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).

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.

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 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

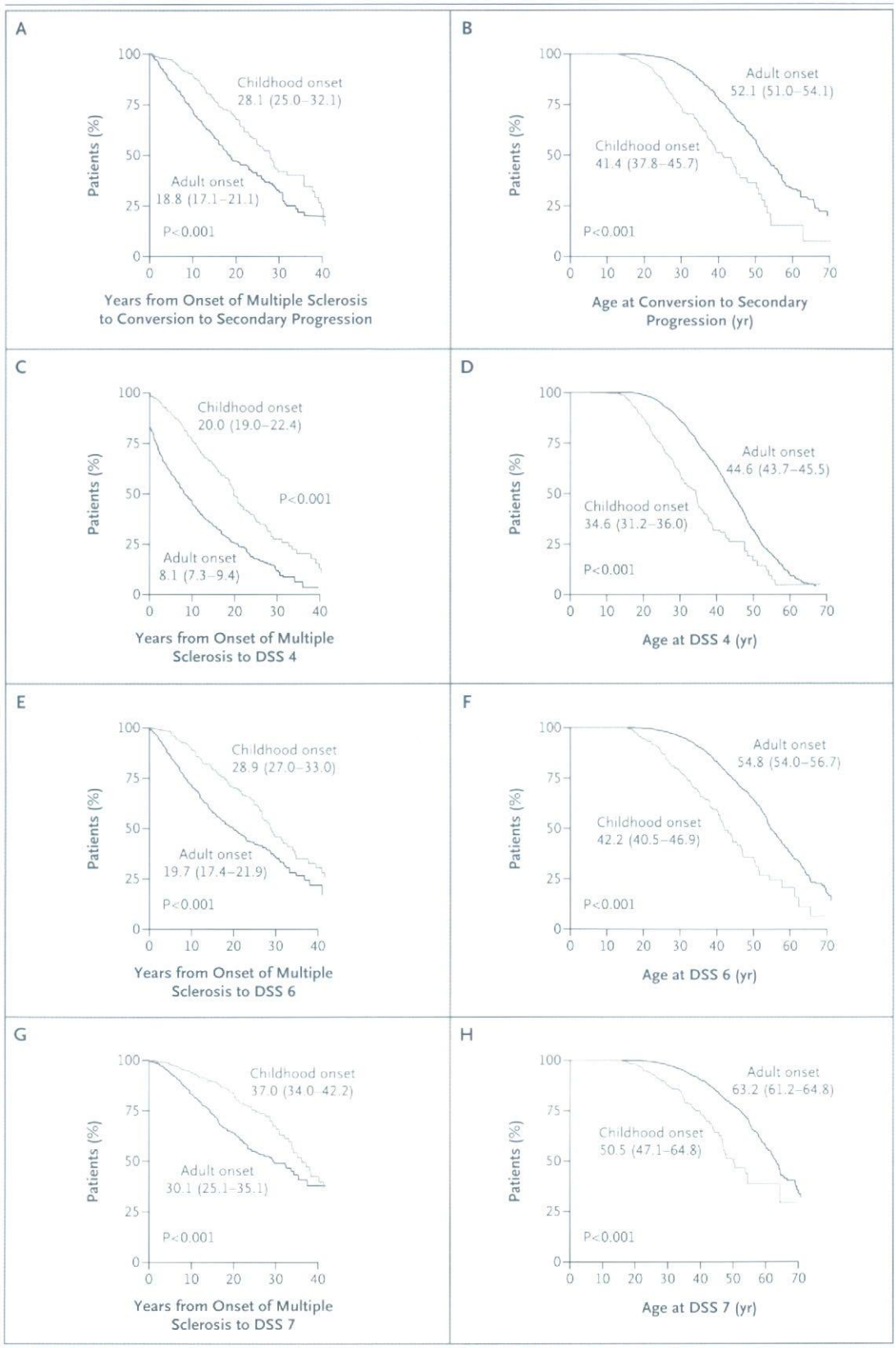

Table 2. Multivariate Analysis of Prognostic Factors of the Time to the Assignment of Irreversible-Disability Scores of 4, 6, and 7 in 394 Patients with Onset of Multiple Sclerosis before 16 Years of Age.*

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.

