ORIGINAL ARTICLE

Natural History of Multiple Sclerosis with Childhood Onset

Christel Renoux, M.D., Sandra Vukusic, M.D., Yann Mikaeloff, M.D.,
Gilles Edan, M.D., Michel Clanet, M.D., Bénédicte Dubois, M.D.,
Marc Debouverie, M.D., Bruno Brochet, M.D., Christine Lebrun-Frenay, M.D.,
Jean Pelletier, M.D., Thibault Moreau, M.D., Catherine Lubetzki, M.D.,
Patrick Vermersch, M.D., Etienne Roullet, M.D., Laurent Magy, M.D.,
Marc Tardieu, M.D., Samy Suissa, Ph.D., and Christian Confavreux, M.D.,
for the Adult Neurology Departments KIDMUS Study Group*

ABSTRACT

BACKGROUND

The course and prognosis of childhood-onset multiple sclerosis have not been well described.

METHODS

We used data from 13 adult neurology departments affiliated with the European Database for Multiple Sclerosis (EDMUS) network to identify a cohort of 394 patients who had multiple sclerosis with an onset at 16 years of age or younger and a comparison group of 1775 patients who had multiple sclerosis with an onset after 16 years of age. We determined the initial clinical features, the dates of disease onset, and the occurrence of outcomes, including relapse, conversion to secondary progression, and irreversible disability as measured by scores of 4 (limited walking ability but ability to walk more than 500 m without aid or rest), 6 (ability to walk with unilateral support no more than 100 m without rest), and 7 (ability to walk no more than 10 m without rest while using a wall or furniture for support) on the Kurtzke Disability Status Scale (range, 0 to 10; higher scores indicate more severe disability).

RESULTS

For patients with childhood-onset multiple sclerosis, the estimated median time from onset to secondary progression was 28 years, and the median age at conversion to secondary progression was 41 years. The median times from onset to disability scores of 4, 6, and 7 were 20.0, 28.9, and 37.0 years, respectively, and the corresponding median ages were 34.6, 42.2, and 50.5 years. In comparison with patients with adult-onset disease, those with childhood-onset disease were more likely to be female than male (female:male ratio, 2.8 vs. 1.8), were more likely to have an exacerbating–remitting initial course (98% vs. 84%), took approximately 10 years longer to reach secondary progression and irreversible disability, and reached these landmarks at an age approximately 10 years younger (P<0.001 for all comparisons).

CONCLUSIONS

Patients with childhood-onset multiple sclerosis take longer to reach states of irreversible disability but do so at a younger age than patients with adult-onset multiple sclerosis.

M ULTIPLE SCLEROSIS GENERALLY AF-
fects young adults between 20 and 40
years of age.[1] Onset occurs in childhood
(before the age of 16 years) in 0.4 to 10.5% of
cases.[2-11] There are few studies on the natural his-
tory of childhood-onset multiple sclerosis, and
most of these studies describe either single cases
or small series. The four largest series include no
more than 200 patients each.[12-15] There are still a
number of unresolved issues regarding childhood-
onset multiple sclerosis. The main objective of
our collaborative study was to describe the natu-
ral history of the disease and determine the prog-
nostic factors for disability in a cohort of patients
with onset of multiple sclerosis before or at the
age of 16 who were being seen in departments of
adult neurology affiliated with the European Data-
base for Multiple Sclerosis (EDMUS) network.
Another objective was to compare the course and
prognosis of childhood-onset and adult-onset
multiple sclerosis.

METHODS

PATIENT POPULATION, DATA COLLECTION, AND DEFINITION OF CASES

Patients were identified from the databases of 13
French and Belgian departments of adult neurol-
ogy participating in the EDMUS network.[16] Data
collection in these centers began in 1976 (Lyon) and
continued through 2001 (Dijon). All centers use the
EDMUS software and collect uniform information
about all patients with multiple sclerosis who have
been examined at least once as outpatients or in-
patients in the department. Information is collect-
ed by neurologists with a special interest in mul-
tiple sclerosis, in a retrospective fashion at the
time of the first visit, and prospectively thereaf-
ter. The EDMUS database has been approved by
the French Commission Nationale de l'Informatique
et des Libertés. Oral informed consent is obtained
from each patient before data are entered in the
database.

