FIRST EPISODE OF ACUTE CNS INFLAMMATORY DEMYELINATION IN CHILDHOOD: PROGNOSTIC FACTORS FOR MULTIPLE SCLEROSIS AND DISABILITY

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Objectives To evaluate prognostic factors for second attack and for disability in children presenting with an initial episode of central nervous system (CNS) demyelination.

Study design A cohort of 296 children having a first episode of acute CNS inflammatory demyelination was studied by survival analysis.

Results The average follow-up was 2.9 ± 3 years. At the end of the follow-up, 57% of patients had a diagnosis of multiple sclerosis (MS), 29% had a monophasic acute disseminated encephalomyelitis, and 14% had a single focal episode. The rate of a second attack was (1) higher in patients with age at onset ≥10 years (hazard ratio, 1.67; 95% CI, 1.04-2.67), MS-suggestive initial MRI (1.54; 1.02-2.33), or optic nerve lesion (2.59; 1.27-5.29); and (2) lower in patients with myelitis (0.23; 0.10-0.56) or mental status change (0.59; 0.33-1.07). Of patients with a second attack, 29% had an initial diagnosis of acute disseminated encephalomyelitis. At the end of the follow-up period, 90% of patients had no or minor disability. Occurrence of severe disability was associated with a polysymptomatic onset (3.25; 1.16-11.01), sequelae after the first attack (26.65; 9.42-75.35), further relapses (1.49; 1.16-1.92), and progressive MS (3.57; 1.21-8.72).

Conclusions Risk of second attack of CNS demyelination is higher in older patients and lower in patients with mental status change. Risk of disability is higher in polysymptomatic and relapsing patients. *(J Pediatr 2004;144:246-52)*

Multiple sclerosis (MS) is regarded as infrequent in children, with 0.2% to 0.7% of total cases having their first episode before the age of 10 years and 2.7% to 4.4% before the age of 16, and it has a better disability prognosis compared with MS with adult onset.[1-7] Conversely, the frequency of acute disseminated encephalomyelitis (ADEM) in children is believed to be higher than in adults.[8-11] ADEM is a disseminated inflammation of the central nervous system (CNS) that is usually associated with multifocal neurologic symptoms and mental status change and remains typically monophasic. However, several recent series of children with ADEM have reported relapses, a situation virtually indistinguishable from MS in the absence of a specific biological characterization.[8,9,11] The prognosis for disability in ADEM is probably more favorable than initially described, according to recent case reports, series of patients, and a cohort study.[8-11]Finally, inflammation occurring at an isolated CNS site (transverse myelitis, optic neuritis, brainstem dysfunction) can also be monophasic or be followed by a further neurologic episode in another CNS site, qualifying for conversion to MS. Thus, more data on the

ADEM	Acute disseminated encephalomyelitis	MRI	Magnetic resonance imaging
CNS	Central nervous system	MS	Multiple sclerosis
DSS	Disability Status Scale		

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prediction of long-term evolution when a first episode of acute demyelination of the CNS occurs in childhood would be useful both for prognosis and therapeutic decisions.

We conducted a cohort study of 296 children who had a first episode of acute inflammatory demyelination of the CNS to determine the prognostic factors for a second attack in relation to the initial characteristics of the disease, including the initial diagnosis (ADEM, MS, or focal episode). Similarly, we evaluated the risk of disability according to the characteristics of the initial episode.

METHODS

Subjects

The cohort was identified through the French Neuropediatric Society. We included children under 16 years of age who had a first neurologic episode compatible with a first attack or the progressive onset of an inflammatory demyelinating disease of the CNS, identified between January 1985 (the date after which all patients could have MRI at the first attack) and June 2001. Patients were followed up during routine clinical visits from the onset of their condition until December 2001, and the outcome included further neurologic episodes and neurologic disability. Patients originated from 12 pediatric neurology reference centers disseminated throughout France (191/296, 65%), coming from three of them (Bicêtre and Saint-Vincent de Paul Hospitals in Paris, Roger Salengro Hospital in Lille). There was no difference in the rate of a second attack in relation to periods of inclusion and no difference in the duration of the follow-up period between centers and in relation to the initial and final diagnoses. Exclusion criteria included a preceding neurologic abnormality, infectious or metabolic cause, and systemic immunologic disorder.

