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Age at disability milestones in multiple sclerosis

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Many efforts have been devoted to the description of the prognosis of multiple sclerosis and its possible influential factors in terms of time to reach disability milestones. By contrast, the age at which patients with multiple sclerosis reach these milestones has not yet stirred much interest. We have tested the hypothesis whether the prognosis of multiple sclerosis depends on the current age of patients and the initial course of the disease. We have assessed disease onset and course, and assignment of scores of irreversible disability in 1844 patients with multiple sclerosis. We have used three scores on the Kurtzke Disability Status Scale as benchmarks of disability accumulation: DSS 4 (limited walking but without aid), DSS 6 (walking with unilateral aid) and DSS 7 (wheelchair-bound). We used Kaplan–Meier analyses to estimate the age of the patients at assignment of disability milestones. The possible influence of the initial course of multiple sclerosis and of other clinical variables early assessable in the disease on these outcome measures was also studied, using the Kaplan–Meier curves for univariate analyses and Cox models for multivariate analyses. For the 1844 patients, median ages at time of assignment of irreversible disability were 44.3 years (95% CI 43.3–45.2) for a score of DSS 4, 54.7 years (95% CI 53.5–55.8) for DSS 6 and 63.1 years (95% CI 61.0–65.1) for DSS 7. These results were essentially similar whether the initial course of multiple sclerosis was exacerbating-remitting or progressive, and whatever the initial symptomatology. Females reached disability milestones at an older age than males. The most influential clinical factor was age at clinical onset of multiple sclerosis: the younger the onset, the younger the age at assignment of disability milestones. Therefore, prognosis in multiple sclerosis appears, at least to some extent, as age-dependent and not substantially affected by the initial course, be it exacerbating-remitting or progressive. Aside acute focal recurrent inflammation and diffuse chronic neurodegeneration, accelerated ageing-related mechanisms may operate in the central nervous system of multiple sclerosis patients.

Keywords: multiple sclerosis; disability; prognosis; age; ageing

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Introduction

For decades, efforts have concentrated on the description of the prognosis of multiple sclerosis and its possible influential factors, providing quite a number of series which are, in many respects, representative of the disease in an essentially untreated population. Many of them are based upon more or less complete prevalence material with a cross-sectional and, in some cases, some longitudinal assessment (Müller, 1949, 1951; McAlpine and Compston, 1952; Leibowitz *et al.*, 1964*a*, *b*; Panelius, 1969; Leibowitz and Alter, 1970, 1973; Poser, 1978; Poser *et al.*, 1982; Clark *et al.*, 1982; Detels *et al.*, 1982; Visscher *et al.*, 1984; Minderhoud *et al.*, 1988; Phadke, 1990; Miller *et al.*, 1992; Riise *et al.*, 1992; Trojano *et al.*, 1995; Kantarci *et al.*, 1998; Amato and Ponziani, 2000; Myhr *et al.*, 2001), whereas four series, that of the United States Army Veterans World War II (Kurtzke *et al.*, 1968, 1970, 1973, 1977), Lyon, France (Confavreux, 1977; Confavreux *et al.*, 1980, 2000, 2003), Gothenburg, Sweden (Broman *et al.*, 1981; Runmarker and Andersen, 1993; Eriksson *et al.*, 2003) and London, Ontario (Weinshenker *et al.*, 1989*a*, *b*, 1991; Cottrell *et al.*, 1999; Kremenchutzky *et al.*, 1999), are based upon long-term longitudinal assessments at more or less close intervals. In their results' analysis, researchers formerly used to consider crude observed data only, gathered from patients who had reached the outcome criteria at the time of the survey. This strategy systematically led to underestimating the time interval to the outcome, as the censored patients (those lost to follow up or who had not yet reached the endpoint at the time of the survey) were not taken into account in the calculations. Modern survival techniques, which take account of data of censored patients, are therefore

always to be preferred, as they provide more accurate estimates. Such techniques have been used in the long-term longitudinal studies of Lyon, Gothenburg and London (Confavreux, 1977; Confavreux *et al.*, 1980, 2000, 2003; Broman *et al.*, 1981; Weinshenker *et al.*, 1989*a*, *b*, 1991*a*; Runmarker and Andersen, 1993; Cottrell *et al.*, 1999; Kremenchutzky *et al.*, 1999; Eriksson *et al.*, 2003), and in several long-term studies with an essentially cross-sectional assessment (Riise *et al.*, 1992; Kantarci *et al.*, 1998; Amato and Ponziani, 2000; Myhr *et al.*, 2001). Overall, the results from these different representative cohorts are consistent. They allow to make several statements with reasonable confidence for a representative population of patients. It takes a median time of 8, 20 and 30 years to reach the irreversible disability levels of DSS 4, 6 and 7, respectively. It takes much longer for cases with an exacerbating-remitting onset than in those with a progressive onset to reach levels of irreversible disability. An older age at onset of multiple sclerosis is associated with a more rapid accumulation of irreversible disability. Last, as lately shown in an Italian study, an older current age is associated with a shorter time to reach disability landmarks and a shift in the distribution of patients towards higher disability levels (Trojano *et al.*, 2002).

