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ARTICLE

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ABSTRACT

OBJECTIVE. The goal was to identify prognostic factors for an early severe course in a cohort of patients with childhood-onset multiple sclerosis, for the construction of a predictive tool.

METHODS. The cohort consisted of 197 children from the French Kid Sclérose en Plaques neuropediatric cohort with relapsing/remitting multiple sclerosis beginning before the age of 16 years. Patients were included from 1990 to 2003. We used multivariate survival analysis (Cox model) to evaluate the prognostic value of clinical, MRI, and biological covariates at onset for the occurrence of a third attack or severe disability ("severity" outcome).

RESULTS. The cohort was monitored for a mean of 5.5 ± 3.6 years. The "severity" outcome was recorded for 144 patients (73%). The risk of severity was higher for girls, for a time between the first and second attacks of <1 year, for childhood-onset multiple sclerosis MRI criteria at onset, for an absence of severe mental state changes at onset, and for a progressive course. A derived childhood-onset multiple sclerosis potential index for early severity was found to have a positive predictive value for severity of >35% for the upper 2 quartiles.

CONCLUSIONS. The clinical and MRI prognostic factors for early severity that were identified were used as the basis of a predictive tool, which will be validated in another cohort. This tool should make it possible to identify subgroups at risk of early severe disease and should facilitate therapeutic studies.

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Key Words
children, multiple sclerosis, cohort, multivariate analysis, survival analysis

Abbreviations
A1—first attack
A2—second attack
A3—third attack
MS—multiple sclerosis
DSS—disability status scale

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One of the main aims of clinical epidemiology is to identify prognostic factors for severity and to score them. Such scoring is important because it improves patient information and treatment evaluation and makes it possible to control for potential confounding factors in pathophysiologic investigations.[1–4] This is particularly useful in chronic diseases with a highly variable course, such as multiple sclerosis (MS), but requires carefully designed cohorts of patients, accurate methods based on prospective observational studies, and survival-analysis methods.[3,5] Several adequately designed studies have identified prognostic factors for severe disability in adult MS patients, but only 3 cohort studies on childhood-onset MS, including ours, have been published.[6–12] Two of those studies used multivariate survival-analysis methods.[8,11,12] Other published studies based on case series, without the homogeneous inclusion criteria required for cohort studies, have been reviewed elsewhere.[13–15]

Our primary objective was to identify prognostic factors for severity, using multivariate survival-analysis methods, in a large unbiased cohort of patients with childhood-onset MS. Our secondary objective was to lay the foundation for the construction of a tool to predict early severity, for validation in another cohort. This tool will be used to constitute a useful score for childhood-onset MS. This score should facilitate the identification of subgroups of patients with high or low risk of early severe disease.

METHODS

Patients and Sources of Data

The cohort studied consisted of 197 children with 2 clinically defined attacks of acute inflammatory demyelination separated by >30 days. MS was defined on the basis of the clinical criterion of spatial and temporal dissemination, the standard method for MS diagnosis, as also recommended for adult studies.[16,17] The first attack (A1) had to have occurred between January 1990 and December 2003, before the age of 16 years (the date of onset of symptoms for A1 was taken as the date of onset of disease). Patients were recruited from the French national Kid Sclérose en Plaques neuropediatric cohort. During the inclusion period, we recruited all patients throughout France with a first demyelinating event who were being monitored at pediatric centers specializing in pediatric neurology, as described previously.[11,12] Four main centers participated in this study (2 in Paris, 1 in Lille, and 1 in Lyons), each of which contributed 20 to 28 patients (50% of the patients); another 3 centers (in Marseilles, Montpellier, and Toulouse) each contributed 10 to 15 patients (accounting for 18% of all patients), and the remaining centers each contributed <10 patients (32% of the patients). Exclusion criteria included previous neurologic abnormalities, infectious (including Lyme disease, if suggested by symptoms) or metabolic cause, and systemic immunologic disorders (including macrophage activation syndrome, if suggested by symptoms).

