinic follow-up after the first visit. A total of 116 subjects were included in this report (figure 1).

The mean longitudinal follow-up (onset to current study) was 19.76 ± 0.90 years (range 1 to 47 years) with 83.6% of subjects having been followed by the UBC MS Clinic for at least 10 years. The patients with higher frequency of relapses during the first 2 and 5 years after onset had a longer period of follow-up (Kendall tau-b correlation with $R = -0.323$ and $R = -0.446$, $p < 0.001$).

Twenty-three of the 116 subjects (19.8%) had onset at age 10 or younger and only six subjects were at age 7 or younger (5.2%) at onset. The overall female to male ratio was 2.87:1 (86 women; 30 men). The most frequent onset symptoms were sensory disturbances (25.9%), optic neuritis (21.6%), and brainstem dysfunction (12.9%). Table 1 compares the frequency of initial symptoms in the study group with the adult group.[26]

Of the 116 subjects, 113 (97.4%) initially had a RRMS course. The remaining three cases were categorized as PPMS. Results of analyses presented in this article, unless otherwise stated, refer to the group of 113 subjects with RRMS.

The average annual relapse rate for the study group was 0.54 ± 0.05 per year. Twenty-seven subjects (23.3%) had at least one additional relapse during the 12-month period following MS onset and 67 (57.8%) during the first 60 months after onset. The main characteristics of clinical course are noted in table 2. None of these characteristics significantly differs in the subgroups with age at MS onset younger than 10 or age at onset 11 through 15 years. Thus in these data we have not been able to find peculiarities of the MS course before 11 years in comparison to other patients with early onset MS.

To date, 60 (53.1%) of the 113 subjects have developed SPMS (mean 17.7 ± 1.17 years, median duration of disease for switch to SPMS 16.0 years, range 2 to 40 years) (figure 2). The 50% risk for the switch from RRMS to SPMS was reached 23 years after onset (Kaplan-Meier method, figure 3) compared to 10 years for the adult group (n = 722).[26]

At the time of the study, EDSS score of 3.0 had been reached by 58.6% of the subjects and 6.0 by 38.8% of the subjects (see table 2). The mean time of progression from EDSS 3.0 to EDSS 6.0 was 4.89 ± 0.56 years. The mean time for progression to EDSS 3 and EDSS 6 in EOMS was compared with an adult group in table 3. Of 97 subjects with disease duration longer than 10 years, 63 (64.9%) had EDSS higher than 3.0 and 42 (43.3%) higher than 6.0. The 50% risk for reaching EDSS scores of 3.0 and 6.0 were 23 and 28 years after onset compared to 10 years and 18 years for the adult group[26] (the Kaplan-Meier method; see figure 4). No significant difference was found in our data in the comparison with age at onset before or after 11 years.

For study subjects with an annual relapse rate of less than 0.6 it took longer to evolve to SPMS compared to those with an annual relapse rate of 0.6 or greater

Table 1 *The distribution of initial symptoms in the early onset MS and adult groups*

Initial symptoms	Onset before age 16, n = 116, n (%)			Comparison group,[27] n = 1,099, %
	Total	Girls	Boys	
Sensory disturbances	30 (25.9)	26 (30.2)	4 (13.3)	45.4
Optic neuritis	25 (21.6)	17 (19.8)	8 (26.7)	17.2
Brainstem dysfunction	15 (12.9)	13 (15.1)	2 (6.7)	12.9
Motor	12 (10.3)	7 (8.1)	5 (16.7)	20.1
Gait disorders	11 (9.4)	6 (7.0)	5 (16.7)	NR
Coordination (cerebellar signs)	8 (6.9)	6 (7.0)	2 (6.7)	13.2
Bladder dysfunction	1 (0.9)	1 (1.2)	0	NR
Polysymptomatic onset	14 (12.1)	10 (11.6)	4 (13.3)	NR

NR = not reported.

Table 2 *Clinical course in 113 patients with early onset MS who initially had relapsing-remitting (RR) MS*

Characteristics	No. (%) or mean ± SE
Relapsing/remitting period	
Mean duration of RR period, y	16.31 ± 0.89
Total number of relapses	5.53 ± 0.32
Annual relapse rate for the whole RR period	0.54 ± 0.05
Mean duration of the first remission, mo	71.32 ± 5.79
Mean duration of the second remission, mo	58.07 ± 8.74
Proportion of patients with RRMS with first remission <1 y	27 of 113 (23.9)
Proportion of patients with RRMS with two or more relapses in first 2 y	33 of 113 (29.2)
Proportion of patients with RRMS with two or more relapses in first 5 y	67 of 113 (59.3)
Secondary progressive (SP) period	
Proportion of patients with RRMS who switched to SP course	60 of 113 (53.1)
Mean time to SPMS (y) for patients with RRMS	17.70 ± 1.17
Proportion of patients with SPMS and disease duration >10 y	58 of 97 (59.8)*
Progression of disability	
Proportion of patients who reached confirmed EDSS 3.0	68 of 113 (58.6)
Mean age at confirmed EDSS 3.0 (y) for patients with RR or SPMS	28.47 ± 1.14
Mean time to confirmed EDSS 3.0 (y) for patients with RR or SPMS	16.03 ± 1.17
Proportion of patients who reached confirmed EDSS 6.0	45 of 113 (38.8)
Mean age at confirmed EDSS 6.0 (y) for patients with RR or SPMS	32.32 ± 1.44
Mean time to confirmed EDSS 6.0 (y) for patients with RR or SPMS	19.39 ± 1.43
Mean time from EDSS 3.0 to EDSS 6.0 for patients with RR or SPMS	4.94 ± 0.57
Proportion of patients with EDSS ≥ 3.0 and MS duration >10 y	63 of 97 (64.9)*
Proportion of patients with EDSS ≥ 6.0 and MS duration >10 y	42 of 97 (43.3)*