Patients included in the database have a diag-
nosis of definite or probable multiple sclerosis
according to the classification of Poser et al.,[17]
which is based on three criteria: dissemination
of lesions in time (at least two distinct neuro-
logic episodes in the course of the disease); spa-
tial dissemination of lesions in the central nervous
system, as demonstrated by clinical findings,
magnetic resonance imaging, computed tomog-
raphy, or testing of evoked potentials; and quan-
titative or qualitative abnormalities of IgG in the
cerebrospinal fluid. Cases are considered clinical-
ly definite when the first two criteria are met,
regardless of the results of the cerebrospinal
fluid test; laboratory-supported definite cases
meet the first and third or the second and third
criteria; clinically probable cases meet the first or
second criterion; and laboratory-supported prob-
able cases meet the third criterion.

We identified a cohort of patients with child-
hood-onset multiple sclerosis from data collected
through 2003 at all 13 centers. Data on eligible
patients were extracted automatically and validat-
ed with the source medical records by one of the
authors. For comparison with this group, we also
identified a cohort of patients with adult-onset
multiple sclerosis from data collected at the Lyon
center through April 1997. Data collected after
April 1997 were not used because only data col-
lected before this time had been validated from
the source medical records by one of the au-
thors.[18-21] Furthermore, before April 1997 almost
no patients had received currently acknowledged
disease-modifying therapies, and therefore this
cohort of patients with adult-onset multiple scle-
rosis can be regarded as essentially a natural-
history cohort.[18-21]

ASSESSMENT OF OUTCOMES

Relapse and the progressive phase of multiple
sclerosis were defined according to established
criteria.[16,18,22,23] The initial course was classified
as exacerbating–remitting or progressive. The over-
all course was classified as relapsing–remitting,
secondarily progressive, or progressive from the
onset.[16,18,23] Dates of onset of the disease, relapses,
and conversion to the progressive phase were re-
corded. Symptoms were classified as isolated op-
tic neuritis, isolated brain-stem dysfunction, isolat-
ed dysfunction of long tracts, or other symptoms
or combinations of symptoms.[16,18]

The Kurtzke Disability Status Scale (DSS) score
(range, 0 to 10, with higher scores indicating
more severe disability) was recorded at each visit to
determine the extent of neurologic disability.[24,25]
Focus was placed on scores that could be easily
assigned, even retrospectively. A score of 4 indi-
cates limited walking ability but able to walk more
than 500 m without assistance and without rest-
ing; a score of 6 indicates the ability to walk only
with unilateral support and no more than 100 m
without resting; and a score of 7 indicates the abil-
ity to walk no more than 10 m without resting

while using a wall or furniture for support. Disability was defined as irreversible when a given score persisted for at least 6 months, excluding transient worsening of disability related to relapses.[18]

PROGNOSTIC FACTORS

Potential prognostic factors considered were sex, age at onset of multiple sclerosis, whether the initial course of the disease was exacerbating–remitting or progressive, initial symptoms, the time interval between the first two neurologic episodes, the number of relapses during the first 2 years of the disease, and the decade of onset of multiple sclerosis.

STATISTICAL ANALYSIS

We performed descriptive analyses using the chi-square and Fisher's exact tests for categorical variables and the Student's t-test and the Wilcoxon test for continuous variables. We used the Kaplan–Meier method to estimate the time to secondary progression, the times to irreversible disability (DSS scores of 4, 6, and 7), and the ages at each of these outcomes. Comparisons between the childhood-onset and adult-onset cohorts were made by the log-rank test. Cox proportional-hazards models were used to identify factors associated with faster development of irreversible disability. Data from patients who had not yet reached the end point were censored at the date of their last visit. Three different time-to-event analyses were performed with three different reference times, depending on the factors under study. The first analysis was performed with the reference time defined as the onset of multiple sclerosis. To assess the prognostic value of the time between the first and the second neurologic episodes, the date of the second neurologic episode was used as the reference time. To assess the prognostic value of the number of relapses during the first 2 years of multiple sclerosis, 2 years after the onset of multiple sclerosis was used as the reference time. Statistical significance was defined by an alpha level of 0.05. All analyses were performed with SAS software for Windows, version 8.

RESULTS

CHILDHOOD-ONSET MULTIPLE SCLEROSIS
Patient Characteristics

Among the 17,934 patients at the 13 participating centers, 394 (2.2%) had multiple sclerosis starting at 16 years of age or younger, and 290 (73.6%) of these patients were women (Table 1). The mean (±SD) duration of disease at the end of the follow-up period was 17.1±13.2 years. At some point during the course of their disease, 231 patients (58.6%) received one or more disease-modifying treatments: interferon beta (36.5%), azathioprine (23.1%), mitoxantrone (12.9%), cyclophosphamide (7.1%), methotrexate (7.1%), glatiramer acetate (3.5%) and mycophenolate mofetil (1.3%). The patients had received azathioprine for an average of 8.6 years and interferon beta for an average of 10.6 years after the onset of the disease.