These studies all focused on the assessment of the time to reach disability milestones in multiple sclerosis, regardless of the age at which patients reach these landmarks. This is somewhat surprising as onset of the relapsing-remitting and of the progressive phases of multiple sclerosis has repeatedly been demonstrated to be age-related, independently of the overall course of the disease, be it relapsing-remitting, secondary-progressive or progressive from onset (Fog and Linneman, 1970; Leibowitz and Alter, 1973; Confavreux, 1977; Poser, 1978; Confavreux *et al.*, 1980; Minderhoud *et al.*, 1988; Cottrel *et al.*, 1999; Kremenchutzky *et al.*, 1999). On average, mean age at the onset of the relapsing-remitting phase is 30 years whilst it is 38 years for the onset of the progressive phase. Furthermore, we have lately shown that clinically detectable relapses, whenever they may occur, have only a marginal effect on the accumulation of disability and that once a clinically detectable threshold of irreversible disability has been reached, the disease enters a final common pathway where subsequent accumulation of disability progresses at a similar rate independently of the initial course of multiple sclerosis, be it exacerbating-remitting or progressive (Confavreux *et al.*, 2000, 2003). Therefore, cases with an exacerbating-remitting initial course and cases with a progressive onset differ with respect to the time from the onset of multiple sclerosis to reach disability milestones, whereas they are similar regarding the time course accumulation of disability further to the reaching of the clinically detectable threshold of irreversible disability. This prompted us to test the hypothesis whether these differences and similarities could reflect differences in ages at onset of multiple sclerosis and similarities in ages at reaching disability milestones in these two settings. For this purpose, we have referred to the Lyon Multiple Sclerosis Cohort, which is a unique natural history database both in terms of its size and the quantity of data gathered since five decades.

Methods

Patient population and data collection

Patients were identified through the Lyon Multiple Sclerosis Cohort which was established in the Lyon Clinique de Neurologie in 1957. Our clinic serves as the single reference centre for diagnosis confirmation, follow-up and treatment of multiple sclerosis patients for Lyon City and the Rhône-Alpes Region (Confavreux *et al.*, 2000, 2003). Lyon is located within the 'département du Rhône' which had 1 575 000 inhabitants in 1999. The Rhône-Alpes Region is made of eight 'départements' (Ain, Ardèche, Drôme, Isère, Loire, Rhône, Savoie, Haute-Savoie) and counted 5 634 000 inhabitants in 1999. Its population is mainly Caucasian with some admixture, in the last decades, from the former French colonies in North Africa (Algeria, Morocco, Tunisia). This being said, the overall population in the area can be considered as essentially stable. The cohort includes all the patients with a diagnosis of multiple sclerosis examined at least once at the clinic. Data were computerized in 1976 and have been entered on the European Database for Multiple Sclerosis (EDMUS) software since 1990 (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 phase, dates of assignment of the successive scores of irreversible disability), biological, electrophysiological and neuro-imaging data and treatment. Data are entered retrospectively when the patient is first seen at the clinic. Thereafter, they are collected prospectively whenever the patient returns, usually on a yearly basis. New data are automatically checked by the system for their consistency with older information. Confidentiality and safety of the data are ensured in keeping with the recommendations of the French Commission Nationale Informatique et Libertés which also provides approval. All patients give informed consent for having their data 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. At that time, the database was locked for the purpose of epidemiological studies. Diagnosis of multiple sclerosis was established according to Poser's classification (Poser *et al.*, 1983).

A relapse of multiple sclerosis was defined as the occurrence, the recurrence, or the worsening of symptoms of neurological dysfunction lasting over 24 h and usually ending up in partial or complete remission (Confavreux *et al.*, 1992; Lublin and Reingold, 1996). Fatigue alone and transient fever-related worsening of symptoms were not considered as a relapse. Symptoms occurring within a 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, the progressive phase continues throughout the disease though occasional plateaus and temporary minor improvements may be observed (Lublin and Reingold, 1996). Course of the disease was categorized according to acknowledged classifications (Confavreux *et al.*, 1992; Lublin and Reingold, 1996). Initial course was considered as exacerbating-remitting or progressive. Overall course was classified relapsing-remitting when the disease exhibited only relapses and remissions; secondary

progressive when an initial relapsing-remitting phase was followed by a progressive phase whether superimposed with relapses or not; progressive from onset when the progressive phase, whether superimposed with relapses or not, took place right from disease onset. Dates of onset of multiple sclerosis, of relapses, and of onset of the progressive phase were systematically assessed for each patient whenever appropriate.