Patients were monitored from onset until June 2005, through routine clinical visits and regular telephone interviews. For 18 (9%) of the 197 patients with childhood-onset MS, follow-up monitoring ceased before June 2005 (no information available for >2 years). However, data obtained before the end of follow-up monitoring were available and were used in this study; 9 of these patients had a third attack (A3), and 5 suffered severe disability.

Data Collection

The baseline data collected included familial MS history, infection during the month preceding A1, age and detailed clinical, biological, and MRI characteristics at A1, date of second attack (A2), clinical characteristics at A2, and sequelae associated with A1 or A2, as reported previously.[11] All A1 MRI scans (brain MRI scans for all patients and spinal cord MRI scans for 53 patients) were reviewed by observers blinded to the clinical course, as described previously.[12] Two sets of MRI characteristics at onset, from previous studies that aimed to predict subsequent MS, were also studied, namely, childhood-onset MS MRI criteria, based on the presence of lesions perpendicular to the long axis of the corpus callosum and/or the presence of only well-defined lesions,[12] and the adult-onset MS criteria described by Barkhof et al.[18]

The data collected for disease course included the dates of subsequent attacks and of the occurrence of any disability. Data were obtained directly from the medical records kept by the pediatric neurologist treating the patient. An annual telephone questionnaire was used to perform follow-up assessments and to obtain additional data for secondary studies. Data were input into a computerized system approved by the Comité National Informatique et Liberté (the French data protection agency). Families were provided with written information and gave consent orally, to the referring physician, for participation in the study.

Outcomes

The outcomes studied were the occurrence of A3 or disability scores of ≥4 on the disability status scale (DSS).[19] Disability was considered irreversible if it persisted for ≥12 months. The 2 events were combined to define the outcome "severity," which was considered to have been reached at the time of occurrence of one of these events.

Statistical Analyses

Descriptive data were compared by using the χ^2 test or Fisher's exact test for proportions and the *t* test or Wilcoxon test for continuous measures. Time 0 for the

survival analysis was taken as the date of onset of symptoms for A2, which was considered to be the first cohort-defining episode. The end point was the date on which the outcome occurred. For event-free subjects, the follow-up period ended on the date of the last known visit. The Cox proportional-hazards model was used to evaluate the prognostic value of each covariate measured at onset. Variables with a significance level of $P < .20$ in univariate analyses were included in the multivariate regression analyses, with backward elimination being used to select the set of variables with independent prognostic significance. Variables with P values of $<.05$ were considered to be associated significantly with the survival function.

Parameters of the Childhood-Onset MS Potential Index for Early Severity

The index parameters were the exact hazard ratio values obtained in multivariate regression analyses. Variables with P values of $<.05$ were considered in the index. Weightings were combined through multiplication. The positive predictive value was calculated for each quartile of the childhood-onset MS potential index for early severity, as the proportion of children with an index in the given quartile who reached severity during the follow-up period (true-positive results divided by all results for the quartile, ie, true-positive results plus false-positive results). Survival curves were estimated for each quartile of the index, with the Kaplan-Meier method. Analyses were conducted with SPSS software for Windows (version 13; SPSS, Chicago, IL).

RESULTS

The median age at disease onset (A1) was 11.9 years (range: 2–16 years; mean ± SD: 11.3 ± 3.8 years). Onset occurred before the age of 6 years for 27 (14%) of the 197 children and before the age of 10 years for 59 (30%) of the 197 children. The median time between A1 and A2 was 7.8 months (range: 1–111 months; mean ± SD: 15.5 ± 20.5 months).

We first evaluated the baseline characteristics of the patients with childhood-onset MS in the cohort studied,

TABLE 1 **Baseline Characteristics According to Age at Onset for Patients With Childhood-Onset MS**