* n = 97 (data were missing for six subjects).

EDSS = Expanded Disability Status Scale score.

(ANOVA with F = 6.87 [$p < 0.001$]; Kendall tau-b correlation with R = −0.575 [$p < 0.001$]). Within the study group, the course of disease (time to EDSS 3.0 and 6.0) was better for those with fewer relapses in the first year of disease (ANOVA with F = 6.52 [$p < 0.001$); Kendall tau-b correlation with R = −0.372 [$p < 0.001$]). The same is applicable for patients with fewer relapses during the first 5 years of the disease (for EDSS 3.0 [R = −0.469; $p < 0.001$] and EDSS 6.0 [R = −0.453; $p < 0.001$]). The study group also showed that the longer the first remission, the longer it took to evolve into a SP disease course (Kendall tau-b correlation R = +0.438, $p < 0.001$; R = +0.333, $p < 0.001$).

There was no correlation between sex or age at MS onset with disease progression for EOMS. However, among 15 subjects with signs of brainstem involvement at onset, there were more frequent relapses (logistic regression, F = 5.52, $p = 0.02$) and relatively faster evolution to SP disease. The overall time to EDSS 6.0 was not significantly reduced for this group.

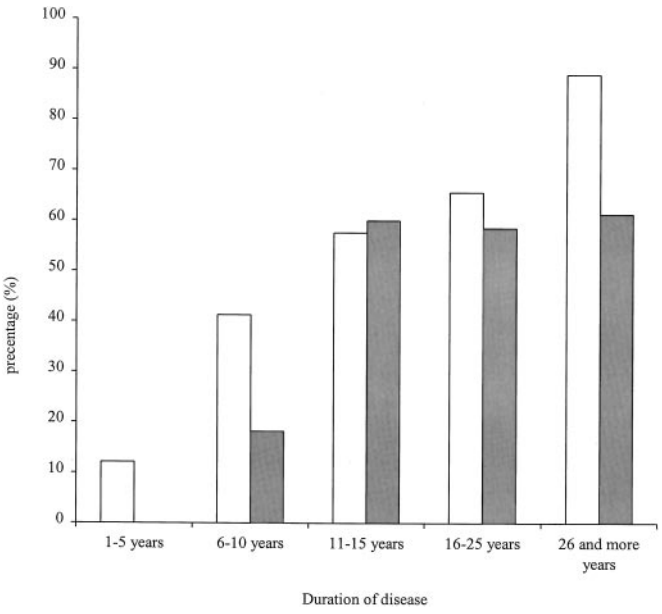

Figure 2. Comparison of proportion of patients who converted to secondary progressive MS among cases of adult MS (white bars) and early onset MS (gray bars).

Discussion. This study and other childhood MS studies showed the female preponderance among EOMS (female/male ratio = 2.87:1) when compared to adults.[22,26] In our study, the female preponderance was highest for subjects with disease onset at ages

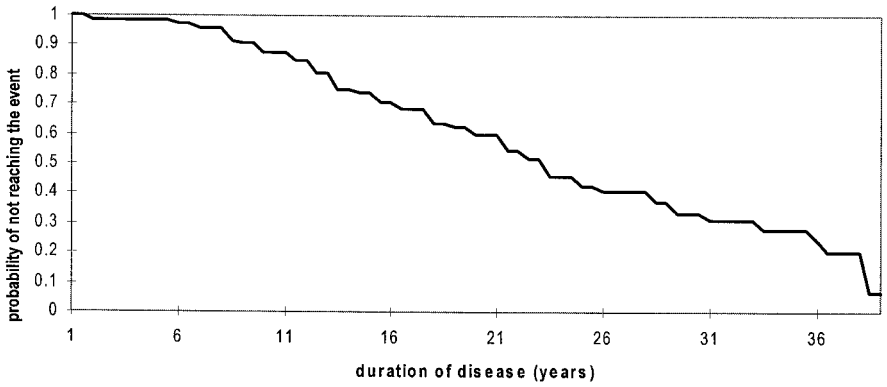

Figure 3. Kaplan-Meier survival curves of the probability of not reaching secondary progression in 113 subjects with an initial relapsing-remitting course.