Data Collection

Data were obtained directly from the medical records by the investigators and entered on the EDMUS system, which allows a systematic collection of medical information for patients with MS.[12] A validation was made by a blinded observer against the medical record for 30 randomly selected patients. Essential data were available for all patients (birth date, sex, onset date, symptoms, and clinical and radiologic characteristics at onset). Written consent was obtained from each referring practitioner to contact the patients' families. They were first contacted by letter for written consent and subsequently by telephone. A telephone questionnaire was used to validate residual disability and the incidence of further neurologic episode(s). Patients were designated as lost to follow-up (60/296, 20%) when their last data were more than 2 years old in December 2001, with no answer to a letter and a call to their neurologist or pediatrician. However, they contributed to the survival analysis up to the date of their last data.

Prognostic Factors and Outcomes

The prognostic factors under study included the patients' general characteristics and history before onset, the clinical presentation, neuroimaging findings and biology of cerebrospinal fluid at onset, and aspects of the disease evolution. Treatments were not considered in this analysis: All patients received steroids after the first attack, and other drugs (interferon [n = 42], azathioprine or cyclophosphamide [n = 17], and intravenous immunoglobulin [n = 22]) were prescribed in 67 disabled patients with further neurologic episodes during the course of the disease.

The onset of the initial inflammatory demyelinating disease of the CNS was described through the use of symptomatic and topographic classifications. Long-tract dysfunction was defined by the presence of motor, sensory, or sphincteric disturbances; optic neuritis, a suggestive decrease of visual acuity; brainstem dysfunction, motor or sensory facial, oculomotor, vestibular, or bulbar abnormalities; and a polysymptomatic onset, by more than one clinical finding. The diagnosis of ADEM at presentation relied on a polysymptomatic onset with mental status change and on suggestive brain MRI (poorly limited lesions, associated at the time with thalamus and/or basal ganglia lesions).[8-11] The diagnosis of definite or probable MS was made through the use of the Poser criteria.[13] The McDonald criteria were not used because they are not recommended before age 10 years.[14] We considered MRI as suggestive of MS when it demonstrated well-limited multiple lesions with periventricular and/or subcortical locations.[15] The diagnosis of suspected MS at presentation relied on these MRI criteria and compatible clinical criteria. At the end of follow-up, cases of ADEM at onset that had a second attack were classified as clinically definite MS, whereas others were designated as monophasic ADEM. Single focal episode was defined as a single episode of transverse myelitis, optic neuritis, or brainstem dysfunction not compatible with the ADEM diagnosis. Acute transverse myelitis was defined by using the accepted criteria as a focal inflammatory disorder of the spinal cord resulting in motor, sensory, and autonomic dysfunction.[16,17]

The outcomes included a second attack (first relapse), conversion to MS, and assignment of a score of 4 of irreversible disability. A relapse was defined as a new occurrence, after the initial event, of neurologic symptoms that lasted more than 24 hours and that stabilized or resolved either partially or completely. Fatigue alone or transient fever-related worsening of symptoms were not considered relapses. New symptoms that occurred within 1 month of clinical onset were considered to be part of the same episode. Progression of MS was defined as a continuous worsening of symptoms and signs for a period of at least 6 months, with or without superimposed relapses, either primarily (at onset of disease) or secondarily (after the first relapse). Neurologic disability was assessed at each visit at the clinic with the use of the Kurtzke Disability Status Scale (DSS).[18] We focused on scores of 4 (limited walking ability but able to walk without aid or rest for more than 500 m) and 6 (ability to walk with unilateral support no more than 100 m without rest). Disability was defined as irreversible when patients retained their given score for more than 6 months, excluding any transient worsening of disability related to relapses.

Table I. Baseline characteristics of patients with multiple sclerosis, monophasic acute disseminated encephalomyelitis, and a single focal episode according to final diagnosis at end of the follow-up period (%)