Characteristics	All ($n = 197$)	13–16 y ($n = 83$)	10–12 y ($n = 55$)	6–9 y ($n = 32$)	<6 y ($n = 27$)
Male gender, *n* (%)	72 (37)	26 (31)	19 (35)	16 (50)	11 (39)
Familial MS history, *n* (%)	16 (8)	7 (8)	4 (7)	3 (9)	2 (7)
Infection during the month preceding onset, *n* (%)	51 (26)	17 (21)	10 (19)	9 (28)	15 (56)
Symptoms at A1, *n* (%)					
Polysymptomatic	91 (46)	34 (41)	21 (38)	17 (53)	19 (70)
Long-tract dysfunction	128 (65)	55 (66)	29 (53)	24 (75)	20 (74)
Brainstem dysfunction	73 (37)	33 (40)	22 (40)	10 (31)	8 (30)
Transverse myelitis	14 (7)	2 (2)	5 (9)	4 (13)	3 (11)
Optic neuritis	67 (34)	27 (33)	24 (44)	10 (31)	6 (22)
Severe mental state changes	30 (15)	5 (6)	4 (7)	7 (22)	14 (52)
MRI at A1, *n* (%)					
Childhood-onset MS MRI criteria[a]	109 (55)	53 (64)	32 (58)	17 (53)	7 (26)
≥3 Barkhof criteria[b]	96 (49)	48 (58)	26 (47)	12 (38)	10 (37)
≥3 periventricular lesions	102 (52)	56 (68)	25 (46)	13 (40)	8 (30)
Juxtacortical and/or cortical lesion	112 (57)	49 (59)	30 (55)	17 (53)	16 (59)
Lesion in brainstem and/or cerebellum	99 (50)	43 (59)	31 (56)	13 (45)	12 (44)
Sum of lesions ≥9 and/or gadolinium enhancement	113 (57)	52 (63)	31 (56)	17 (53)	13 (48)
Lesion in thalamus and/or basal ganglia	48 (24)	14 (17)	13 (24)	11 (34)	10 (37)
Lesion in spinal cord (*n* studied = 53)	36 (18)	11 (13)	11 (20)	8 (25)	6 (22)
Cerebrospinal fluid findings at A1, *n* (%)					
Cell count of ≥10 cells per μL	84 (43)	36 (43)	19 (35)	13 (41)	16 (59)
Protein level of ≥5 g/dL	39 (20)	15 (18)	7 (13)	7 (22)	10 (37)
Oligoclonal bands before A2 (*n* studied = 168)	88 (45)	46 (55)	26 (47)	12 (38)	4 (15)
Sequelae of A1, DSS score of <4, *n* (%)	13 (7)	3 (4)	4 (7)	1 (3)	5 (19)
Time between A1 and A2, mo					
Mean ± SD	15 ± 20	12 ± 15	14 ± 16	21 ± 26	21 ± 26
Median (range)	8 (1–111)	6 (1–73)	8 (1–93)	12 (1–111)	10 (1–87)
Age at A2, y					
Mean ± SD	13 ± 4	16 ± 2	13 ± 2	10 ± 3	6 ± 3
Median (range)	13 (2–21)	15 (13–21)	13 (10–20)	9 (6–19)	5 (2–12)
Polysymptomatic A2, *n* (%)	64 (33)	23 (29)	18 (33)	10 (32)	13 (48)
Progressive course, *n* (%)	9 (5)	2 (2)	5 (9)	0 (0)	2 (7)

[a] Lesions perpendicular to the corpus callosum or only well-defined lesions.

[b] Three of the following criteria: ≥1 gadolinium-enhancing, T1-weighted lesion or ≥9 T2-weighted lesions, ≥1 infratentorial T2-weighted lesion, ≥1 juxtacortical T2-weighted lesion, or ≥3 periventricular lesions.

focusing in particular on age at onset (Table 1). The proportion of boys with early onset was greater than that of boys with late onset (46% for age at onset of <10 years, compared with 33% for age at onset of >10 years). Younger and older patients differed significantly with respect to several characteristics. Younger patients were more likely to have had infections during the month preceding A1 (41% vs 20%). Clinical symptoms at A1 included more-frequent severe mental state changes (36% for age at onset of <10 years, compared with 9% for age at onset of >10 years), and such symptoms were more numerous for younger patients (multiple symptoms at onset: 61% vs 40%). On brain MRI scans obtained at A1, childhood-onset MS MRI criteria (41% vs 62%) and Barkhof criteria (≥3: 37% vs 54%) were observed less frequently for younger patients than for older patients. Oligoclonal bands were detected less frequently in cerebrospinal fluid from younger patients than in cerebrospinal fluid from older patients (27% vs 52%). The mean time between A1 and A2 was significantly longer for younger patients (<10 years of age at onset) than for older patients (>10 years of age at onset). Finally, very young children were more likely to display mild disability (DSS scores of 1–3) after A1 (19%, compared with 6% for all other patients).