Onset of Disease

The mean age at the onset of multiple sclerosis was 13.7±2.4 years. Onset occurred at the age of 10 years or younger in 30 patients (7.6%), at 12 years or younger in 71 patients (18.0%), and at 14 years or younger in 159 patients (40.4%). Encephalitic signs, such as headache, vomiting, seizures, or disorders of consciousness, were present in 29 patients (7.4%). The initial course was exacerbating–remitting in all except nine patients (2.3%) who had a progressive initial course; these nine patients were all over 13 years of age at onset.

Course of Disease

The estimated median time between the first two neurologic episodes was 2.0 years. Among the 385 patients with an exacerbating–remitting initial course, 110 (28.6%) converted to secondary progression during follow-up. The estimated median time from the onset of multiple sclerosis to conversion to secondary progression was 28.1 years (95% confidence interval [CI], 25.0 to 32.1) (Fig. 1A). The estimated median age at conversion to secondary progression was 41.4 years (95% CI, 37.8 to 45.7) (Fig. 1B).

Time to Development of Irreversible Disability

The estimated median times from the onset of multiple sclerosis to the assignment of DSS scores of 4, 6, and 7 were 20.0 years (95% CI, 19.0 to 22.4), 28.9 years (95% CI, 27.0 to 33.0), and 37.0 years (95% CI, 34.0 to 42.2), respectively. These time intervals were longer for patients who were 12 years of age or younger at the onset of multiple sclerosis. However, the difference between those who were 12 years of age or younger and those who were older than 12 years at onset was significant only for time to a DSS score of 4 (median, 28.0 years [95% CI, 21.0 to 31.6] vs. 19.1 years [95% CI, 16.2 to 21.0]; P=0.02).

Table 1. Characteristics of 394 Patients with Onset of Multiple Sclerosis at the Age of 16 Years or Younger.*

Characteristic	All Patients (N=394)	Onset at ≤12 Yr (N=71)	Onset at >12 Yr (N=323)	P Value
Sex — no. (%)				0.4
Male	104 (26.4)	22 (31.0)	82 (25.4)	
Female	290 (73.6)	49 (69.0)	241 (74.6)	
Diagnosis — no. (%)†				0.5
Clinically definite	297 (75.4)	52 (73.2)	245 (75.9)	
Laboratory-supported definite	29 (7.4)	4 (5.6)	25 (7.7)	
Clinically probable	65 (16.5)	15 (21.1)	50 (15.5)	
Laboratory-supported probable	3 (0.8)	0	3 (0.9)	
Familial history of multiple sclerosis — no. (%)				0.8
Yes	53 (13.5)	7 (9.9)	46 (14.2)	
No	328 (83.2)	61 (85.9)	267 (82.7)	
Unknown	13 (3.3)	3 (4.2)	10 (3.1)	
Age at onset of multiple sclerosis — yr				
Mean	13.7±2.4	9.5±2.3	14.6±1.1	<0.001
Median	14.5	10.3	14.9	
Range	1.5–16.0	1.5–11.9	12.1–16.0	
Initial symptoms — no. (%)				0.9
Isolated optic neuritis	92 (23.4)	18 (25.4)	74 (22.9)	
Isolated brain-stem symptoms	66 (16.8)	14 (19.7)	52 (16.1)	
Isolated long-tract symptoms	149 (37.8)	23 (32.4)	126 (39.0)	
Other symptoms or combination of symptoms	87 (22.1)	16 (22.5)	71 (22.0)	
Initial course of multiple sclerosis — no. (%)				0.4
Exacerbating–remitting	385 (97.7)	71 (100)	314 (97.2)	
Progressive	9 (2.3)	0	9 (2.8)	
Kaplan–Meier estimate of time between first 2 relapses — yr				
Mean	5.0±0.4	7.3±1.0	4.5±0.4	0.005
Median	2.0	4.6	2.0	
Range	0–40.8	0–40.1	0–40.8	
No. of relapses during the first 2 yr‡				
Mean	1.9±1.4	1.6±0.9	2.0±1.5	0.04
Median	1	1	1	
Range	1–10	1–4	1–10	
Duration of multiple sclerosis at last follow-up — yr				
Mean	17.1±13.2	22.6±15.6	15.8±12.3	<0.001
Median	15.0	20.9	14.1	
Range	0.01–69.04	0.20–69.04	0.01–60.51	

* Plus–minus values are means ±SD. Percentages may not sum to 100 because of rounding.
† The diagnoses were made according to the classification of Poser et al.[17]
‡ Data are for the 354 patients who had had multiple sclerosis for at least 2 years.