Data at first attack	All patients n = 296	Final diagnosis: MS[†] n = 168	Final diagnosis: Monophasic ADEM n = 85	Final diagnosis: Single focal episode[*] n = 43
Age at onset (y)				
Mean ± SD	9.9 ± 4.5	12 ± 3.4	7.1 ± 4.3	8.8 ± 4.7
Median (range)	11 (0.7–16)	13.1 (2–16)	6.4 (0.7–16)	9.8 (0.7–16)
Sex, male	127 (43)	55 (33)	48 (56)	24 (56)
Familial history MS	15 (5)	12 (7)	2 (2)	1 (2)
White	235 (79)	133 (79)	63 (74)	39 (91)
Infection during month preceding onset	94 (32)	27 (16)	43 (51)	24 (56)
Vaccination during 6 mo preceding onset	16 (5)	11 (7)	3 (4)	2 (4)
Symptoms at first attack				
Polysymptomatic	230 (78)	113 (67)	85 (100)	32 (74)
Transverse myelitis	42 (14)	13 (8)	2 (2)	27 (63)
Long-tract dysfunction	226 (76)	116 (69)	73 (86)	37 (86)
Brainstem dysfunction	121 (41)	61 (36)	47 (55)	13 (30)
Optic neuritis	67 (22)	58 (35)	6 (7)	3 (7)
Severe mental status change	85 (28)	21 (13)	64 (75)	0
Other symptoms	136 (46)	46 (27)	76 (89)	14 (32)
MRI at first attack				
Suggestive of ADEM	119 (40)	34 (11)	85 (100)	0
Suggestive of MS	96 (32)	96 (57)	0	0
Subtentorial lesion	196 (66)	121 (72)	73 (86)	2 (4)
Thalamus and/or basal ganglia lesion	47 (16)	13 (8)	34 (40)	0
Optic nerve lesion[§]	12 (4)	10 (6)	0	2 (4)
Subtentorial lesion	110 (37)	64 (38)	39 (46)	7 (16)
Spinal cord lesion	54 (18)	32 (19)	9 (11)	13 (30)
Tumor-like lesion	36 (12)	20 (12)	15 (18)	1 (2)
Gadolinium enhancement	64 (21)	47 (28)	9 (11)	8 (18)
Positive cerebral TDM at onset	39 (13)	22 (13)	16 (19)	1 (2)
CSF findings at first attack				
Cells ≥10/μL	118 (40)	62 (37)	43 (51)	13 (30)
Proteins ≥0.5 g/dL	71 (24)	31 (18)	31 (36)	9 (21)
Oligoclonal bands[‡]	72 (24)	68 (40)	4 (5)	0

CSF, Cerebrospinal fluid.
*Not compatible with the diagnosis of ADEM or MS.
†definite: n = 143 or probable: n = 25 (Poser criteria).
‡at any time during the follow-up period.
§259 patients studied.

Statistical Analyses

Descriptive data were compared by means of the χ^2 test or Fisher exact test for proportions and the *t* test or the Wilcoxon test for continuous measures. Time zero for the survival analysis was taken as the date of the very first cohort-defining episode. The end point was the date when the outcome occurred (second attack, qualifying for conversion to MS, or assignment of a score of 4 of irreversible disability).

For event-free subjects, the follow-up period ended on the date of the last known visit. Survival curves were estimated by means of the Kaplan-Meier method; the Cox proportional hazards model was used to evaluate the prognostic value of each factor measured at onset. A time-dependent Cox model was used to assess over time the effect of relapses on the onset of irreversible disability.[19] Variables with a significance level of $P < .20$ in the univariate analyses were selected to be entered

Table II. Patients with initial diagnosis of ADEM who had a second attack

Patients among total number of initial diagnosis of ADEM	34/119 (29%)
Age at onset (y)	
Mean ± SD	8.3 ± 4.2
Median (range)	6.7 (0.7–16)
No. of patients with >2 attacks*	17
Interval between first and second attack (y)	
Mean ± SD	1.6 ± 2.3
Median (range)	0.4 (0.2–9.4)
Interval between first and third attack (y)	
Mean ± SD	2.5 ± 2.3
Median (range)	1.8 (0.2–14.7)
Follow-up (y), mean ± SD	2.3 ± 2.7
No. of patients with CSF-positive OB†	6

*Eight patients had >3 attacks; second attack occurred within 3 or 6 months after the first attack for 13 and 18 patients respectively, among them 5 and 6 of who had a third attack.
†At any time during the follow-up period (not done for 5 patients).

into the multiple regression analysis, with backward elimination of variables to identify the set of variables with independent prognostic significance. A variable with a value of $P < .05$ was considered significantly associated with the survival function. All analyses were performed with the use of SPSS software for Windows (version 11.0) and SAS software.

RESULTS

The cohort included 296 children with a mean follow-up period of 2.9 ± 3 years (median, 1.9 years; range, 0.5 to 14.9), including 61 of 296 (21%) who were followed for more than 5 years. The characteristics of the group and those related to the final diagnosis at the end of the follow-up period are reported in Table I. The age at onset was significantly different among the three groups of patients, patients with ADEM being the youngest. MRI at onset was performed in all patients (brain: 264/296 [90%]; brainstem and spinal cord only: 32/296 [10%]; brain and spinal cord: 76/296 [26%]) and demonstrated CNS lesions in 261 of 296 (88%). Initial diagnosis was suggestive of MS in 96 of 296 (33%), ADEM in 119 of 296 (40%), and focal episode in 81 of 296 (27%) of subjects.

