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Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process

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Summary

Prognosis of multiple sclerosis is highly variable. Clinical variables have been identified that are assessable early in the disease and are predictors of the time from the disease onset to the onset of irreversible disability. Our objective was to determine if these clinical variables still have an effect after the first stages of disability have been reached. We determined the dates of disease onset and assignment of scores of irreversible disability in 1844 patients with multiple sclerosis. We used three scores on the Kurtzke Disability Status Scale as benchmarks of disability accumulation: 4 (limited walking but without aid); 6 (walking with unilateral aid); and 7 (wheelchair bound). We used Kaplan–Meier analyses and Cox regression models to determine the influence of the clinical variables on the time to disability onset. Median times from onset of multiple sclerosis to assignment of a score of 4, 6 and 7 were significantly influenced by gender, age, symptoms and course (relapsing–remitting or progressive) at onset of the disease, degree of recovery from the first relapse, time to a second neurological episode, and the number of relapses in the first 5 years of the disease. Similarly, times from onset of multiple sclerosis to a score of 6 and 7 were influenced by time to a score of 4. In contrast, none of the variables substantially affected the time from a score of 4 to a score of 6 or 7, or from a score of 6 to a score of 7. Early assessable clinical variables significantly influence the time from the onset of multiple sclerosis to the assignment of a disability score of 4, but not the subsequent progression of irreversible disability.

Keywords: clinical predictors; disability; multiple sclerosis; prognosis; progression

Introduction

Multiple sclerosis is the most common chronic disabling disease of the CNS in young adults in Western countries, with 1 in 1000 people affected (Sadovnick and Ebers, 1993). Its overall prognosis is well known, with irreversible limitation in ambulation, a unilateral aid required for walking, and patients becoming wheelchair-bound after median times of approximately 8, 20, and 30 years of evolution, respectively. However, life expectancy is only marginally reduced (Muller, 1949; Thygesen, 1949; Hyllested, 1961; McAlpine, 1961; Fog and Linnemann, 1970; Leibowitz and Alter, 1973; Poser and Hauptvogel, 1973; Confavreux *et al*., 1980; Phadke, 1987; Weinshenker *et al*., 1989*a*; Phadke 1990; Confavreux *et al*., 2000). Another hallmark of the disease is the high degree of variability in the final outcome from one patient to another, with the full spectrum of disease ranging from benign, and even asymptomatic, to more malignant cases (Fog and Linnemann, 1970; Leibowitz and Alter, 1973; Confavreux *et al*., 1980). Therefore the determination of clinical factors identifiable early in the disease that reliably predict the long-term outcome in a given individual is highly desirable.

A number of demographic and clinical variables have been identified that are assessable early in the disease and are predictors of the time from the onset of multiple sclerosis to the onset of irreversible disability (Leibowitz and Alter, 1973; Kurtzke *et al*., 1977; Confavreux *et al*., 1980; Poser *et al*., 1986; Weinshenker *et al*., 1991; Runmarker and Andersen, 1993; Trojano *et al*., 1995; Kantarci *et al*., 1998). However, whether these factors only influence the early stages of the disease or its entire course is unknown. In other words, are these factors also predictive of disability progression once the first stages of irreversible disability have been reached? The

Lyons Multiple Sclerosis Cohort is a unique natural history database, both in terms of its size and quantity of data gathered since 1957. In this paper, we describe the use of this database to address this issue.

Methods

Patient population and data collection

Patients were identified through the Lyons Multiple Sclerosis Cohort, which was set up in the Lyons Clinique de Neurologie in 1957. Since then, the cohort has included all the patients with a diagnosis of multiple sclerosis examined at least once at the clinic. The surveillance system was computerized in 1976 and served as a basis for the development of the standardized, computerized European Database for Multiple Sclerosis (EDMUS) system (Confavreux *et al*., 1992).

Individual case reports include identification and demographic data, medical history, key episodes in the multiple sclerosis course (relapses, onset of the progressive course, times of assignment of the successive scores of irreversible disability), biological, electrophysiological and neuroimaging data, and treatment. Data are entered retrospectively when the patient is first seen at the clinic. A special effort is always made to obtain data from the original medical files, especially for data on the first neurological episode, and on the clinical course and disability. This effort is facilitated by the existing regional network of neurologists in our area. Data are then collected prospectively whenever the patient returns, usually on a yearly basis. New data are automatically checked for their consistency with older information. Confidentiality and safety of the data are ensured in accordance with the recommendations of the French Commission Nationale Informatique et Libertés (CNIL), which also provides approval. All patients give their informed consent for their data to be saved in the database.

Definition of cases and assessment of patients

By April 1997, a cohort of 2021 patients had been included in the database. Diagnosis of multiple sclerosis was established according to Poser's classification (Poser *et al*., 1983). This classification consists of the distribution of patients into definite, probable and possible categories.

A relapse of multiple sclerosis was defined as the occurrence, recurrence or worsening of symptoms of neurological dysfunction lasting >24 h and usually ending with a remission, which is either partial or complete. Fatigue alone and transient fever-related worsening of symptoms were not considered as a relapse. Symptoms occurring within 1 month were considered as part of the same relapse.

The progressive phase was defined as the steady worsening of symptoms and signs for at least 6 months, whether superimposed with relapses or not (Schumacher *et al*., 1965). Once started, it goes on continuously throughout the disease, although occasional plateaus and temporary minor improvements may be observed (Lublin and Reingold, 1996).