The Kurtzke Disability Status Scale score was recorded at each visit to determine the extent of disability (Kurtzke, 1961, 1983). We focused on scores which could be easily identified, even when 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 no greater than 100 m without rest; and a score of 7 corresponds to the ability to walk no greater than 10 m without rest while leaning against a wall or holding onto furniture for support. Disability was defined as irreversible when a given score persisted at least 6 months, excluding 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 score. For each patient, the date of assignment to a given score of irreversible disability was assessed whenever appropriate.

Statistical analysis

End-points were ages at the time of assignment of an irreversible score of DSS 4, DSS 6 and DSS 7. They were first estimated for the entire patient cohort. In a second approach, they were estimated following stratification according to the initial course of the disease, and to other clinical variables. Age can be considered as a survival data. This is the time interval from birth to assignment of the chosen disability scores. Whenever the end-points had not been reached, data were censored at the age at the last visit. All the estimates were made using the Kaplan–Meier technique and displayed as cumulative probabilities to reach the end-point under study at a given age. Survival curves were compared using the log-rank test. Cox models were used for continuous data and for multivariate analyses. All computations were performed using SPSS for Windows, version 11.0.

Results

Clinical and demographic characteristics

Among the 2021 patients potentially eligible, 170 classified as possible multiple sclerosis only (Poser *et al.*, 1983) and seven whose initial symptoms were unknown were excluded. The baseline characteristics of the remaining 1844 patients with a diagnosis of definite or probable multiple sclerosis have already been described (Confavreux *et al.*, 2000, 2003). During the follow-up of the 1844 patients, a total of 1026 patients (56%), 595 (32%) and 380 (21%) reached the end-point of DSS 4, DSS 6 and DSS 7, respectively.

Age at time of assignment of irreversible disability levels

For the whole population of 1844 patients, the Kaplan–Meier analysis provided estimates of the median age at time of assignment of an irreversible score of disability. This age was 44.3 years (95% CI, 43.3–45.2) for DSS 4, 54.7 years (95% CI, 53.5–55.8) for DSS 6 and 63.1 years (95% CI, 61.0–65.1) for DSS 7 (Table 1).

Influence of the initial course of multiple sclerosis

The 1562 patients with an exacerbating-remitting initial course were compared to the 282 patients with a progressive initial course of multiple sclerosis with respect to age at time of assignment of irreversible scores of disability. Patients with an exacerbating-remitting onset were older than those progressive from onset for assignment of DSS 4 ($P < 0.001$) and DSS 6 ($P = 0.002$). However, for both assignments, there was some overlap in the 95% CI of the median estimates. As for age at assignment of DSS 7, it was similar in both groups ($P = 0.24$) (Table 1 and Fig. 1).

By contrast, when we analysed the subgroup of 496 patients with a secondary-progressive course among the whole group of 1562 patients with an exacerbating-remitting initial course, we found a significantly younger age at time of assignment of DSS 4 (median: 37.6 years; 95% CI, 36.1–39.1; $P < 0.001$), DSS 6 (median: 45.5 years; 95% CI, 43.6–47.4; $P < 0.001$) and DSS 7 (median: 53.3 years; 95% CI, 51.0–55.7; $P < 0.001$) in this subgroup by comparison to the group of 282 patients with a progressive initial course (Fig. 2).

Influence of other clinical variables

The analysis of the possible influence of other clinical factors essentially showed that male gender was associated with an earlier age at assignment of the irreversible disability landmarks. Similarly, the earlier the age at onset of multiple sclerosis, the earlier the age at assignment of the landmarks of disability ($P < 0.001$ for all the comparisons) (Fig. 3). By contrast, initial symptoms of multiple sclerosis essentially did not influence the age at the time of assignment of irreversible disability (Table 1). These results were confirmed by the multivariate analysis using Cox regression models, showing that a female gender, an older age at onset, and an exacerbating-remitting onset were independently associated with an older age at assignment of irreversible disability levels (Table 2).