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.

Our data agree with another Canadian series[2] that the most common initial symptoms in EOMS are sensory signs (26%[1] vs 25.9% in current study), followed by optic neuritis (14% vs 21.6%), brainstem signs (11% vs 12.9% in current study), and gait disturbance (8% vs 8.6%). Sensory and brainstem disorders are more frequent in girls, whereas boys present mainly with motor problems and gait disturbances.

Table 3 *Comparison of rate of disability in the early onset MS (EOMS) and the adult groups[26] initially presented as relapsing-remitting MS*

Level of disability	Adult group (n = 722)[26]	EOMS group (n = 113)
Time to EDSS 3.0	7.69 ± 0.42	15.58 ± 1.16*
Time to EDSS 6.0	14.97 ± 0.31	19.13 ± 1.41*

Values are mean (SD) years to level of disability.

* $p < 0.05$.

EDSS = Expanded Disability Status Scale score.

PPMS has been reported rarely in children in some studies[5] but not in others.[4,14,16] The current study suggests that PPMS (2.6% of all cases) is relatively rare compared to the adult group.[26] PPMS is associated with early degenerative changes and seems to be rare in children and adolescents when the inflammation reaction is dominating. The rate of progression to SP was low compared to the adult group[26] (see table 3, figure 4).

The current data confirm[4,5] that patients with EOMS tend to have a good recovery from the initial relapse with relatively long first and second remissions and a slow rate of progression. Some children with very benign courses may have poor follow-up, whereas the patients with high frequency of relapses during the first years of MS had longer follow-up. A relatively benign course of EOMS compared to adult onset was found previously.[1,4] In the current study, among subjects with disease duration of more than 10 years, 59.8% had progressed to SPMS, 64.9% had reached EDSS 3.0, and 43.3% had reached EDSS 6.0. Nevertheless, as has been reported by others,[8,10,12,14,16] the current study included several subjects who had malignant MS with very early development of disability. As previously discussed, malignant MS is a group that may be under-represented in the current series. At the same time, the mean ages at confirmed EDSS of

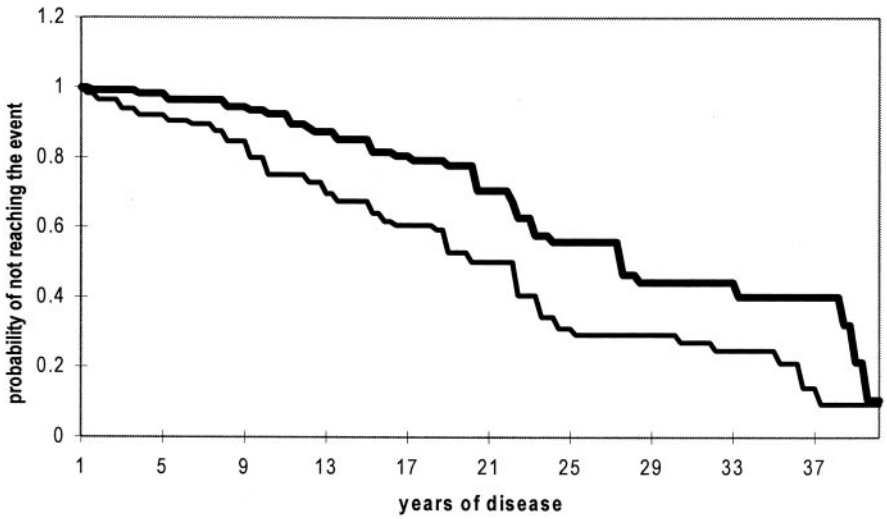

Figure 4. Kaplan-Meier survival curves of the probability of not reaching Expanded Disability Status Scale score (EDSS) 3.0 (thin line) and EDSS 6.0 (thick line) for 113 subjects with an initial relapsing-remitting course.

3.0 (28.47 ± 1.14 years) and EDSS of 6.0 (32.32 ± 1.44) showed that the disease of these patients could not be called benign concerning the early age of irreversible disability.

The frequency of relapses, especially during the first 5 years of the disease, and the duration of the first and the second remission appear to correlated with the risk of early SP and permanent disability in EOMS. This phenomenon has also been seen in the adult group.[26] Sex and exact age at disease onset do not appear to correlate with prognosis in EOMS but onset symptoms of brainstem involvement appear to predict a poor prognosis.

Although further studies are needed to fully delineate the natural history of EOMS, the current study adds considerable information. The observation that this group includes individuals with a high frequency of relapses, an early age at permanent disability, and presence of malignant cases raises the question about the advisability of the use of disease-modifying therapy in cases of active EOMS and potential prevention of severe early disability. First experiences in this field showed good tolerability of such therapy in EOMS.[28]

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Appendix

The UBC MS Clinic neurologists are Drs. Stanley Hashimoto, John Hooge, Lorne Kastrukoff, Joel Oger, and Tony Traboulsee.

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