When the time of onset of multiple sclerosis was used as the reference time in multivariate analysis, the nature of the initial course was the only significant prognostic factor: a progressive onset was associated with shorter times to reach irreversible disability (Table 2). At the time of the second neurologic episode, the time interval between the first two neurologic episodes did not show any consistent effect on the time to reach irreversible disability. Two years after onset, the main prognostic factor remained a progressive course at onset. The other significant prognostic factor was the number of relapses during the first 2 years of the disease, with each additional relapse increasing the rate of disability by 31 to 41%. Age at onset of multiple sclerosis was not a prognostic factor for time to development of disability, either as a continuous variable or as a categorical variable with cutoff at 10 or 12 years (data not shown). The neurologic department at which the patient was seen did not influence the time to development of irreversible disability in any analysis (data not shown).

Age at Development of Irreversible Disability

The estimated median ages at assignment of DSS scores of 4, 6, and 7 were 34.6 years (95% CI, 31.2 to 36.0), 42.2 years (95% CI, 40.5 to 46.9), and 50.5 years (95% CI, 47.1 to 64.8), respectively. The only significant prognostic factor for age at development of irreversible disability was the initial course of the disease: a progressive initial course was associated with a younger age of development of disability (adjusted hazard ratios, 2.94 [95% CI, 1.34 to 6.42] for a DSS score of 4, 4.48 [95% CI, 2.01 to 10.00] for a DSS score of 6, and 3.13 [95% CI, 1.18 to 8.28] for a DSS score of 7).

COMPARISON OF CHILDHOOD-ONSET AND ADULT-ONSET MULTIPLE SCLEROSIS

Patient Characteristics

The cohort of patients with adult-onset multiple sclerosis included 1775 patients, 64.1% of whom were women. The mean age at onset of multiple sclerosis was 32.2±9.9 years (median, 30.8), and the mean duration of disease was 11.5±9.3 years (median, 9.7). The female:male ratio was higher in the childhood-onset cohort than in the adult-onset cohort (2.8 vs. 1.8, P<0.001).

Onset of Disease

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). Encephalitic symptoms were observed in 7% of patients with childhood-onset disease and were virtually absent in patients with adult-onset disease. The initial course of multiple sclerosis was more often exacerbating–remitting in patients with childhood-onset multiple sclerosis than in patients with adult-onset disease (97.7% vs. 84.3%, P<0.001).

Course of Disease

The estimated median time from the onset of multiple sclerosis to the second neurologic episode did not differ significantly between patients with childhood-onset and those with adult-onset disease (2.0 vs. 2.2 years, P=0.2). The estimated median time to conversion to secondary progression was approximately 10 years longer (P<0.001), and the estimated median age at conversion to secondary progression was approximately 10 years younger (P<0.001), in patients with childhood-onset disease than in patients with adult-onset disease (Fig. 1).

Time to Development of Irreversible Disability

As shown in Figure 1, the estimated median times to assignment of DSS scores of 4, 6, and 7 were approximately 10 years longer in patients with childhood-onset multiple sclerosis than in patients with adult-onset multiple sclerosis (P<0.001 for all comparisons). Once a score of 4 was attained, the median time to reach a score of 6 was 6.0 years (95% CI, 5.0 to 7.0) for patients with childhood-onset disease and 5.7 years (95% CI, 5.0 to 6.4) for those with adult-onset disease (P=0.4). Similarly, after a score of 6 was reached, the median time to reach a score of 7 was 4.9 years (95% CI, 3.5 to 6.5) for patients with childhood-onset disease, as compared with 3.4 years (95% CI, 3.0 to 4.0) for patients with adult-onset disease (P=0.2). The median time to reach a score of 7 once a score of 4 was reached was 12.2 years (95% CI, 10.7 to 15.6) for patients with childhood-onset disease and 12.2

years (95% CI, 11.0 to 14.7) for patients with adult-onset disease (P=0.8).

Age at Development of Irreversible Disability
On average, patients with childhood-onset disease reached DSS scores of 4, 6, and 7 at an estimated median age 10 years younger than did patients with adult-onset disease (P<0.001 for all comparisons) (Fig. 1).