Discussion

In this observational study of the natural history of multiple sclerosis, median ages at assignment of irreversible disability scores of DSS 4, DSS 6 and DSS 7 were estimated by the Kaplan–Meier technique at 44, 55 and 63 years, respectively. The initial course of multiple sclerosis had a statistically significant influence on ages at assignment of DSS 4 and DSS 6. Patients with an exacerbating-remitting initial course indeed reached these landmarks at an older age than patients with a progressive initial course. However, the differences were only 2.7 and 2.3 years for median ages at assignment of DSS 4 and

Table 1 Kaplan–Meier estimates of the age of the patients at the time of assignment of the irreversible disability scores of DSS 4, DSS 6, and DSS 7 among 1844 patients with multiple sclerosis

Variable	No. of patients (*N* = 1844)	Age at assignment of DSS 4*				Age at assignment of DSS 6 *				Age at assignment of DSS 7 *			
		Median - yr [95% CI]	25th/75th percentiles	Patients who did not reach the end point (%) #	*P*-value **	Median - yr [95% CI]	25th/75th percentiles	Patients who did not reach the end point (%) #	*P*-value **	Median - yr [95% CI]	25th/75th percentiles	Patients who did not reach the end point (%) #	*P*-value **
Overall	1844	44.3 [43.3–45.2]	34.8/52.6	44	NA	54.7 [53.5–55.8]	43.8/65.5	68	NA	63.1 [61.0–65.1]	51.2/74.8	79	NA
Initial course of multiple sclerosis													
Exacerbating remitting	1562	44.8 [43.8–45.9]	35.2/54.9	52	Reference	55.3 [54.2–56.7]	44.7/70.3	73	Reference	62.8 [60.3–65.4]	51.5/NA	82	Reference
Progressive	282	42.1 [40.2–44.0]	32.9/49.4	4	<0.001	53.0 [51.1–54.9]	41.5/63.2	40	0.002	63.1 [60.0–66.2]	49.2/70.5	64	0.24
Gender													
Male	657	42.2 [41.0–43.4]	34.3/51.8	40	Reference	52.1 [49.3–54.9]	41.6/63.6	63	Reference	61.8 [58.1–65.6]	47.8/74.8	77	Reference
Female	1187	46.0 [44.9–47.1]	35.4/53.4	47	0.003	56.1 [54.5–57.6]	46.1/65.8	70	<0.001	63.1 [62.1–65.4]	53.7/82.1	81	0.012
Age at onset of multiple sclerosis													
0–19 years	216	31.6 [28.3–34.9]	22.3/44.7	50	Reference	46.8 [41.6–52.1]	31.8/58.2	70	Reference	50.3 [42.6–57.6]	34.1/NA	78	Reference
20–29 years	690	36.4 [34.9–38.0]	29.4/48.6	51	<0.001	51.2 [47.6–54.8]	37.0/69.8	73	<0.001	58.2 [50.1–66.3]	42.3/71.2	82	<0.001
30–39 years	558	42.8 [41.6–44.0]	37.3/51.8	44	<0.001	52.5 [50.3–54.7]	43.1/74.8	67	<0.001	59.1 [54.4–63.8]	49.3/NA	79	<0.001
40–49 years	272	48.2 [47.3–49.0]	44.8/51.8	32	<0.001	56.7 [54.3–59.0]	52.0/65.6	61	<0.001	64.8 [61.4–68.3]	56.8/NA	79	<0.001
More than 50 years	108	57.1 [55.6–58.5]	53.2/60.7	24	<0.001	63.8 [62.7–65.0]	58.8/71.6	50	<0.001	70.1 [64.7–75.4]	62.8/74.8	70	<0.001
			<**0.001**				<**0.001**				< **0.001**		

Initial symptoms													
Overall													
Isolated optic neuritis	335	46.1 [43.6–48.6]	37.3/55.6	53	Reference	57.8 [53.7–61.8]	45.7/65.9	73	Reference	65.8 [? - ?]	52.4/NA	84	Reference
Isolated brainstem dysfunction	159	42.7 [39.5–45.8]	35.0/52.2	52	0.36	54.9 [52.3–57.5]	44.5/71.6	72	0.78	61.1 [50.2–71.9]	47.2/NA	79	0.13
Isolated dysfunction of long tracts	964	43.8 [42.6–45.0]	34.8/51.3	49	0.01	54.0 [52.5–55.5]	43.3/64.3	72	0.11	62.8 [57.7–64.3]	51.5/82.1	82	0.39
Combination of symptoms	386	44.3 [42.2–46.3]	33.3/54.7	38	0.11	54.8 [51.3–58.4]	43.8/64.5	63	0.25	61.0 [60.6–65.1]	51.0/72.5	77	0.27
				0.10				**0.36**				**0.57**	
Long tracts involvement													
Yes	1287	43.9 [42.8–45.0]	34.6/52.1	41	0.03	54.2 [52.8–55.5]	43.3/64.3	65	0.06	62.3 [60.2–64.3]	51.4/72.5	78	0.79
No	557	44.8 [43.1–46.6]	36.0/55.6	52	Reference Reference	56.7 [52.2–61.1]	45.0/71.6	74	Reference	65.8 [59.6–71.9]	51.0/NA	82	
Brainstem involvement													
Yes	411	44.7 [42.7–46.7]	33.3/54.2	50	0.99	55.1 [51.6–58.6]	43.3/71.6	71	0.75	61.1 [55.0–67.1]	49.3/74.8	80	0.45
No	1433	44.1 [43.0–45.1]	35.2/52.3	43	Reference	54.5 [53.1–55.9]	44.0/64.8	67	Reference	63.3 [61.4–65.1]	51.5/82.1	79	Reference
Optic neuritis													
Yes	476	45.5 [43.7–47.3]	36.5/55.6	53	0.02	56.7 [53.0–60.3]	45.6/NA	75	0.11	65.8 [? - ?]	51.0/NA	84	0.26
No	1368	43.9 [42.9–45.0]	34.5/52.1	41	Reference	54.2 [52.8–55.5]	43.0/64.5	65	Reference	62.3 [60.3–64.2]	51.2/74.8	78	Reference