A series of clinical variables that can be determined at the clinical onset of multiple sclerosis were systematically assessed for each patient. They included gender and age at onset of multiple sclerosis. Initial symptoms were categorized into isolated optic neuritis, isolated brainstem dysfunction, isolated dysfunction of long tracts, and combination of these symptoms. Initial course of the disease was classified as relapsing–remitting or progressive. Recovery from the first relapse was classified as incomplete or complete depending on the persistence or absence of at least minimal neurological symptoms, respectively (Confavreux *et al*., 1992). Date of onset of the second neurological episode of multiple sclerosis, which may be a relapse or the onset of the progressive phase, was also systematically assessed whenever appropriate. The same was true for the subsequent neurological episodes.

The Kurtzke Disability Status Scale was referred to at each visit of the patient at the clinic to determine the extent of neurological disability (Kurtzke, 1983). It is based on the results of neurological examinations and the walking abilities of the patient. Scores range from 0 (no neurological abnormality) to 10 (death from multiple sclerosis), with nine intermediary steps. Focus was placed on scores that could be easily identified even through interviewing the patient retrospectively. A score of 4 corresponds to limited walking ability, but without aid or rest for >500 m; a score of 6 corresponds to ability to walk with unilateral support for no more than 100 m without rest; and a score of 7 corresponds to ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support. Disability was defined as irreversible when the assignment to a given score had been reached and had persisted for at least 6 months, excluding any transient worsening of disability related to relapses. By definition, when a given score of irreversible disability had been assigned to a given patient, all the scores of disability that could be subsequently assessed during the follow-up of the patient were either equal to or higher than that one. This was automatically checked by the EDMUS software through an appropriate algorithm. The long duration of the follow-up inherent to a natural history study allowed sufficient observation time to ensure that the disability was genuinely irreversible.

Statistical analysis

The predictive value of demographic (gender, age at onset of multiple sclerosis) and clinical data (symptoms and course at onset of multiple sclerosis, degree of recovery from the first relapse, time from onset of multiple sclerosis to the second neurological episode, number of relapses during the first 5 years of the disease, and time to assignment of a score of 4) was evaluated using Kaplan–Meier survival analyses. Endpoints were time to assignment of scores of 4, 6 and 7. Survival curves were compared using the log-rank test. A complementary analysis was performed using the Cox

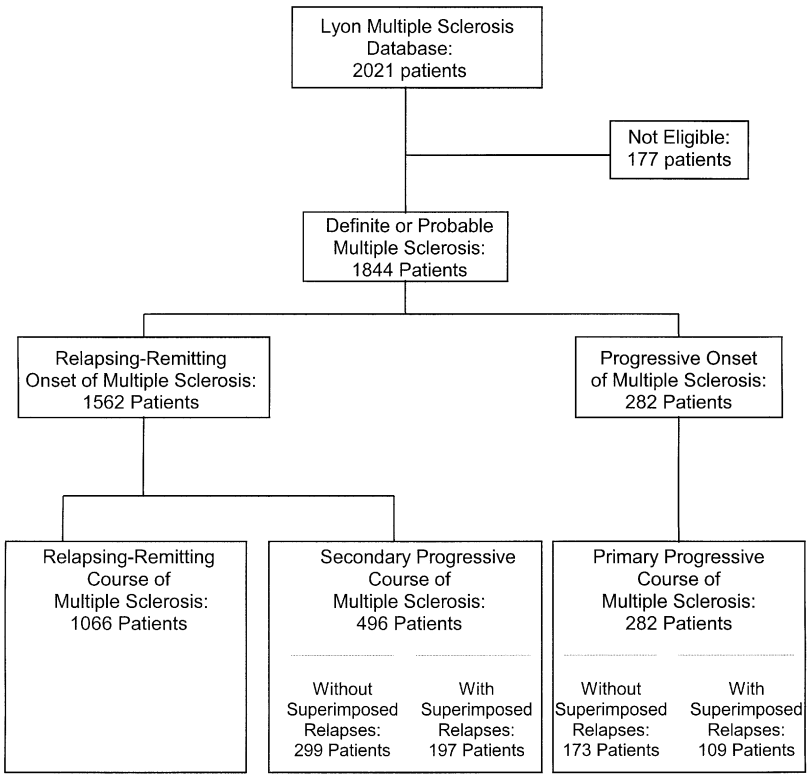

Fig. 1 Initial and subsequent course of multiple sclerosis in the study patients.

regression models. In a first step, computations were made from the onset of multiple sclerosis. In a second step, they were made from the time of assignment to the above-defined scores of irreversible disability 4 and 6. All computations were performed using SPSS for Windows, version 9.0.

Results

Characteristics of the patients with multiple sclerosis

Among the 2021 patients who were potentially eligible for the study, 170 were excluded due to lack of confidence in the diagnosis as they were classified as possibly having multiple sclerosis according to the classification of Poser (Poser *et al*., 1983) and seven because their initial symptoms were unknown (Fig. 1). The baseline characteristics of the remaining 1844 patients with a diagnosis of definite or probable multiple sclerosis are given in Table 1.

There were 903 patients (49%) having received a disease-modifying treatment at some time. The most widely used treatment in our series was azathioprine (820 patients, among which 804 had been treated for at least 6 months), followed by cyclophosphamide (78 cases), interferon beta (72 cases), methotrexate (60 cases) and mitoxantrone (18 cases). The only administered treatment with an acknowledged efficacy in our series was interferon beta, but it was not available in our area earlier than February 1996 and the database was locked for the purpose of this study by April 1997. Compared with non-treated patients, treated patients showed a slightly higher frequency of relapses and a more severe course of the disease at onset, reflecting a presumable selection bias in drug administration. Overall, administered treatments had been prescribed for a limited period of time relative to the total duration of the disease in a given patient.