The proportion of patients with an initial diagnosis of MS who relapsed was 80 of 96 (83%). Among them, 58 of 96 (60%) had more than 1 relapse. After 2 years, 156 of 296 (53%) of all studied patients had a second attack and met the criteria for final diagnosis of MS. At the end of the follow-up period, 168 of 296 (57%) patients met the criteria for final diagnosis of MS. Monophasic ADEM was the final diagnosis for 85 of 296 (29%) of patients at the end of the follow-up period. A final diagnosis of single focal episode concerned 43 of 296 (14%) of the patients. Thus, among 168 patients with MS diagnosis, 34 (20%) were considered to have ADEM at clinical onset, but the occurrence of a second attack modified the final diagnosis. This group also represents 34 of 119 (29%) of all patients

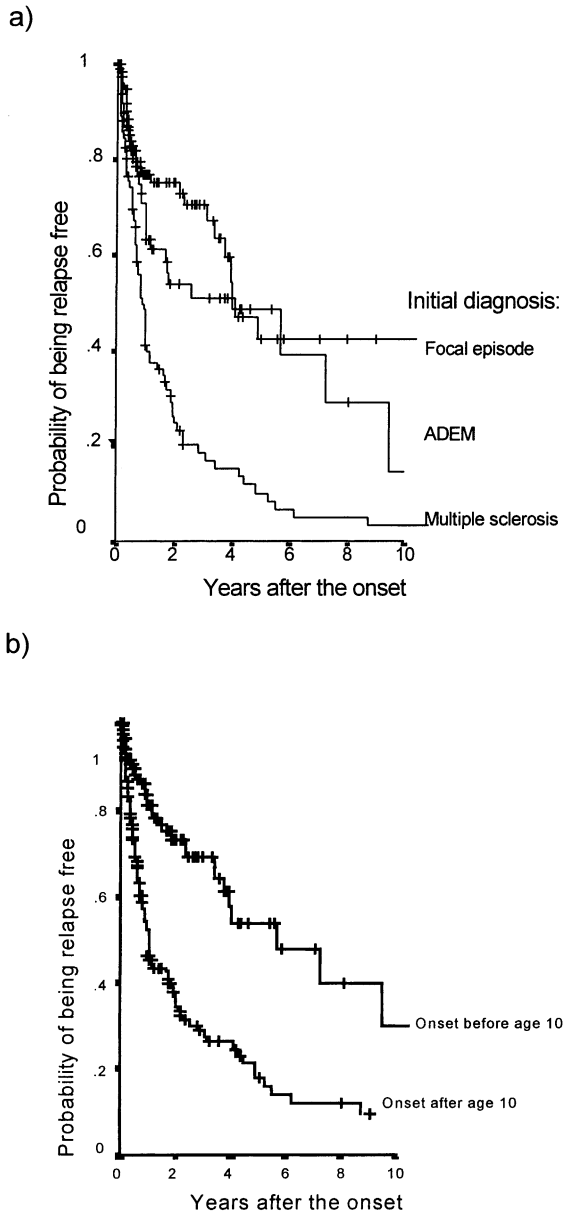

Fig 1. Kaplan-Meier estimates of the time interval between first and second attacks. **a**, According to initial diagnosis: initial MS diagnosis (especially on MRI criteria), ADEM, and focal episode ($P < .001$, calculated with the use of the log-rank test). **b**, According to age at the first attack: less than age 10 years, age 10 or older ($P < .001$, calculated with the use of the log-rank test).

initially diagnosed with ADEM; its characteristics are given in Table II. Moreover, among patients with MS diagnosis, 9 (5%) were considered to have a focal episode at the first attack (transverse myelitis, 2/29; brainstem dysfunction, 4/17; optic neuritis, 3/8). Six patients had conversion to progressive MS during evolution: 1 primarily and 5 secondarily. Figure 1 shows the survival functions in relation to the time preceding the second attack according to initial diagnosis and age at onset. The median time for the second attack is 1 year after initial diagnosis of MS and 4 years after initial diagnosis of ADEM or focal episode. For patients with onset before age 10 years, the median time for the second attack is 6 years after the