*The Kurtzke Disability Status Scale was used to determine the extent of disability (Kurtzke, 1961, 1983). On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for more than 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. A given score of disability was defined as irreversible when a patient had had that score or more for at least 6 months, excluding any transient worsening of disability related to relapses. **P-values were calculated with use of the log-rank test. #Data on the patients who did not reach an end point were censored at the time of the last clinic visit.

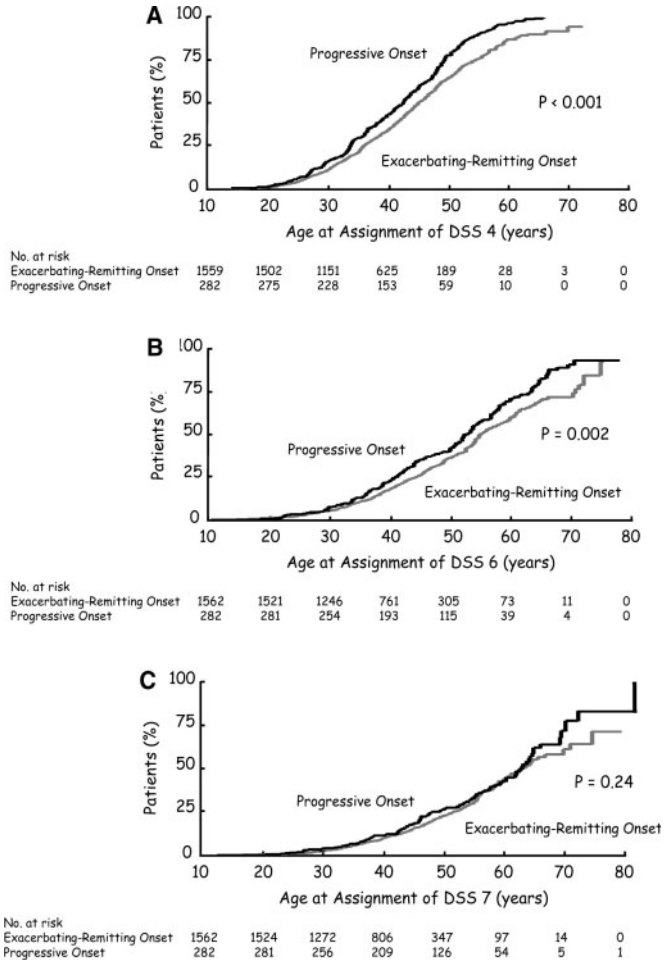

Fig. 1 Kaplan–Meier estimates of the age of the patients at the time of assignment of the irreversible scores of DSS 4 (**A**), DSS 6 (**B**) and DSS 7 (**C**) among 1844 patients with multiple sclerosis, according to the initial course of multiple sclerosis. (**A**) Among the 1562 patients with an exacerbating-remitting onset of multiple sclerosis, three did reach the score of 4 before the age of 10 years. The Kurtzke Disability Status Scale was used to determine the extent of disability (Kurtzke 1961, 1983). On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for more than 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. A given score of disability was defined as irreversible when a patient had had that score or more for at least 6 months, excluding any transient worsening of disability related to relapses.