Initial clinical variables, and the time from the onset of multiple sclerosis to the onset of irreversible disability

During the follow-up of the 1844 patients, a total of 1026 (56%), 595 (32%) and 380 patients (21%) reached the end-point of a score of 4, 6 and 7 on the Kurtzke Disability Status Scale, respectively. The median time from the onset of multiple sclerosis to the assignment of a score of 4, 6 and 7 was 8.4 years [95% confidence interval (CI) = 7.8 to 9.6], 20.1 years (95% CI = 18.1 to 22.5) and 29.9 years (95% CI = 25.1 to 34.5), respectively. The median interval from the onset of the disease to the assignment of each of these scores was significantly longer in females than in males, and in the patients with a younger age of onset of multiple sclerosis. This interval was also longer: (i) in those with an initial relapsing–remitting course of multiple sclerosis versus those with a progressive one; (ii) in those with a complete recovery from the first relapse versus those with an incomplete recovery; and (iii) in those with longer times from onset of multiple sclerosis to the second neurological episode. Times

Table 1 *Baseline demographic and disease-related characteristics of the 1844 patients with multiple sclerosis*

Characteristics	Value
Gender, *n* (%)	
Male	657 (36)
Female	1187 (64)
Age at onset of multiple sclerosis (years)	
Mean ± SD	31 ± 10
Median	30
Range	5–67
Distribution, *n* (%)	
0–19 years	216 (12)
20–29 years	690 (37)
30–39 years	558 (30)
40–49 years	272 (15)
>50 years	108 (6)
Initial symptoms, *n* (%)	
Overall	
Isolated optic neuritis	335 (18)
Isolated brain-stem dysfunction	159 (9)
Isolated dysfunction of long tracts	964 (52)
Combination of symptoms	386 (21)
Initial long tracts involvement	
Yes	1287 (70)
No	557 (30)
Initial brain-stem involvement	
Yes	411 (22)
No	1433 (78)
Initial optic neuritis	
Yes	476 (26)
No	1368 (74)
Initial course of multiple sclerosis, *n* (%)	
Relapsing–remitting	1562 (85)
Progressive	282 (15)
Time from onset of multiple sclerosis to initial clinic visit (years)	
Mean ± SD	6 ± 8
Median	3
Range	0–53
Kaplan–Meier estimate of time from onset of multiple sclerosis to the second neurological episode (years)	
Mean	6
Median	2
Range	0–63
Kaplan–Meier estimate of time from onset of multiple sclerosis to assignment of a score of 4 (years)*	
Mean	12
Median	8
Range	0–41
Duration of multiple sclerosis (years)	
Mean ± SD	11 ± 10
Median	9
Range	0–63
Overall course of multiple sclerosis, *n* (%)	
Relapsing–remitting	1066 (58)
Secondary progressive	496 (27)
Progressive from onset	282 (15)
Diagnosis classification, *n* (%)**	
Clinically definite	1125 (61)
Laboratory-supported definite	251 (14)
Clinically probable	365 (20)
Laboratory-supported probable	103 (6)

*The Kurtzke Disability Status Scale was used to determine the extent of disability; **the diagnoses were established according to the classification of Poser *et al*. (1983).

to assignment of a score of 6 or 7 were also influenced by the time interval from onset of multiple sclerosis to a score of 4, with those with slower progression to 4 also showing slower progression to 6 or 7 (Table 2 and Fig. 2). With respect to initial manifestations of the disease, the median intervals were significantly longer for cases with an isolated optic

Table 2 *Kaplan–Meier estimates of the time from the onset of multiple sclerosis to the onset of irreversible disability among 1844 patients with multiple sclerosis, according to initial clinical variables**

Variable	No. of patients (n = 1844)	Time from onset of multiple sclerosis to assignment of a score of 4			Time from onset of multiple sclerosis to assignment of a score of 6			Time from onset of multiple sclerosis to assignment of a score of 7		
		Median (years)	95% CI	P value**	Median (years)	95% CI	P value**	Median (years)	95% CI	P value**
Gender										
Males	657	7.2	6.0–8.3	Reference	17.2	14.4–20.0	Reference	25.1	19.9–30.3	Reference
Females	1187	9.6	8.4–10.8	0.005	23.1	19.9–26.3	0.003	30.4	25.5–35.3	0.03
Age at onset (years)										
0–19	216	15.9	10.7–21.1	Reference	31.1	24.2–38.0	Reference	36.3	30.2–42.4	Reference
20–29	690	11.8	9.9–13.7	0.02	26.1	22.1–30.0	0.21	30.4	26.3–34.5	0.52
30–39	558	8.6	7.1–10.0	<0.001	17.4	15.1–19.7	<0.001	24.0	?–?	0.04
40–49	272	3.1	1.9–4.2	<0.001	12.7	9.5–15.9	<0.001	21.1	17.1–25.1	<0.001
⩾50	108	0.3	?–?	<0.001	7.1	6.2–7.9	<0.001	16.0	8.7–23.3	<0.001
			<0.001			<0.001			<0.001	
Initial symptoms										
Overall										
Isolated optic neuritis	335	14.1	12.1–16.1	Reference	27.9	23.1–32.7	Reference	?	?–?	Reference
Isolated brain-stem dysfunction	159	10.5	6.2–14.8	0.02	29.0	17.6–40.4	0.41	41.3	22.7–59.8	0.08
Isolated dysfunction of long tracts	964	6.0	5.0–7.0	<0.001	16.1	13.6–18.6	<0.001	24.8	20.4–29.1	<0.001
Combination of symptoms	386	9.1	6.8–11.4	<0.001	24.4	18.1–30.8	0.01	28.3	21.3–35.4	0.01
			<0.001			<0.001			<0.001	
Long tracts involvement										
Yes	1287	6.5	5.7–7.3	Reference	17.2	15.0–19.3	Reference	26.1	22.3–29.9	Reference
No	557	12.7	11.2–14.2	<0.001	27.9	23.4–32.4	<0.001	41.3	25.4–57.1	<0.001
Brain-stem involvement										
Yes	411	9.1	7.3–10.8	Reference	29.0	17.3–40.7	Reference	36.3	25.5–47.0	Reference
No	1433	8.3	7.4–9.3	0.04	19.1	16.8–21.4	0.13	28.3	24.4–32.3	0.76
Optic neuritis										
Yes	476	13.5	11.7–15.3	Reference	27.9	23.3–32.6	Reference	42.3	?–?	Reference
No	1368	7.1	6.2–7.9	<0.001	17.3	15.0–19.5	<0.001	26.6	22.9–30.3	<0.001
Initial course										
Relapsing–remitting	1562	11.4	10.5–12.3	Reference	23.1	20.1–26.1	Reference	33.1	29.2–37.0	Reference
Progressive	282	0	?–?	<0.001	7.1	6.3–7.9	<0.001	13.4	11.0–15.9	<0.001
Recovery from the first relapse†										
Complete	1288	13.1	11.9–14.3	Reference	27.1	23.5–30.7	Reference	34.1	30.2–38.0	Reference
Incomplete	274	1.0	?–?	<0.001	13.0	9.7–16.3	<0.001	25.1	21.2–29.0	<0.001
Time from onset of multiple sclerosis to the second neurological episode (years)										
<2	818	6.6	5.4–7.8	Reference	17.1	14.2–19.9	Reference	23.8	?–?	Reference
2–5	341	9.6	7.8–11.3	<0.001	20.1	15.7–24.5	0.02	33.1	26.5–39.6	<0.001
>5	325	16.1	14.2–18.0	<0.001	27.9	23.9–31.9	<0.001	35.1	28.9–41.3	<0.001
			<0.001			<0.001			<0.001	