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APPENDIX

In addition to the authors, the following investigators participated to the Adult Neurology Departments KIDMUS study: *Hôpital Pellegrin, Bordeaux, France* — H. Brochet, J.C. Ouallet; *Hôpital Général, Dijon, France* — G. Couvreur, A. Fromont; *University Hospital Gasthuisberg, Leuven, Belgium* — O. Deryck, P. Ketelaer; *Hôpital Roger Salengro, Lille, France* — H. Zéphir; *Hôpital Neurologique Pierre Wertheimer, Lyon, France* — I. Ionescu-Achiti; *Hôpital de La Timone, Marseille, France* — B. Chabrol, J. Mancini, I. Malikova; *Hôpital Saint Julien, Nancy, France* — S. Pittion-Vouyovitch; *Hôpital de la Pitié–Salpêtrière, Paris* — B. Fontaine, O. Lyon-Caen, S. Mrejen, B. Stankoff, A. Tourbah; *Hôpital Pontchaillou, Rennes, France* — M. Coustans, E. Le Page, E. Leray; *Hôpital Purpan, Toulouse, France* — D. Brassat, G. Lau.

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難治性疾患に関する有効な治療法選択等のための情報収集体制の構築に関する研究

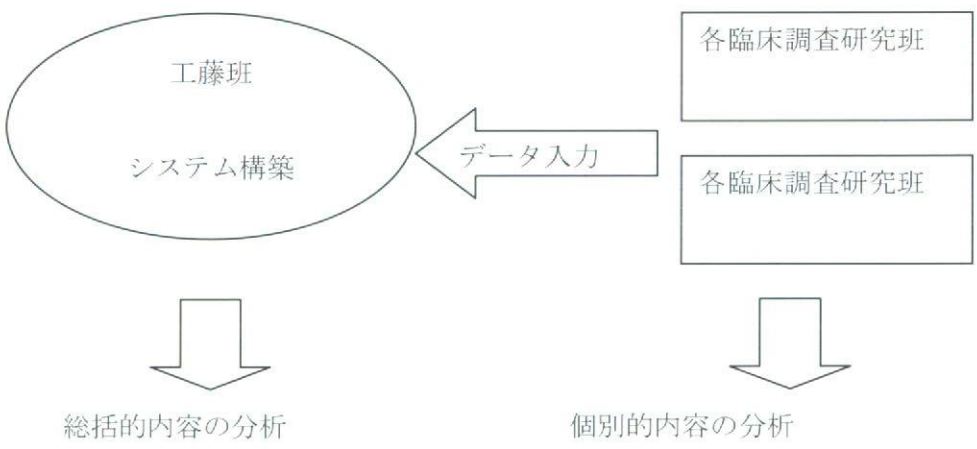
1．治療法選択に資する症例追跡研究の実施状況の確認

先進事例の把握、諸課題及び対処方法の整理

2．治療法選択に資する症例追跡研究を、一部の疾患でモデル的に実施

疾患ごとの臨床調査研究班（任意参加）を支援して、長期的に医学的に必要な症例データの収集を実施

対象：難治性疾患克服研究事業の対象疾患（123疾患）のうち、各研究班が必要性が高いと考えた疾患



3．症例登録及びフォローアップを数年以上にわたり継続

これとは別に、行政的には難治性疾患克服研究事業の対象疾患の医療費について

外来＋院外処方の合計、入院についてどの程度であるかを調査する必要性が高いため、
医療費に関する調査の実施方法について検討することが望ましい。

難病の臨床情報収集に関する課題と展望

	特定疾患治療研究事業対象45疾患	難治性疾患克服研究事業対象123疾患
現状	・医師が記入した臨床調査個人票を都道府県に提出し、都道府県がシステムに入力したものを研究班が研究に活用	・各研究班が個別に研究 ・一部の疾患については分担研究者の医療機関において登録・追跡システムを構築（骨髄異形成症候群等）
課題	・医師による記入、都道府県による入力の負担が大きい ・死亡や治癒などの転帰が不明	・公費対象疾患以外では包括的な情報収集はほとんどなされていない ・研究班の自主的な活動に委ねられており長期的な継続が難しい