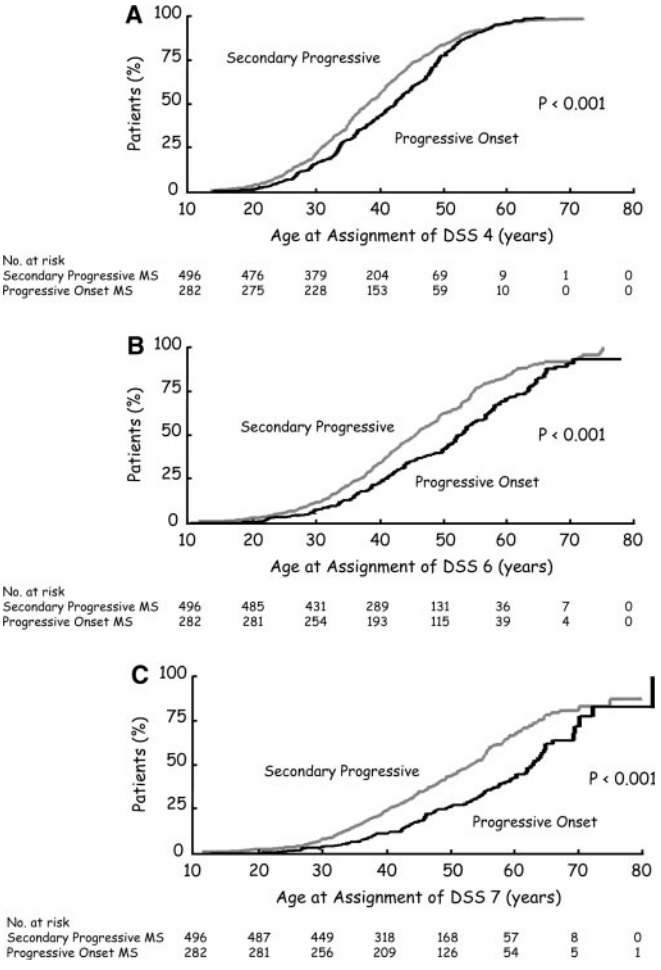

Fig. 2 Kaplan–Meier estimates of the age of the patients at the time of assignment of the irreversible scores of DSS 4 (**A**), DSS 6 (**B**) and DSS 7 (**C**) among 1844 patients with multiple sclerosis, according to a secondary progressive or a progressive from onset course of multiple sclerosis. The Kurtzke Disability Status Scale was used to determine the extent of disability (Kurtzke 1961, 1983). On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for more than 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. A given score of disability was defined as irreversible when a patient had had that score or more for at least 6 months, excluding any transient worsening of disability related to relapses.

DSS 6, respectively, for a disease usually encompassing several decades of life. For both assignments, there was also an overlap in the 95% CI of these medians. There was no difference when the two groups of patients were compared with respect to assignment of DSS 7. One should notice that patients with a secondary-progressive course of multiple sclerosis were younger at time of assignment of DSS 4, DSS 6 and DSS 7 than those with a course progressive from onset. Conversion from the initial relapsing-remitting phase to the secondary progression, as estimated by the Kaplan–Meier technique, occurs at a rather constant rate of 2.5% of patients converting per year. This rate remains quite stable throughout the course of the disease. The median survival time for the conversion is 19.1 years (Vukusic and Confavreux, 2003). Considering therefore a cohort of patients with multiple sclerosis studied at a given time, some of them not yet in secondary progression, the patients who already have experienced a secondary-progressive course at the time of the survey are distinct: they represent a subgroup of more rapidly worsening forms of multiple sclerosis within the entire group of patients with an exacerbating-remitting initial course. Furthermore, the difference in the percentage of censored patients among