DISCUSSION

This large, collaborative, multicenter, observational study revealed several distinctive features of childhood-onset multiple sclerosis. The female:male ratio was high (2.8). The initial course of the disease was exacerbating–remitting in 98% of the patients. The estimated median time from onset of disease to conversion to secondary progression was 28 years, and the median age at conversion was 41 years. The estimated median times from the onset of multiple sclerosis to the assignment of DSS scores of 4, 6, and 7 were 20.0, 28.9, and 37.0 years, respectively, and the corresponding estimated median ages were 34.6, 42.2, and 50.5 years. In comparison with a representative cohort of patients with adult-onset multiple sclerosis, the patients with childhood-onset multiple sclerosis were more likely to be female; were more likely to have isolated optic neuritis, isolated brain-stem syndrome, or encephalitic symptoms at presentation; were more likely to have an exacerbating–remitting initial course of the disease; and took 10 years longer to convert to secondary progression and to reach disability landmarks but did so at an age 10 years younger.

All patients were recruited from the French and Belgian EDMUS network. In France, this network covers the entire country uniformly and includes all departments of adult neurology with acknowledged interest in the care of patients with multiple sclerosis. Each of the 13 participating departments acts as a referral center for multiple sclerosis in its area, and case acquisition is performed in a similar manner in all of them.

A potential source of selection bias could have been that some patients with childhood-onset multiple sclerosis may not have been seen in adult neurology departments because they had either very severe disease, leading to death before adulthood, or very benign disease, requiring no specialized consultation during adulthood. We think

Figure 1 (facing page). Kaplan–Meier Estimates of the Time to (Panel A) and the Age at (Panel B) Conversion to Secondary Progression and of the Time to (Panels C, E, and G) and the Age at (Panels D, F, and H) Assignment of Scores According to the Kurtzke Disability Status Scale (DSS), among Patients with Childhood-Onset and Those with Adult-Onset Multiple Sclerosis.

Panels A and B refer to the subgroup of patients with an exacerbating–remitting initial course of multiple sclerosis (385 patients with childhood-onset disease and 1496 patients with adult-onset disease). Panels C through H refer to the entire population of patients with multiple sclerosis (394 with childhood-onset disease and 1775 with adult-onset disease). Panels A, C, E, and G include median number of years and 95% confidence intervals, and Panels B, D, F, and H include median age and 95% confidence intervals. Irreversible-disability scores on the DSS[24,25] range from 0 to 10, with higher scores indicating more severe disability. A score of 4 indicates limited walking ability but the ability to walk more than 500 m without assistance and without resting, 6 indicates the ability to walk with unilateral support no more than 100 m without resting, and 7 indicates the ability to walk no more than 10 m without resting while using a wall or furniture for support.

both situations are rare. When we looked at our cohort of patients with childhood-onset multiple sclerosis, we did not find that the center had any effect on the outcome. In the Lyon EDMUS database, which contributed 34% of the cohort with childhood-onset multiple sclerosis and the entire cohort with adult-onset disease, case acquisition and data collection have been performed simultaneously and similarly for childhood-onset and adult-onset cases since 1976.