今後の取組	個人票作成支援システム ・各医療機関で臨床調査個人票をコンピュータ入力により簡便に作成 ・定期的に医療機関が電子情報を都道府県に提出する等により、都道府県の個人票入力事務を軽減	臨床追跡調査システム ・各医療機関で臨床情報を登録し予後を追跡するシステム構築 ・一部の疾患においてモデル的に実施し、経験を踏まえシステムを改善 ・予後因子等の研究の推進
中期的目標	・個人票データを医療機関からネットワークにより伝送 ・予後に関する情報の登録（治癒、死亡等）	・臨床追跡調査システムに参加する疾患数及び施設数の増加 ・電子カルテに連動する簡易入力システムの開発 ・疾患間の予後や治療効果の比較 ・検体バンクとの連動？
長期的目標	難治性疾患克服研究事業の全疾患について、必ずしも公費助成制度に依存せず、臨床情報を診療現場で入力し長期的に追跡できる「難病登録システム」の構築	

難治性疾患克服研究事業　厚生科学研究

研究課題名

「難治性疾患に関する有効な治療法選択等のための情報収集体制の構築に関する研究」

平成１９年度　第２回班会議議事録

日時：平成１９年７月２３日（月）　１７時３０分より 18 時 40 分まで

場所：東大学士会分館　　２階７号室

〒113-0033

東京都文京区本郷７－３－１（東京大学構内赤門隣り）

電話：03（3814）5541（代表）

http://www.gakushikai.or.jp/facilities/facilities_1.html

１．班長挨拶　　班長 工藤

２．アンケート調査について

1. 挨拶文案（資料 7）　　工藤

2. アンケート案（資料 8）　　埼玉医科大学 永井先生

３．配布資料

難治性疾患の IDC10 コードリスト（資料 9）

平成 19 年度厚生労働省難治性疾患克服研究班名簿

平成 10 年度特定疾患重症度基準

４．次回検討会等

班会議出席者（順不同、敬称略）

（班員）

主任研究者	工藤　翔二	日本医科大学内科学講座　呼吸器・感染・腫瘍部門
分担研究者	永井　正規	埼玉医科大学医学部公衆衛生学
	宮坂　信之	東京医科歯科大学膠原病・リウマチ内科
	針谷　正祥	東京医科歯科大学大学院医歯学総合研究科薬害監視学
研究協力者	林　敬	静岡県厚生部
（事務局）	滋野　恭子	日本医科大学情報科学センター

第２回議事録

1. 挨拶文（資料７）について
   (ア) 厚生労働科学研究　○○班の様に実際の班名を入れる（計３９班）
   (イ) 提出締め切りは９月１０日（月）
   (ウ) 問合せ窓口は日本医科大学情報科学センター　シゲノが担当
   　　質問内容によっては工藤先生や永井先生へ転送して対応する

2. アンケート案（資料８）について
   (ア)（２ページ目）班名・主任研究者・研究対象疾患を明記する
   (イ)（２ページ目）連絡先にメールアドレスを追加する
   (ウ)（３ページ目）別紙質問票は研究対象疾患が複数ある場合には送付した１枚を各自でコピーしてもらい、記入する
   (エ)（３ページ目）項目「９」は年間の概算費用に変更する
   (オ)（３ページ目）登録システムを構築する場合、登録実施計画書があるはずなので、同封してもらう

3. 難治性疾患のIDC10コードリスト（資料９）について
   (ア) このリストは、永井先生の論文（「難治性疾患克服研究における治療法の有効性に関する調査」研究計画書　２００５年９月２６日）より、１２１疾患名およびICD10コードリストを抽出したもの
   (イ)（ア）をもとに、都内附属病院で１２１疾患について、来院人数および医療費（薬代は除く）の調査を行なう予定である。
   (ウ) 特定疾患45疾患については、各都道府県および国で把握している。
   (エ) まずは45疾患に関して、病院ＶＳ国（全体）を見比べてみると、信頼度の把握ができるのでは？