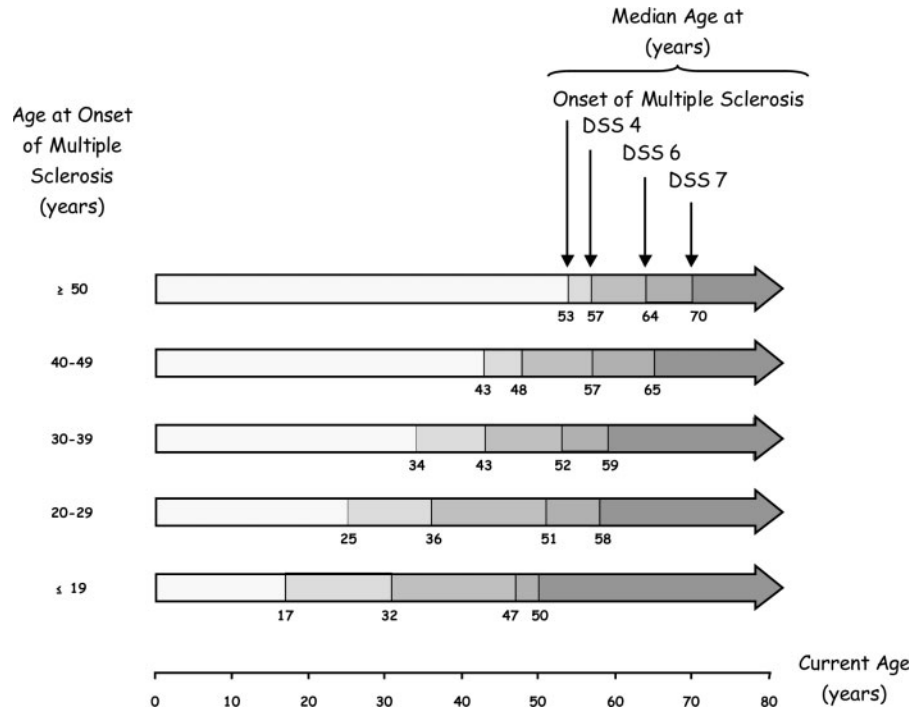

Fig. 3 Age at onset of multiple sclerosis and age at times of assignment of the irreversible disability scores of DSS 4, DSS 6 and DSS 7 among 1844 patients with multiple sclerosis. Each horizontal arrow represents a category of patients by age at onset of multiple sclerosis. The digits below the horizontal arrows indicate the median ages (years) for the corresponding category of patients at onset of multiple sclerosis (*left*), and at assignment of DSS 4 (*middle left*), of DSS 6 (*middle right*), and of DSS 7 (*right*). Ages are estimated by the Kaplan–Meier technique. The Kurtzke Disability Status Scale was used to determine the extent of disability (Kurtzke 1961, 1983). On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for more than 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. A given score of disability was defined as irreversible when a patient had had that score or more for at least 6 months, excluding any transient worsening of disability related to relapses.

exacerbating-remitting and progressive cases, which is greater for the lower disability scores (DSS 4 and DSS 6) with a higher censoring for cases with an exacerbating-remitting initial course, can contribute to the difference in the estimates. Indeed, censoring usually leads to overestimating the medians. It can thus be presumed that the actual age at assignment of irreversible disability levels of patients with an exacerbating-remitting initial course lies somewhere in-between the ages we found for this whole group of patients and the ages we found for the subgroup of patients with a secondary-progressive course, that is closer to the ages we found for patients with a course progressive from onset. Concretely, it can be considered that the initial course of the disease, whether exacerbating-remitting or progressive, does not substantially influence age at disability milestones in multiple sclerosis.

Prevalence of multiple sclerosis in the Rhône-Alpes Region has been estimated to circa 50 per 100 000 inhabitants according to the most recent regional epidemiological study performed (Confavreux *et al.*, 1987). More recently, a nationwide survey of the registries of the 'Mutualité Sociale Agricole', which serves as a mandatory and exclusive health insurance system for the rural population in France, led to a prevalence estimate for multiple sclerosis of 71 per 100 000 inhabitants in the Rhône-Alpes Region by January 1, 2003 (Van Bockstael *et al.*, 2004). The Lyon Multiple Sclerosis Cohort strictly speaking is not a population-based but essentially a clinic-based cohort. However, considering the number of patients with multiple sclerosis enrolled in the cohort and the number of patients that could be expected according to the local prevalence studies, one can reasonably admit that our cohort is representative of the population of patients with multiple sclerosis in the area. About half of the patients in the cohort received immunosuppressive drugs, mostly azathioprine, at some point during their disease, mainly during the relapsing-remitting phase, and not before the third relapse. None of these drugs have proven to reduce progression of irreversible disability in multiple sclerosis and therefore should not have biased the chosen end-point measures in our study (Rudick *et al.*, 1997; Noseworthy *et al.*, 2000; Compston and Coles, 2002). Betaseron®, the first disease-modifying agent approved for multiple sclerosis which became available in France in February 1996, has unlikely biased the results of this study, as the database was locked in April 1997.

The demographic and disease-related characteristics of the 1844 patients of our cohort are consistent with those from representative series in the literature (Müller, 1949, 1951;

Table 2 Final Cox regression models of the age of the patients at the time of assignment of an irreversible disability score of DSS 4, DSS 6, and DSS 7 among 1844 patients with multiple sclerosis