Table III. Multivariate analysis of prognosis factors for a second attack

	No. of patients (%)	Hazard ratio (95% CI)	*P* value
Age at onset ≥10 y	171 (56)	1.67 (1.04–2.67)	.03
MRI suggestive of MS at onset	96 (32)	1.54 (1.02–2.33)	.04
Optic nerve lesion on MRI at onset	12 (4)	2.59 (1.27–5.29)	.009
Myelitis at onset	42 (14)	0.23 (0.10–0.56)	.001
Severe mental status change	85 (29)	0.59 (0.33–1.07)	.08

initial episode compared with 1 year for those with onset after age 10. In multivariate Cox analysis, the rate of a second attack was closely associated with age at onset, the presence of myelitis, optic nerve lesions and severe mental state change at onset, and MRI at onset that was suggestive of MS (Table III). Initial diagnosis of ADEM was a significant protective prognosis factor for a second attack in univariate analysis (hazard ratio [HR], 0.48; 95% CI, 0.32-0.70, $P < .001$) but not in multivariate analysis.

By the end of the follow-up period, 267 of 296 (90%) of patients had either no impairments (83%, 245/296) or a disability score between 1 and 3 (7%, 22/296). This percentage was similar in patients with MS and patients with ADEM, at 149 of 168 (89%) and 78 of 85 (92%), respectively. A score of 4 or more was reached by 31 of 296 (10%) patients (18/168, 11%) with MS and 6 of 85 (7%) with ADEM. A score of 6 or more was reached by 14 of 296 (5%). One patient died. Figure 2 shows the survival functions in relation to the time preceding the assignment of an irreversible disability score of 4 for the entire cohort and according to the sequelae after the first episode. The median time could not be calculated because less than 50% of patients had reached that point. The mean time for the assignment of an irreversible disability score of 4 is 11 years. For patients with sequelae after the first episode, the mean time for the assignment of an irreversible disability score of 4 is 5 years after the initial episode compared with 12 years for those without sequelae after the first episode. In multivariate Cox analysis, the rate of an irreversible disability score of 4 was closely associated with sequelae after the first episode, relapses, polysymptomatic onset, and progression during evolution (Table IV). Age at onset was not a significant prognosis factor for disability either in multivariate or univariate analyses.

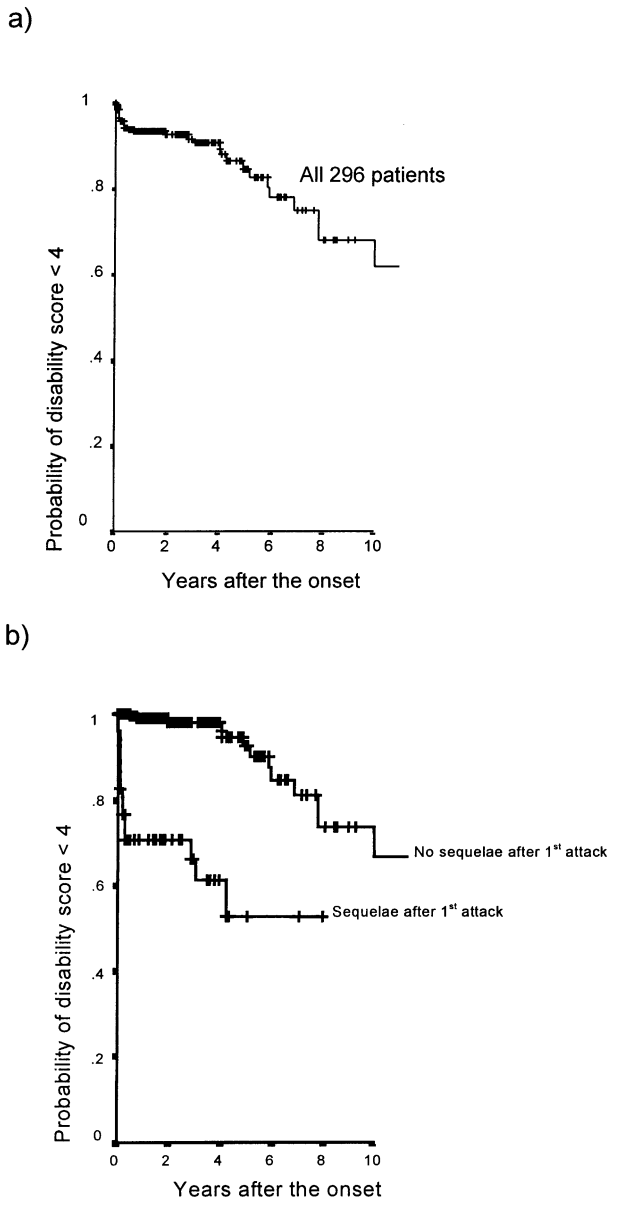

Fig 2. Kaplan-Meier estimates of the time interval between onset of the disease and assignment of an irreversible disability DSS score of 4 or more. **a**, All patients; **b**, sequelae (DSS score ≥1) or no sequelae (DSS score = 0) after the first attack *(P* < .001, calculated with the use of the log-rank test).