4. 次回検討事項
   (ア) 回収したアンケート結果についての議論
   (イ) 日本医科大学の来院人数および医療費の調査について
   (ウ) 平成１０年度と平成１８年度の難治性疾患重症度基準の比較

5. その他
   (ア) 挨拶文およびアンケート内容についての修正　（工藤・永井）
   (イ) アンケート送付・回収・集計（返信用封筒を入れる）　（しげの）

平成１９年７月２５日

難治性疾患克服研究事業
厚生労働科学研究　臨床班
主任研究者　殿

難治性疾患克服研究事業　厚生科学研究
「難治性疾患に関する有効な治療法選択等のための
情報収集体制の構築に関する研究」班
主任研究者　工藤翔二

アンケート調査へのご協力のお願い

拝啓

盛夏の候、先生にはご健勝のこととお慶び申し上げます。

ご承知のように、現在、特定疾患のうち治療研究対象45疾患については、個人調査票によって当該疾患に関する一定の情報収集がなされていますが、123特定疾患全体に関しては、このような情報収集体制は構築されておりません。

私どもは、特定疾患に関するより有用な情報収集体制の構築を目的とする研究を担当しておりますが、このたびその第1段階として、各臨床班が分担されている特定疾患の臨床症例に関して、班としてどのように登録ないし追跡を行っておられるかについて、アンケートによる調査をさせて頂くことになりました。

お忙しいところ誠に申し訳ございませんが、本調査にご協力を賜りますようお願い申し上げます。アンケートにご記入頂き、9月10日（月）までにご返送頂ければ幸いに存じます。

敬具

連絡先
なお、本研究班の構成は以下の通りです。
主任研究者
工藤翔二（日本医科大学　呼吸器・感染・腫瘍内科、主任教授）
分担研究者
永井正規（埼玉医科大学医学部公衆衛生学、教授）
宮坂信之（東京医科歯科大学膠原病・リウマチ内科、教授）
木内貴弘（東京大学医学部附属病院大学病院医療情報ネットワーク研究センター、教授）
名川弘一（東京大学大学院医学系研究科・医学部、教授）
針谷正祥（東京医科歯科大学大学院医歯学総合研究科薬害監視学、教授）
林　敬（静岡県厚生部、）理事
伊藤高司（日本医科大学情報科学センター、准教授）
吾妻安良太（日本医科大学 呼吸器・感染・腫瘍内科、准教授）

2007.7.

難治性疾患に関する有効な治療法選択等のための情報収集体制の構築に関する研究
平成19年度班宿題
臨床各班への「患者登録システムに関する質問票調査」調査票案

埼玉医科大学公衆衛生学教室　永井正規

作成した案は別紙の通り。調査票のはじめに、班名、主任研究者名、対象疾患名を記載して主任研究者あて記載を依頼する。以下は特発性造血障害に関する調査研究班宛ての例。

疾患ごとの別紙質問票は、臨床班で適宜複写して回答していただく。質問項目は案としてやや多めで削減可能と考えられる。

「患者登録システムに関する質問票調査」調査票（案）

本調査は、貴班が研究対象としている難病それぞれについて、いわゆる患者登録を貴班が実施しているかどうか、また実施している場合はその登録がどのようなものであるかを調査させていただくものです。ここで患者登録とは、貴班所属の研究者または研究協力者が把握した複数の患者についての情報を貴班が責任を持って運営する組織（主任研究者、分担研究者を問わず、また班外の情報処理組織に委託するかどうかを問わない）に収集し、集計解析するシステムを指します。
下記の質問にお答え下さい。

貴班名：特発性造血障害に関する調査研究班
主任研究者：小澤敬也先生
研究対象疾患：１．再生不良性貧血
２．溶血性貧血（自己免疫性溶血性貧血）
３．溶血性貧血（発作性夜間ヘモグロビン尿症）
４．骨髄線維症