Another 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. However, for this bias to occur, the probability of a diagnosis of multiple sclerosis in patients with optic neuritis must be higher in only one study group; if the diagnosis is more likely in both child and adult patients with optic neuritis at the onset of disease, then there is no potential for bias. Even if a diagnosis of multiple sclerosis were more likely in patients with childhood-onset multiple sclerosis presenting with optic neuritis, the presence of symptoms other than optic neuritis at onset would probably only delay the time to the diagnosis of multiple sclerosis and not reduce the probability of the diagnosis itself. Because our study recruited patients
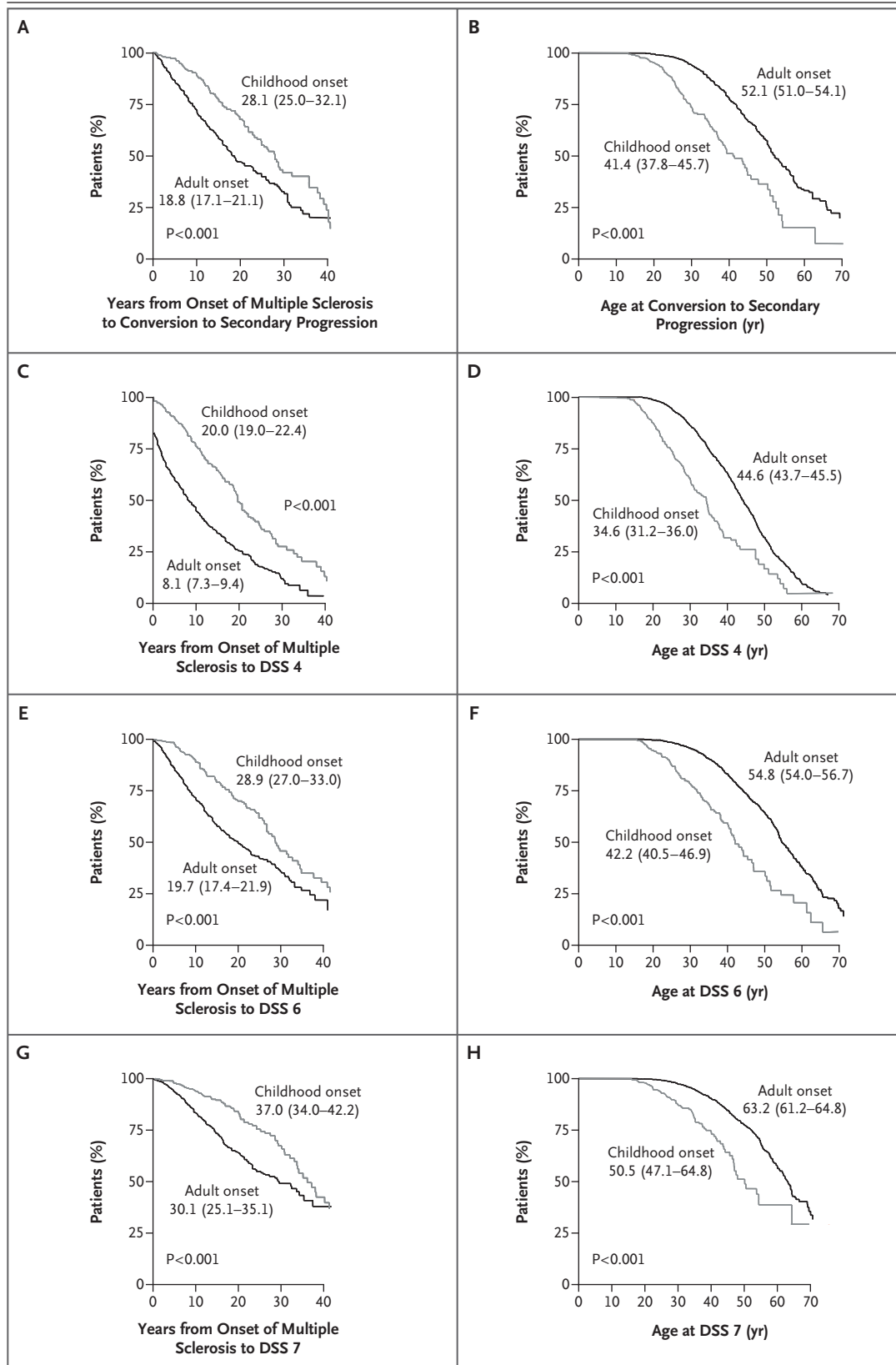
A

Childhood onset
28.1 (25.0–32.1)

Adult onset
18.8 (17.1–21.1)

P<0.001

Years from Onset of Multiple Sclerosis
to Conversion to Secondary Progression

B

Adult onset
52.1 (51.0–54.1)

Childhood onset
41.4 (37.8–45.7)

P<0.001

Age at Conversion to Secondary
Progression (yr)

C

Childhood onset
20.0 (19.0–22.4)

P<0.001

Adult onset
8.1 (7.3–9.4)

Years from Onset of Multiple
Sclerosis to DSS 4

D

Adult onset
44.6 (43.7–45.5)

Childhood onset
34.6 (31.2–36.0)

P<0.001

Age at DSS 4 (yr)

E

Childhood onset
28.9 (27.0–33.0)

Adult onset
19.7 (17.4–21.9)

P<0.001

Years from Onset of Multiple
Sclerosis to DSS 6

F

Adult onset
54.8 (54.0–56.7)

Childhood onset
42.2 (40.5–46.9)

P<0.001

Age at DSS 6 (yr)

G

Childhood onset
37.0 (34.0–42.2)

Adult onset
30.1 (25.1–35.1)

P<0.001

Years from Onset of Multiple
Sclerosis to DSS 7

H

Adult onset
63.2 (61.2–64.8)

Childhood onset
50.5 (47.1–64.8)

P<0.001

Age at DSS 7 (yr)

Table 2. Multivariate Analysis of Prognostic Factors of the Time to the Assignment of Irreversible-Disability Scores of 4, 6, and 7 in 394 Patients with Onset of Multiple Sclerosis before 16 Years of Age.*