The median duration of follow-up monitoring after A2 was 4.8 years (range: 0.5–15.5 years; mean ± SD: 5.5 ± 3.6 years); the duration did not vary significantly as a function of age at A1. The severity outcome was recorded for 144 children; 139 patients experienced A3 and 30 patients reached DSS scores of ≥4, but only 5 patients reached DSS scores of 4 before A3 (all after A2). Nine patients displayed secondary progression, and 8 of those patients reached DSS scores of 4 during the follow-up period. The results of multivariate Cox survival analysis are reported in Table 2. The frequency of severity was higher among girls, in the absence of severe mental state changes at onset, in the presence of childhood-onset MS MRI criteria at onset, and among patients with a time between A1 and A2 of ≤1 year and a progressive course. Age at onset was not retained as a prognostic factor, whether considered as a continuous variable or as a categorical variable according to age group. Similarly, neither the detection of an infection during the month preceding A1 nor the presence of Barkhof MRI criteria was retained as a prognostic factor.

The childhood-onset MS potential index for early severity was derived from multivariate Cox survival analysis. This index had a positive predictive value for severity of >35% for the 2 upper quartiles (Table 3). Figure 1 shows Kaplan-Meier curves for severity-free survival, as a function of index quartile. In quartile 1 (median index value: 1.91; range: 1–2.95), the mean time to a severity event was 75 months (median: 53 months). In quartile 2 (median index value: 4.3; range: 2.98–4.32), the mean time to severity was 41 months (median: 13 months). The mean time to severity was 26 months (median: 13 months) in quartile 3 (median index value: 5.63; range: 5.23–6.63) and 12 months (median: 7 months) in quartile 4 (median index value: 8.17; range: 8.17–23.9).

DISCUSSION

For this cohort of 197 patients with childhood-onset MS (the largest cohort studied to date), we showed, through survival analysis, that early severity was associated with being female, with 2 characteristics of the initial attack (the absence of severe mental state changes and the presence of childhood-onset MS MRI criteria), and with 2 characteristics of the initial course (<1 year between the first 2 attacks and a progressive course). It is difficult to establish a childhood-onset MS cohort without selection bias at the time of inclusion. An episode of acute central nervous system inflammatory demyelination in a child may be the first episode of childhood-onset MS. However, it may remain unique, with the characteristics of acute disseminated encephalomyelitis. Acute disseminated encephalomyelitis is more common than childhood-onset MS among children <10 years of age, and we showed that it is difficult to distinguish between these 2 conditions.[11] Published studies on prognostic factors for childhood-onset MS have been based largely on historical cohorts of patients monitored in adult neurology departments specializing in MS, with disease onset before 16 years of age.[8–10]

Our cohort was assembled from a larger cohort containing all patients with a first demyelinating event observed at French pediatric neurology centers during a

TABLE 2 **Cox Proportional-Hazard Models for Identification of Baseline Prognostic Factors for Severity (Occurrence of A3 or Severe Disability, ie, DSS Score of ≥4)**

	Severity Outcome Reached (n = 144), n (%)	Crude Hazard Ratio[a]	Hazard Ratio[a,b] (95% Confidence Interval)	P[b]
Female gender (n = 125)	98 (68)	1.54	1.45 (1.01–2.09)	.05
Time between A1 and A2 of ≤1 y (n = 134)	106 (73.5)	1.48	1.56 (1.07–2.28)	.02
Childhood-onset MS MRI criteria (n = 109)	94 (65.5)	2.29	1.89 (1.26–2.85)	<.01
No severe mental state changes (n = 167)	129 (89.5)	2.33	1.91 (1.05–3.49)	.04
Progressive course (n = 9)	9 (6)	2.39	2.93 (1.37–6.26)	<.01

[a] Reference category is 0 or the lowest.