Table 2 *Continued*

Variable	No. of patients (n = 1844)	Time from onset of multiple sclerosis to assignment of a score of 4			Time from onset of multiple sclerosis to assignment of a score of 6			Time from onset of multiple sclerosis to assignment of a score of 7		
		Median (years)	95% CI	P value**	Median (years)	95% CI	P value**	Median (years)	95% CI	P value**
Number of relapses during the first 5 years of the disease‡										
n = 1	399	15.1	13.4–16.8	Reference	25.3	21.9–28.6	Reference	34.5	28.7–40.3	Reference
n = 2	253	11.1	9.5–12.6	<0.001	21.9	15.3–28.6	0.01	33.3	27.4–39.2	0.20
$n \geqslant 3$	422	9.5	7.8–11.2	<0.001	24.7	16.9–32.4	0.001	26.1	19.2–33.0	<0.001
			<0.001			0.003			0.002	
Time from onset of multiple sclerosis to assignment of a score of 4 (years)										
<2	470				6.3	5.6–7.0	Reference	13.2	10.8–15.5	Reference
2–5	171				8.1	7.3–8.9	0.003	15.3	12.0–18.5	0.30
>5	385				20.7	18.6–22.8	<0.001	30.1	25.2–35.0	<0.001
						<0.001			<0.001	
Azathioprine therapy for at least 6 months										
No	1039	10.1	8.7–11.5	Reference	21.8	18.9–24.6	Reference	33.3	26.7–40.0	Reference
Yes	804	7.8	6.5–9.0	0.003	18.8	16.5–21.0	0.37	29.9	25.2–34.6	0.62

*The Kurtzke Disability Status Scale was used to determine the extent of disability. On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for >500 m, a score of 6 indicates the ability to walk with unilateral support for no more than 100 m without rest, and a score of 7 indicates the ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support. Disability was defined as irreversible when a patient had had a given score for at least 6 months, excluding any transient worsening of disability related to relapses. **P values are calculated using the log-rank test. †Cases with a relapsing–remitting onset only (n = 1562). ‡Cases with a relapsing–remitting onset and at least 5 years of follow-up (n = 1074). CI = confidence interval.