Variable	DSS 4		DSS 6		DSS 7	
	Crude Hazard Ratio	Adjusted Hazard Ratio (95% CI)	Crude Hazard Ratio	Adjusted Hazard Ratio (95% CI)	Crude Hazard Ratio	Adjusted Hazard Ratio (95% CI)
Date at onset of multiple sclerosis						
Age at onset	1.06	1.04 (0.98–1.12)	1.05	1.04 (0.96–1.12)	1.04	1.00 (0.92–1.09)
Female sex	1.10	1.09 (0.75–1.57)	1.02	1.02 (0.66–1.58)	0.81	0.79 (0.46–1.34)
Progressive course at onset	3.10	2.96 (1.36–6.49)	5.32	4.76 (2.13–10.64)	3.67	3.13 (1.18–8.30)
Symptoms at onset						
Isolated optic neuritis (reference)						
Isolated brain-stem symptoms	1.07	1.09 (0.67–1.77)	0.89	0.91 (0.49–1.70)	0.94	0.96 (0.45–2.03)
Isolated long-tract symptoms	0.87	0.84 (0.56–1.26)	0.98	0.94 (0.58–1.53)	1.00	0.97 (0.54–1.74)
Other symptoms or combination of symptoms	1.05	0.99 (0.60–1.63)	1.34	1.29 (0.74–2.25)	0.84	0.67 (0.31–1.42)
Decade of onset of multiple sclerosis	1.21	1.17 (1.00–1.36)	1.28	1.22 (1.00–1.48)	1.37	1.37 (1.06–1.77)
Date at second episode of multiple sclerosis†						
Age at onset	1.03	1.03 (0.96–1.10)	1.00	1.00 (0.93–1.08)	0.99	0.98 (0.89–1.08)
Female sex	1.18	1.08 (0.72–1.62)	1.07	1.00 (0.62–1.62)	0.81	0.68 (0.39–1.19)
Interval between 1st and 2nd episodes						
≤2 yr (reference)						
2–6 yr	0.80	0.72 (0.46–1.13)	0.78	0.74 (0.44–1.25)	0.46	0.38 (0.18–0.78)
>6 yr	1.04	0.91 (0.56–1.47)	1.28	1.21 (0.70–2.11)	1.29	1.19 (0.61–2.31)
Symptoms at onset						
Isolated optic neuritis (reference)						
Isolated brain-stem symptoms	0.66	0.69 (0.41–1.15)	0.61	0.64 (0.33–1.23)	0.68	0.67 (0.31–1.47)
Isolated long-tract symptoms	0.58	0.58 (0.38–0.88)	0.72	0.68 (0.41–1.13)	0.69	0.53 (0.28–1.01)
Other symptoms or combination of symptoms	0.63	0.65 (0.38–1.11)	0.87	0.88 (0.48–1.60)	0.61	0.46 (0.21–1.01)
Decade of onset of multiple sclerosis	0.98	0.94 (0.80–1.10)	0.95	0.96 (0.80–1.16)	0.97	1.04 (0.81–1.33)

with childhood-onset multiple sclerosis from departments of adult neurology, we included patients with a long duration of disease. Regardless of the symptoms at onset and the delay in diagnosis resulting from the initial presentation, all patients with childhood-onset multiple sclerosis were probably captured in our cohort. The likelihood that the presence of initial symptoms of optic neuritis led to a differential selection bias is therefore very low.

All participating centers used the EDMUS software with a standardized common language for each patient, thus producing a high level of homogeneity in the definition of clinical measures.[26] To ensure accuracy of the descriptions of initial disease presentation, we consulted the pediatric-department records of patients with childhood-onset disease whenever possible. Furthermore, records from departments of adult neurology were systematically reviewed for the current study.

About half of our patients with childhood-onset multiple sclerosis received immunoactive

Table 2. (Continued.)

Variable	DSS 4		DSS 6		DSS 7	
	Crude Hazard Ratio	Adjusted Hazard Ratio (95% CI)	Crude Hazard Ratio	Adjusted Hazard Ratio (95% CI)	Crude Hazard Ratio	Adjusted Hazard Ratio (95% CI)
2 Yr after onset of multiple sclerosis‡						
Age at onset	1.07	1.04 (0.96–1.11)	1.05	1.03 (0.96–1.11)	1.04	1.00 (0.91–1.09)
Female sex	1.13	1.07 (0.72–1.58)	0.99	0.94 (0.61–1.46)	0.79	0.73 (0.43–1.25)
Progressive course at onset	3.56	4.40 (1.96–9.88)	5.53	6.34 (2.76–14.61)	3.74	4.43 (1.61–12.19)
No. of relapses during 1st 2 yr	1.36	1.33 (1.16–1.54)	1.32	1.31 (1.10–1.56)	1.37	1.41 (1.13–1.76)
Symptoms at onset						
Isolated optic neuritis (reference)						
Isolated brain-stem symptoms	0.97	0.91 (0.54–1.51)	0.84	0.78 (0.41–1.48)	0.94	0.87 (0.40–1.86)
Isolated long-tract symptoms	0.78	0.71 (0.47–1.09)	0.98	0.88 (0.54–1.44)	1.00	0.88 (0.48–1.59)
Other symptoms or combination of symptoms	0.93	0.76 (0.45–1.29)	1.29	1.05 (0.59–1.87)	0.78	0.47 (0.21–1.06)
Decade of onset of multiple sclerosis	1.31	1.18 (0.99–1.40)	1.31	1.17 (0.96–1.44)	1.40	1.30 (0.99–1.70)