[b] Multivariate regression analysis with backward elimination of variables, with Cox's proportional-hazard models.

TABLE 3 **Positive Predictive Value for Severity in Quartiles of the Childhood-Onset MS Potential Index for Early Severity**

Childhood-Onset MS Potential Index for Early Severity Quartiles[a] ($n = 197$)	Positive Predictive Value for Severity ($n = 144$), % (% of Subjects)
Quartile 1 ($n = 49$) (median index value: 1.91)	24 (16.7)
Quartile 2 ($n = 50$) (median index value: 4.30)	33 (22.9)
Quartile 3 ($n = 47$) (median index value: 5.63)	37 (25.7)
Quartile 4 ($n = 51$) (median index value: 8.17)	50 (34.7)

[a] The index parameters are the exact hazard ratio values obtained in multivariate regression analysis. Variables with *P* values of ≥.05 were not considered in the index. Weightings were combined through multiplication.

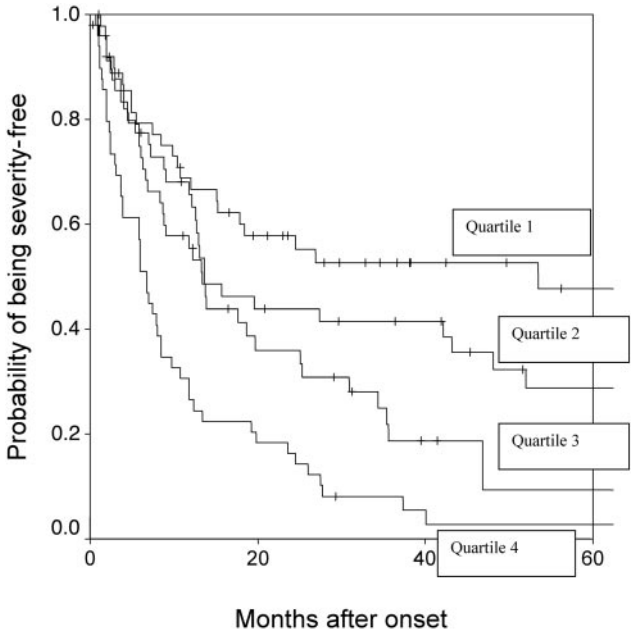

FIGURE 1
Kaplan-Meier curves for severity-free survival (free of A3 or DSS score of ≥4), according to quartiles of childhood-onset MS potential index for early severity. Top curve indicates quartile 1; second curve, quartile 2; third curve, quartile 3; bottom curve, quartile 4.

period of 14 years. From this larger cohort, we selected patients who demonstrated 2 clinically defined attacks separated by >30 days. This method of cohort assembly increased the representation of young patients; the median age at onset (defined as the onset of symptoms for A1) was 11.9 years in our cohort, with the disease beginning before the age of 10 years for 30% of the patients. The median age at onset was 14.3 years in the Italian cohort, with the disease beginning before the age of 10 years for 15.5% of the patients, whereas the Russian-Canadian cohorts exhibited a median age at onset of 13.5 years, with 20% of the patients being <10 years of age at the time of A1.[8–10] For patients >10 years of age at disease onset, the ratios of patients 10 to 13 years of age to patients 13 to 16 years of age were similar in the 3 cohorts. This finding is consistent with the underinclusion of younger patients and an age distribution skewed in favor of patients with adolescent-onset MS in previously studied cohorts. Because the true frequency and characteristics of the disease in younger patients were unknown, we first evaluated the baseline characteristics of patients with MS according to the age group at the time of A1. We found differences between age groups. Some of these differences were retained in the multivariate survival analysis, although age itself was not. These findings may have implications for the validity of certain results from previous studies. However, one possible bias not taken into account in our study was the effect of disease-altering interventions. This bias is a limitation of observational cohort studies of this type.