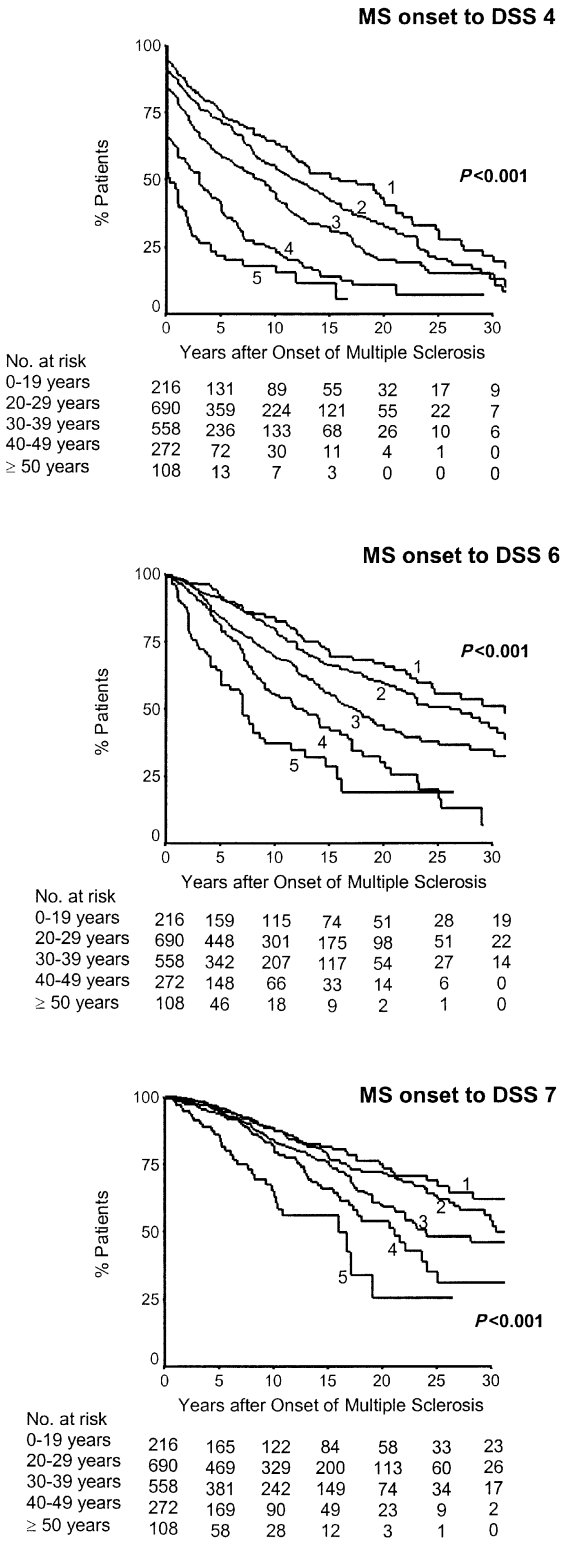

Fig. 2 Kaplan–Meier estimates of the time from the onset of multiple sclerosis to the assignment of a score of 4 (upper panel), 6 (central panel) and 7 (lower panel) on the Kurtzke Disability Status Scale among 1844 patients with multiple sclerosis, according to patient age at the onset of disease. 1 = 0–19 years; 2 = 20–29 years; 3 = 30–39 years; 4 = 40–49 years; 5 = ⩾50 years.

neuritis at onset than for cases with an isolated dysfunction of long tracts, whereas cases with an isolated brainstem dysfunction showed intermediate results (Table 2). Cox regression models led to similar results (data not shown). The only significant difference associated with the azathioprine treatment administered for at least 6 months was observed with the time from onset of multiple sclerosis to assignment of a score of 4 ($P = 0.003$; Table 2).

Initial clinical variables, and the time from the assignment of a given score of irreversible disability to the assignment of a higher score

Among the 1844 patients, the median time from the assignment of a score of 4 to the assignment of a score of 6 was 5.7 years (95% CI = 5.0 to 6.3). From the assignment of a score of 4 to a score of 7, it was 12.1 years (95% CI = 10.3 to 13.9), and from the assignment of a score of 6 to a score of 7, it was 3.4 years (95% CI = 3.0 to 3.8). The median times required for each of these changes to occur were not influenced by gender, age at onset of multiple sclerosis, initial symptoms, relapsing–remitting or progressive initial course of the disease, number of relapses during the first 5 years of the disease, time from the onset of multiple sclerosis to assignment of a score of 4, and azathioprine treatment (Table 3 and Fig. 3). Similar results were obtained using Cox regression models (data not shown), although times from assignment of a score of 4 to assignment of a score of 6 or 7 were longer for females than for males ($P = 0.02$ and $P = 0.04$, respectively). Additionally, the Kaplan–Meier analysis showed that the degree of recovery from the first relapse did not influence time from assignment of a score of 4 to assignment of a score of 6 ($P = 0.56$; Table 3). Unexpectedly, assignments from a score of 4 to a score of 7, and from a score of 6 to a score of 7 took longer in cases with an incomplete recovery than in cases with a complete recovery from the first relapse ($P = 0.004$ and 0.009, respectively; Table 3). The Kaplan–Meier analysis also showed that a longer time from onset of multiple sclerosis to the second episode of the disease did not influence time from assignment of a score of 4 to assignment of a score of 6 ($P = 0.14$; Table 3). It did correlate with a longer time from assignment of a score of 4 or a score of 6 to assignment of a score of 7 ($P = 0.003$ and 0.002, respectively; Table 3). However, this influence was no longer seen when the time from onset of multiple sclerosis to the second episode was treated as a continuous variable in a Cox regression model ($P = 0.38$ and 0.27, respectively).

Subanalyses according to the initial course of multiple sclerosis

Among the 1844 patients, the initial course of the disease was relapsing–remitting in 1562 (85%), whereas it was progressive in 282 (15%) patients. In the group of 1562 patients with a relapsing–remitting onset of multiple sclerosis, the analysis

Table 3 *Kaplan–Meier estimates of the time course of progressive irreversible disability among 1844 patients with multiple sclerosis, according to initial clinical variables**