上記、に誤りがあったら修正下さい。
この件について、ご回答いただく主任研究者の代理の方、後程ご連絡させていただくご担当の方がありましたら下にご記入下さい。

代理回答者（連絡担当者）
ご氏名：
連絡先：〒

電話：　　ﾌｧｸｼﾐﾘ：
メールアドレス：

質問

１．貴班研究対象疾患の中で患者登録を行っている疾患がありますか。（現在登録を行っていなくても、過去に行っていた、あるいは過去に登録し、現在はフォローアップを行っている等の場合は、あるとお答え下さい）

1. ない
2. ある　（疾患名；　　）
（疾患名；　　）
（疾患名；　　）
（疾患名；　　）
（疾患名；　　）

1. ない　の場合、質問はこれで終了です。
2. ある　の場合、別紙の質問について、登録を行っている疾患ごとにお答え下さい。

別紙質問票

登録を行っている（行っていた）疾患についての質問票（案）

疾患名：＿＿＿＿＿＿＿＿＿＿＿＿

１．登録はいつから始まりましたか（　　年から）

２．登録は現在も行っていますか。
1. 行っている
2. 現在は行っていない
3. その他（　　）

（以下の質問について、現在登録を行っていない場合は過去の登録についてお答え下さい）

３．どなたが登録しますか（複数回答可）
1. 分担（主任）研究者
2. 研究協力者
3. 上記以外の関連施設の医師
4. その他（　　）

４．どこに登録しますか
1. 分担（主任）研究者または研究協力者の施設
2. 上記以外の情報処理技術を持った（専門）機関
3. その他（　　）

５．登録情報の送付方法はどれですか（複数回答可）
1. 紙に書いて、郵送またはファクシミリ送信
2. インターネットを使ったメールでの文書ファイル添付による送信
3. 登録する者が入力、送信すると自動的にデータベースが更新される、いわゆるオンライン登録
4. その他（　　）

６．これまでにおよそ何件（患者人数）登録されていますか（　　件）

７．最近の１年間ではおよそ何件（患者人数）登録されましたか（　　件）

８．登録された患者のフォローアップ（死亡した、治癒した等、登録後の経過についての情報を確認すること）は実施していますか。

1. している
2. していない
3. その他（　　）

９．登録にかかる費用はどの程度でしょうか。年間の概算費用をお答え下さい。

１０．登録を実行する上での問題点をあげて下さい。

１１．患者の個人情報保護のために実施されている事をあげて下さい。

１２．登録実施計画書はありますか？（お手数ですが、別刷りを同封いただければ誠に幸甚です）

１３．これまでに登録を基礎として行われた研究報告があれば、文献名を以下に記入下さい。（ご迷惑、お手数ですが別刷りを同封いただければ誠に幸甚です）

研究報告

1）
2）
3）

NO	病名	ICD10
1	再生不良性貧血	D61.3
	再生不良性貧血	D619
	肝炎後再生不良性貧血	D612
	先天性再生不良性貧血	D610
	体質性再生不良性貧血	D610
	特発性再生不良性貧血	D613
	二次性再生不良性貧血	D612
	本態性再生不良性貧血	D619
	薬剤性再生不良性貧血	D611
2	溶血性貧血	D55-D59
	溶血性貧血	D589
	温式自己免疫性溶血性貧血	D591
	家族性溶血性貧血	D589
	機械的溶血性貧血	D594
	酵素異常による遺伝性溶血性貧血	D559
	後天性溶血性貧血	D599
	自己免疫性溶血性貧血	D591
	術後溶血性貧血	D594
	中毒性溶血性貧血	D594
	特発性溶血性貧血	D599
	非自己免疫性溶血性貧血	D594
	微小血管障害性溶血性貧血	D594
	薬剤性自己免疫性溶血性貧血	D590
	薬剤性溶血性貧血	D592
	溶血性貧血に伴う葉酸欠乏症	D528
3	不応性貧血(骨髄異形成)	D46.0-D46.6
	骨髄異形成症候群	D469
	不応性貧血	D464
	RAEB	D462
	芽球増加型不応性貧血	D462
	RARS	D461
	原発性鉄芽球性貧血	D461
4	骨髄線維症	C94.5/D47.1/D75.8