We chose to combine 2 events, A3 and severe disability, to define the outcome severity. This outcome was considered to have been reached as soon as 1 of these 2 events occurred, in accordance with previous results linking relapses in the first few years of the disease and subsequent severity.[8–11] Two previous studies reported that a large number of relapses in the first 1 or 2 years of disease increased the risk of secondary progression, which was also a prognostic factor for severe disability.[8,9] Finally, in a previous study of our cohort of all children monitored after the first demyelinating event, relapses (considered as a time-dependent variable) were found to be an independent prognostic factor for severe disability.[11] Relapses were not identified as a prognostic factor for disability in a recent adult-onset MS cohort study. However, relapses were considered only as a dichotomous variable (presence or absence during the course of the disease), without any time-dependent characteristics being taken into account.[20]

The prognostic factors for early severity were related to clinical characteristics at disease onset and differed from those in previous studies. Age at onset (>14 years) was retained as a prognostic factor in the Italian study[8] but not in ours. However, severe mental state changes at onset, a clinical characteristic that is more frequent among but is not restricted to young patients, was retained as a prognostic factor in our study. This factor was not considered in other studies. With our previous results being taken into account, this factor also protected against the occurrence of A2.[11] Sphincter involvement was retained as a prognostic factor in the Italian study,[8] whereas we did not consider this factor, instead studying long-tract dysfunction and myelitis. The detection on initial MRI scans of white-matter lesions perpendicular to the long axis of the corpus callosum and the presence of only well-defined lesions were also retained as prognostic factors for severity. We showed previously that these 2 MRI characteristics, which define the childhood-onset MS MRI criteria, were the best predictors of the occurrence of A2 after an initial demyelinating event.[18] Furthermore, these characteristics were predictive of early severity, whereas the Barkhof adult-onset MS criteria were not retained in the multivariate analysis in this study.

Two characteristics of the initial course were also retained as prognostic factors for severity. The first was secondary progression, which was identified as a prognostic factor in other studies of childhood-onset MS and adult-onset MS.[7–11,20,21] The second was a short interval between the first 2 attacks, a factor not evaluated in previous studies of childhood-onset MS but suggested as a prognostic factor in studies of adult-onset MS.[7]

The identification of prognostic factors for severity, with multivariate survival-analysis methods, can be used to prepare for the construction of a predictive tool. Some MS scoring systems for adult patients were designed for diagnostic or prognostic purposes, through consensus conferences, and do not take into account the specific features of childhood-onset MS.[5,16,17,22] If the childhood-onset MS potential index for early severity could be validated as a specific score for childhood-onset MS in subsequent studies with another cohort, then this score could be considered useful for classifying patients into subgroups according to the risk of an early severe course. This would make it possible to carry out therapeutic trials, taking the patients' level of risk into account.

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THE INFLUENCE OF ORAL HABITS ON THE DEVELOPING DENTITION AND THEIR TREATMENT: CLINICAL AND HISTORICAL PERSPECTIVES

"For uncounted millenniums, humans raised their children with mothers breast-feeding their children for 2 to 3 years. In some cultures the use of wet nurses was also common. In the mid 18th Century, Hunter, a Scottish doctor, emphasized the need for mothers to breast feed their children in order to minimize the risk of getting 'milk fever.' In more modern and industrialized societies, women started to schedule the breast feeding to set periods of 4 to 6 times per day. This, in turn, increased the child's need for additional sucking time to satisfy the sucking urge. In some cultures, it was common to provide the child with a knotted strip of clothes that enclosed honey or other foods for the child to suck on. The concept is similar to the use of the modern pacifiers introduced in the second part of the 19th Century. In many parts of the world, 80 to 90% of the children start a digit or pacifier sucking habit. For the child, it is especially difficult to break his thumb sucking habit since the finger is always available. As a result, the habit often leads to various malocclusions e.g. the maxillary arch is forced forward and the upper incisors become protruded. Pacifier sucking, on the other hand, often stops between 2 and 4 years of age. Pacifier sucking opens the bite and affects the transverse dimensions of the jaws, which manifest itself as a cross bite at the time of the eruption of the deciduous canines. These changes that accompany such habits could adversely affect the development of the dental arches. Therefore, dental occlusion should be evaluated periodically even in young children. Any malocclusion present should be diagnosed and if needed treated by the medical and dental professionals who are dealing with the well being of these children."

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