Variable	Time from assignment of a score of 4 to a score of 6				Time from assignment of a score of 4 to a score of 7				Time from assignment of a score of 6 to a score of 7			
	No. of patients (n = 1026)	Median (years)	95% CI	P value**	No. of patients (n = 1026)	Median (years)	95% CI	P value**	No. of patients (n = 595)	Median (years)	95% CI	P value**
Gender												
Male	397	5.0	4.3–5.7	Reference	397	10.0	8.0–12.0	Reference	241	3.0	2.2–3.8	Reference
Female	629	6.2	5.2–7.1	0.09	629	13.0	11.5–14.5	0.11	354	3.8	3.1–4.4	0.21
Age at onset (years)												
0–19	207	5.5	4.1–6.9	Reference	207	11.8	9.4–14.2	Reference	65	2.8	1.3–4.2	Reference
20–29	341	6.0	4.9–7.1	0.86	341	11.3	9.6–12.9	0.66	184	3.2	2.5–3.9	0.57
30–39	311	5.0	3.8–6.2	0.56	311	12.6	9.3–15.8	0.49	186	4.3	3.3–5.3	0.12
40–49	185	7.0	5.5–8.5	0.61	185	14.0	10.6–17.4	0.20	106	4.0	2.7–5.3	0.08
⩾50	82	4.8	3.6–5.9	0.16	82	10.2	8.0–12.3	0.69	54	3.2	2.7–3.6	0.88
			0.40				0.34				0.19	
Initial symptoms												
Overall												
Isolated optic neuritis	158	5.0	3.7–6.3	Reference	158	12.6	6.7–18.4	Reference	86	3.5	2.4–4.6	Reference
Isolated brain-stem dysfunction	77	6.3	3.0–9.7	0.77	77	13.2	9.7–16.6	0.56	45	2.3	1.3–3.4	0.30
Isolated dysfunction of long tracts	595	5.8	5.1–6.6	0.77	595	12.0	10.5–13.5	0.64	357	4.0	3.3–4.7	0.31
Combination of symptoms	196	5.5	3.8–7.2	0.84	196	12.1	8.3–15.9	0.95	107	3.0	2.1–3.9	0.91
			0.97				0.83				0.25	
Long tracts involvement												
Yes	758	5.7	4.9–6.4	Reference	758	12.0	10.5–13.5	Reference	449	3.8	3.1–4.4	Reference
No	268	5.7	4.0–7.3	0.75	268	13.0	9.7–16.3	0.42	146	3.0	2.2–3.8	0.06
Brain-stem involvement												
Yes	207	6.0	4.4–7.6	Reference	207	13.2	10.7–15.6	Reference	117	2.8	2.2–3.4	Reference
No	819	5.6	4.9–6.3	0.81	819	12.0	10.5–13.5	0.71	478	3.8	3.1–4.4	0.39
Optic neuritis												
Yes	222	5.4	4.3–6.5	Reference	222	12.6	7.9–17.3	Reference	120	3.5	2.2–4.8	Reference
No	804	5.7	5.0–6.3	0.94	804	12.1	10.2–13.9	0.88	475	3.4	3.0–3.8	0.26
Initial course												
Relapsing–remitting	755	5.7	4.9–6.4	Reference	755	12.1	10.0–14.2	Reference	426	3.3	2.8–3.9	Reference
Progressive	271	5.4	4.3–6.6	0.74	271	12.0	10.1–13.9	0.70	169	4.0	2.9–5.1	0.48
Recovery from the first relapse†												
Complete	592	5.6	4.8–6.4	Reference	592	11.3	9.9–12.6	Reference	308	3.0	2.5–3.5	Reference
Incomplete	193	6.3	4.3–8.2	0.56	193	20.3	14.7–26.0	0.004	118	5.0	3.6–6.4	0.009
Time from onset of multiple sclerosis to the second neurological episode (years)												
<2	438	5.0	4.1–5.9	Reference	438	9.9	7.9–11.9	Reference	247	2.6	2.1–3.1	Reference
2–5	204	6.2	4.3–8.0	0.36	204	15.7	10.8–20.5	0.009	120	4.0	2.6–5.4	0.004
>5	204	6.3	4.6–7.9	0.05	204	14.9	9.9–19.9	0.005	121	4.6	3.7–5.5	0.005
			0.14				0.003				0.002	

Table 3 *Continued*

Variable	Time from assignment of a score of 4 to a score of 6				Time from assignment of a score of 4 to a score of 7				Time from assignment of a score of 6 to a score of 7			
	No. of patients (n = 1026)	Median (years)	95% CI	P value**	No. of patients (n = 1026)	Median (years)	95% CI	P value**	No. of patients (n = 595)	Median (years)	95% CI	P value**
Number of relapses within the first 5 years of the disease‡												
n = 1	245	6.0	4.8–7.2	Reference	245	12.2	7.1–17.2	Reference	151	4.3	3.0–5.6	Reference
n = 2	159	6.2	4.4–8.0	0.97	159	12.6	7.4–17.8	0.80	94	3.4	2.4–4.4	0.50
$n \geqslant 3$	251	5.5	4.2–6.8	0.60	251	12.1	8.9–15.2	0.15	143	3.0	2.2–3.8	0.07
			0.81				0.24				0.21	
Time from onset of multiple sclerosis to assignment of a score of 4 (years)												
<2	470	6.0	5.2–6.8	Reference	470	13.1	11.0–15.2	Reference	293	3.4	2.8–4.0	Reference
2–5	171	4.8	3.5–6.0	0.43	171	10.0	7.2–12.8	0.12	102	3.3	2.4–4.1	0.20
>5	385	5.7	4.7–6.6	0.76	385	12.0	9.7–14.4	0.76	200	3.9	3.0–4.9	0.85
			0.62				0.27				0.38	
Azathioprine therapy for at least 6 months												
No	514	5.7	4.7–6.6	Reference	514	12.0	10.6–13.4	Reference	304	3.3	2.8–3.7	Reference
Yes	508	5.7	4.8–6.5	0.51	508	14.7	12.1–17.2	0.09	287	4.0	3.3–4.7	0.05

*The Kurtzke Disability Status Scale was used to determine the extent of disability. On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for >500 m, a score of 6 indicates the ability to walk with unilateral support for no more than 100 m without rest, and a score of 7 indicates the ability to walk no more than 10 m without rest while leaning against a wall or holding onto furniture for support. Disability was defined as irreversible when a patient had had a given score for at least 6 months, excluding any transient worsening of disability related to relapses. **P values are calculated with use of the log-rank test. †Cases with a relapsing–remitting onset only. ‡Cases with a relapsing–remitting onset and at least 5 years of follow-up. CI = confidence interval.