* Scores on the Kurtzke Disability Status Scale (DSS)[24,25] range from 0 to 10, with higher scores indicating more severe disability. A score of 4 indicates limited walking ability but the ability to walk more than 500 m without assistance and without resting; a score of 6 indicates the ability to walk only with unilateral support and no more than 100 m without resting; and a score of 7 indicates the ability to walk no more than 10 m without resting while using a wall or furniture for support. All analyses were adjusted for age at onset of disease, sex, symptoms at onset, and decade during which the onset occurred. For the analyses with onset of multiple sclerosis as the reference time, adjustments were also made for the initial course of the disease. For the analyses with a second episode of multiple sclerosis as the reference time, adjustments were also made for the interval between the first and the second episodes. For the analyses with 2 years after onset of multiple sclerosis as the reference time, adjustments were also made for the initial course of the disease and the number of relapses during these 2 years. CI denotes confidence interval.

† For the category of DSS 4, the data are from the 347 patients with an exacerbating–remitting onset of disease, a second neurologic episode, and no occurrence of a DSS score of 4 before the second episode. For the category of DSS 6, the data are from the 367 patients with an exacerbating–remitting onset of disease, a second neurologic episode, and no occurrence of a DSS score of 6 before the second episode. For the category of DSS 7, the data are from the 367 patients with an exacerbating–remitting onset of disease, a second neurologic episode, and no occurrence of a DSS score of 7 before the second episode.

‡ For the category of DSS 4, the data are from the 329 patients followed for at least 2 years after the onset of disease with no occurrence of a DSS score of 4 during these 2 years. For the category of DSS 6, the data are from the 352 patients followed for at least 2 years after the onset of disease with no occurrence of a DSS score of 6 during these 2 years. For the category of DSS 7, the data are from the 353 patients followed for at least 2 years after the onset of disease with no occurrence of a DSS score of 7 during these 2 years.

drugs. None of these drugs has a proven effect on the long-term development of disability.[27] The treatments were usually given a long time after the onset of multiple sclerosis and therefore could not have modified the early course of the disease. However, we cannot definitively rule out an effect of treatment on the long-term course of the disease. That said, treated patients had more severe disease than untreated patients, and removing them from the analysis would have led to overestimation of the times to development of irreversible disability. Data on patients with adult-onset disease were taken from the Lyon EDMUS database, which was locked in April 1997 at a time when almost no patients received currently acknowledged disease-modifying therapies.[18-21] About half of these patients received azathioprine at some point during the course of their disease, mainly during the relapsing–remitting phase, and not before the third relapse. Azathioprine has no proven effect on the development of irreversible disability in multiple sclerosis.[28]

Our results are consistent with those of other studies of childhood-onset multiple sclerosis from departments of adult neurology with regard to onset, course, prognosis, and clinical predictors of disability,[1,11-14,29-31] and in particular with regard to times to development of secondary progression and irreversible disability[14] and the ages at which these events occur.[11] Our results are also

consistent with those from the group recruited from pediatric neurology departments in the Kids with Multiple Sclerosis (KIDMUS) study, which included 296 children with a first episode of acute inflammatory demyelination of the central nervous system seen in French pediatric neurology departments.[15,32,33] Furthermore, the Lyon Natural History Multiple Sclerosis Cohort, from which our cohort of patients with adult-onset multiple sclerosis was extracted, has already been described extensively,[1,18-21] with results consistent with those from other major cohorts.[34-36] For these reasons, we think the present results, drawn entirely from one region of Europe, can be generalized to other populations.

In conclusion, despite a slower development of irreversible disability, patients with childhood-onset multiple sclerosis reach secondary-progression and disability milestones at ages approximately 10 years younger than do patients with adult-onset disease. Efforts to improve therapy for multiple sclerosis have focused on the population with adult-onset disease. Patients with childhood-onset multiple sclerosis clearly deserve similar attention.

APPENDIX

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