DISCUSSION

This study applies wide inclusion criteria not related only to ADEM or MS but to a first acute inflammatory event of demyelination of the CNS in childhood, to assess long-term evolution without bias caused by mode of inclusion. To improve the accuracy of data (history before the onset, MRI at the first attack) we limited the date of eligibility and maintained a homogeneous geographic area. The cohort is representative of patients that are referred to neuropediatric centers for a first episode of acute CNS inflammatory demyelination in childhood and is not population-based. Most published series of pediatric patients with acute CNS inflammatory demyelination described either childhood-onset MS, isolated or nested in adult neurology wider cohorts, ADEM, or focal episodes, especially myelitis or optic neuritis and have the same limitation concerning data collection.[1,2,5-11,16,20-25] When considering our patients gathered in three groups according to the final diagnosis, they shared the general characteristics of those series. Two points should be emphasized. First, patients with ADEM

Table IV. Multivariate analyses of prognosis factors of irreversible disability score of 4 or more

	No. of patients (%)	Hazard ratio (95% CI)	*P* value
Relapses (time-dependent variable)	140 (47.5)	1.49 (1.16–1.92)	.002
Sequelae after first episode	53 (18)	26.65 (9.42–75.35)	< .0001
Polysymptomatic at onset	230 (78)	3.25 (1.16–11.01)	.02
Progressive evolution	6 (2)	3.57 (1.21–8.72)	.03

diagnosis were slightly older than patients with ADEM in other series. Second, the number of patients with isolated optic neuritis was low because most cases of isolated optic neuritis are treated in ophthalmology departments. We observed that an optic nerve lesion on MRI was a risk factor for conversion to MS, but, given the underreporting, it might be a measurement bias because of more accurate description of the lesions in patients with suspected MS. Hospital-based selection bias is possible but limited because most pediatric patients are referred at least once to a reference center. An effort was also made to obtain long-term information from patients by letter and telephone.

The rate of a second attack in patients with ADEM at onset (29%) was of special interest because relations between ADEM and MS are controversial.[26] The usual definition of ADEM is a monophasic disease, but relapses that occur at different sites and times are reported in 10% (8/84), 13% (4/31), and 20% (7/35) of patients in three other studies with ADEM diagnosis criteria in childhood, similar to ours, and were reported in other studies in adults.[8,9,11,27,28]Obviously, the risk of observing a relapse depends on the length of the follow-up period. Analysis of the early course of our cohort already represents the whole possible spectrum of evolution. The survival curves showed that the second attack occurs later if the initial diagnosis is ADEM (compared with MS) or if the first attack is before the age of 10 years (compared with a later onset). Moreover, within the follow-up period, half of patients with ADEM who had a relapse had a third attack, further supporting the diagnosis of MS in a large subgroup of patients initially diagnosed as ADEM.

The favorable evolution of the patients with ADEM was similar to that observed in another cohort.[11] In the current study, an irreversible disability score of 4 on the DSS occurred more often in patients with initial sequelae (even minor) after the first episode, which is consistent with a previous report on patients with childhood-onset MS.[20] Progression during evolution of MS was also a poor prognostic factor for disability in this study, as reported in adult patients.[3,4,29,30] Polysymptomatic onset was another prognostic factor in our cohort, as was the occurrence of relapses, the latter being considered as a time-dependent variable. In an adult MS cohort, relapses as a dichotomous variable are not a prognostic factor for disability.[30] Nevertheless, recent prospective studies suggest that there is an association between the prognosis of disability in childhood-onset MS and the number of relapses in the first 2 years.[6,7,20]

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APPENDIX

Y. Mikaeloff coordinated the study and wrote the first draft with S. Suissa and M. Tardieu. The study was designed and supervised by G. Ponsot, C. Confavreux, and M. Tardieu. L. Vallée and C. Lubetzki were major contributors of the KIDMUS study group. All investigators contributed to data interpretation and revision of the article. Y. Mikaeloff and S. Suissa were responsible for statistical analyses.

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