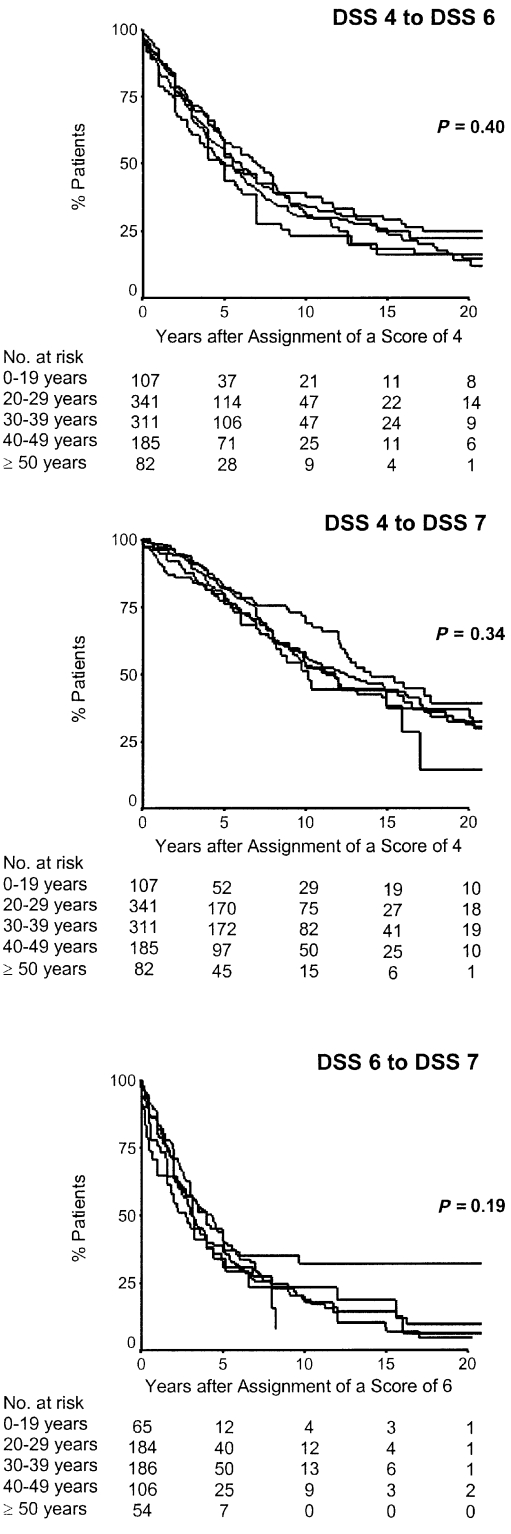

Fig. 3 Kaplan–Meier estimates of the time from the assignment of a score of 4 to the assignment of a score of 6 (upper panel) or 7 (central panel) on the Kurtzke Disability Status Scale, and the time from the assignment of a score of 6 to a score of 7 (lower panel) among 1844 patients with multiple sclerosis, according to the age of the patient at the onset of disease. 0–19 years; 20–29 years; 30–39 years; 40–49 years; ⩾50 years.

of the influence of the clinical variables on disease progression was similar to the effects seen on the full cohort. These results were obtained when using the Kaplan–Meier technique and the Cox regression models as well (data not shown).

In contrast, in the group of 282 patients with a progressive onset of the disease, clinical variables had no influence either on the time from the onset of multiple sclerosis to the assignment of a score of 4, 6 and 7, or the time from the assignment of a given score of irreversible disability to the assignment of a higher score when using the Kaplan–Meier technique and the Cox regression models (data not shown). The only exception was related to gender, with a slower progression in females when using the Kaplan–Meier technique to assess the times from the onset of multiple sclerosis to the assignment of a score of 4, 6 and 7 ($P = 0.12$, $P = 0.03$ and $P = 0.02$, respectively), from a score of 4 to a score of 6 ($P = 0.008$), from a score of 4 to a score of 7 ($P = 0.006$), and from a score of 6 to a score of 7 ($P = 0.07$). Similar results were obtained when using Cox regression models (data not shown). Results were also essentially similar in the subgroup of patients with relapses superimposed on primary progression and in the subgroup of patients without (data not shown).

Discussion

This observational study of the natural history of multiple sclerosis suggests that clinical variables that can be assessed early in the disease are strong predictors of the time from onset of multiple sclerosis to the onset of irreversible disability. These factors are gender, age, initial symptoms and course of disease, degree of recovery from the first relapse of the disease, time from multiple sclerosis onset to the second neurological episode, number of relapses during the first 5 years of the disease, and time from multiple sclerosis onset to the assignment of a score of 4 on the Kurtzke Disability Status Scale. In contrast, once a score of 4 has been reached, these variables are no longer predictive of the time course of the subsequent disability progression. This phenomenon was observed in our total population of multiple sclerosis patients as well as in the subgroup of patients with a relapsing–remitting onset of multiple sclerosis. However, in the subgroup of patients with a progressive course from onset, clinical variables did not show any significant influence, even on the time from onset of multiple sclerosis to the assignment of a disability score of 4, 6 and 7. This is presumably explained by the close time relationship between the onset of the disease and the time of assignment to a score of 4 in these patients.

Our clinic serves as the reference centre for multiple sclerosis for Lyons City and the Rhône-Alpes region. Lyon is located within the 'département du Rhône' which had 1 575 000 inhabitants in 1999. The Rhône-Alpes region is made up of eight 'départements' (Ain, Ardèche, Drôme, Isère, Loire, Rhône, Savoie and Haute-Savoie) and included 5 634 000 inhabitants in 1999. Prevalence of multiple

sclerosis in the area has been estimated to be ~ 50 per 100 000 inhabitants according to the most recent epidemiological study (Confavreux *et al*., 1987). The Lyons Multiple Sclerosis Cohort can be considered representative of the population of patients with multiple sclerosis in this area, thus making it an appropriate cohort from which one can study the natural history of the disease. For the purpose of this study, the database was locked in April 1997. Approximately half of the patients in the cohort received immunosuppressive drugs at some point during their disease, mainly during the relapsing–remitting phase of the disease, and not before the third relapse. Therefore treatment could not have interfered with the measure of the time between the first and the second relapse. None of these drugs have a commonly acknowledged effect on the progression of irreversible disability in multiple sclerosis (Rudick *et al*., 1997). With respect to azathioprine, which was by far the most prescribed drug in this cohort, a total of 804 patients (44%) had been treated at least 6 months after a mean of 6.2 years after the onset of the disease. The only significant difference associated with azathioprine treatment in this series was related to the time from onset of multiple sclerosis to the assignment of a score of 4, consistent with our decision to prescribe the drug selectively in more rapidly worsening forms of the disease. In contrast, there was no difference between treated and non-treated patients in the time from onset of multiple sclerosis to assignment of a score of 6 or 7, nor in the time from a score of 4 to a score of 6, from a score of 4 to a score of 7, or from a score of 6 to a score of 7. In addition, Betaseron®, the first disease-modifying agent to have been approved for multiple sclerosis, was made available in France no earlier than February 1996.

Numerous studies on the natural history of multiple sclerosis have consistently shown that it takes longer to reach landmarks of irreversible disability in the following patient groups: (i) females and younger patients; (ii) in cases with an initial relapsing–remitting course and a complete recovery from the first neurological episode; (iii) in cases with an optic neuritis and no involvement of long tracts as initial symptoms; (iv) in those with a low number of relapses during the first years of the disease; and (v) in those with longer periods of time between onset of multiple sclerosis and the second neurological episode or the assignment of a score of 4 (Muller, 1949; Thygesen, 1949; Hyllested, 1961; McAlpine, 1961; Fog and Linnemann, 1970; Leibowitz and Alter, 1973; Poser and Hauptvogel, 1973; Kurtzke *et al*., 1977; Confavreux *et al*., 1980, 2000; Clark *et al*., 1982; Poser *et al*., 1986; Phadke, 1987, 1990; Minderhoud *et al*., 1988; Weinshenker *et al*., 1989*a*, *b*, 1991; Riise *et al*., 1992; Runmarker and Andersen, 1993; Midgard *et al*., 1995; Trojano *et al*., 1995; Ebers, 1998; Kantarci *et al*., 1998). The originality of our study is that it is the first to assess the possible influence of the same clinical variables on the progression of irreversible disability from the time of assignment of a score of 4 or 6. None of these variables remained predictive of the time course of disability past this point, which is in accordance with the results seen in primary progressive multiple sclerosis (Cottrell *et al*., 1999).

Our results indicate that the influence of the clinical variables on the progression of irreversible disability is limited to the time from onset of multiple sclerosis to the assignment of a score of 4. This would further indicate that multiple sclerosis is a two-stage disease, with an initial phase of variable duration influenced by clinical variables, and a second phase that is rather invariant with respect to baseline characteristics, course, signs and symptoms assessed at the onset of the disease. This indicates that when a detectable threshold of irreversible disability has been reached, the disease enters a final common pathway, where subsequent progression of disability becomes a seemingly self-perpetuating process amnesic to the clinical history of the disease.

Interestingly, the period from the time of onset of multiple sclerosis to the assignment of a score of 4 takes place mainly during the relapsing–remitting phase of the disease, whereas the subsequent accumulation of irreversible disability to the assignment of a score of 4 develops mainly during the progressive phase of the disease. Our observations, therefore, give credence to the fact that relapses have essentially no influence on the progression of irreversible disability in the long term in multiple sclerosis (Confavreux *et al*., 2000).

The amnesic phenomenon observed in this study may have a biological explanation. There is good evidence that relapses are the clinical counterpart of recurrent acute focal inflammation, whereas progression is that of chronic diffuse degeneration of the central nervous system (Confavreux, 2002; Confavreux and Vukusic, 2002). Our results suggest that inflammation may have only a limited effect on the course of neurodegeneration.

This kind of dissociation between inflammation and neurodegeneration may reflect another dissociation: that between inflammation and its clinical expression. Whereas progression and presumably neurodegeneration appear to be tightly linked in a relentless process, the clinical expression of inflammation essentially operates at random. Serial brain MRI assessments demonstrate that only about one-tenth of the new or active multiple sclerosis lesions give rise to clinical relapse (Compston and Coles, 2002). The clinical expression of a lesion depends on the ability of the lesion to interfere with nerve conduction, as well as the neurological clinical eloquence of the area in which it is located and the lesional volume required to alter the corresponding clinical function.

Two additional points deserve discussion to preclude misunderstanding of our results. First, the detectable threshold of disability was set in our study at a score of 4 for practical reasons. However, this amnesic phenomenon is also observed when the time of assignment of a score of 6 is taken as point of reference. When using other clinical (Fog and Linnemann, 1970) and paraclinical (Rudick *et al*., 1999; Fox *et al*., 2000) approaches, the same observation might be made earlier in the disease using a more sensitive threshold.

Secondly, our results, which have been obtained at the level of a cohort of patients with multiple sclerosis, do not contradict the well known and well documented high variability in disability progression observed among individuals with multiple sclerosis. The amnesic phenomenon shown here surmounts this, remaining consistent and robust at the cohort level. These findings and their suggested biological aetiology may have implications for the design of future therapeutics targeted at later stages of the disease.

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