Variable	No. of patients (N = 1844)	Age at assignment of DSS 4*		Age at assignment of DSS 6*		Age at assignment of DSS 7*	
		Hazard ratio** [95% CI]	*P*-value	Hazard ratio** [95% CI]	*P*-value	Hazard ratio** [95% CI]	*P*-value
Initial course of multiple sclerosis							
Exacerbating-remitting	1562	–	Reference	–	Reference	–	Reference
Progressive	282	3.89 [3.25–4.65]	<0.001	2.72 [2.21–3.35]	<0.001	2.39 [1.84–3.10]	<0.001
Gender							
Male	657	–	Reference	–	Reference	–	Reference
Female	1187	0.85 [0.75–0.96]	0.01	0.75 [0.63–0.88]	0.001	0.74 [0.60–0.91]	0.001
Age at onset of multiple sclerosis							
0–19 years	216	–	Reference	–	Reference	–	Reference
20–29 years	690	0.54 [0.43–0.67]	<0.001	0.55 [0.42–0.73]	<0.001	0.49 [0.35–0.69]	<0.001
30–39 years	558	0.23 [0.18–0.28]	<0.001	0.29 [0.22–0.39]	<0.001	0.24 [0.17–0.34]	<0.001
40–49 years	272	0.10 [0.08–0.13]	<0.001	0.13 [0.10–0.19]	<0.001	0.10 [0.07–0.16]	<0.001
More than 50 years	108	0.04 [0.03–0.05]	<0.001	0.07 [0.05–0.11]	<0.001	0.06 [0.04–0.10]	<0.001
			<0.001		**<0.001**		**<0.001**
Initial symptoms							
Isolated dysfunction of long tracts	964	–	Reference	–	–	–	–
Isolated optic neuritis	335	0.76 [0.63–0.91]	0.004	–	–	–	–
Isolated brainstem dysfunction	159	0.96 [0.75–1.22]	0.72	–	–	–	–
Combination of symptoms	386	1.03 [0.88–1.22]	0.71	–	–	–	–
			0.02				

Data on the patients who did not reach an end point were censored at the time of the last clinic visit. *The Kurtzke Disability Status Scale was used to determine the extent of disability (Kurtzke, 1961, 1983). On this scale, a score of 4 indicates limited walking ability but able to walk without aid or rest for more than 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 score of 4 or more for at least 6 months, excluding any transient worsening of disability related to relapses. **A hazard ratio below 1 denotes an older age at disability milestones than the reference group whereas a hazard ratio over 1 denotes a younger age at disability milestones.

McAlpine and Compston, 1952; Leibowitz *et al.*, 1964*a*, *b*; Kurtzke *et al.*, 1968, 1970, 1973, 1977; Panelius, 1969; Leibowitz and Alter, 1970, 1973; Poser, 1978; Fog and Linneman, 1970; Broman *et al.*, 1981; Poser *et al.*, 1982; Clark *et al.*, 1982; Detels *et al.*, 1982; Visscher *et al.*, 1984; Phadke, 1990; Minderhoud *et al.*, 1988; Weinshenker *et al.*, 1989*a*, *b*, 1991; Miller *et al.*, 1992; Riise *et al.*, 1992; Runmarker and Andersen, 1993; Trojano *et al.*, 1995; Kantarci *et al.*, 1998; Cottrell *et al.*, 1999; Kremenchutzky *et al.*, 1999; Amato and Ponziani, 2000; Myhr *et al.*, 2001; Eriksson *et al.*, 2003). They have already been described in detail (Confavreux *et al.*, 2000, 2003). The median time from onset of multiple sclerosis to the initial visit in our clinic was 3 years, with a range from 0 to 53 years. This being said, a specific effort is always made to obtain data from the original medical files, especially for the first neurological episode, and on the clinical course and disability until the initial clinic visit. This effort is facilitated by the existing regional network of neurologists in our area. Most of them have been trained in our hospital in Lyon and maintain tight connections with our clinic for their patients suffering from multiple sclerosis. This organization helps updating regularly the database with follow-up data once the patient has been registered in the database. Except for very few cases, the results of the neurological examinations registered in the database are those of the neurological examinations performed in the clinic.

By definition, the date of onset of progression is assessed in retrospect, once the required six-month duration of continuous neurological worsening has been confirmed. Therefore, there is always some uncertainty regarding this parameter. However, in the collaborative multicentre EVALUED study using the EDMUS system (Confavreux *et al.*, 1992) which involved the Lyon clinic and five other European centres—with 180 patients with multiple sclerosis in all, that is to say two examiners and 30 patients for each centre—the inter-examiner reliability was almost perfect with a κ-value of 0.92 when cases had to be categorized according to an exacerbating remitting or progressive onset (Amato *et al.*, 2004). When both examiners had to decide on the development of secondary progression, agreement was again substantial with a κ-value of 0.76. When they had to date the onset of secondary progression, agreement between both examiners was reached with $\leq$1 year difference in 72% of cases. Concerning the Kurtzke Disability Status Scale, both examiners reached the same score or with $\leq$1.0 point difference in 78 and 97% of the examinations, respectively (Amato *et al.*, 2004).

The originality of our study lies in its being the first ever to show that age at assignment of disability landmarks is not substantially influenced by the type of the initial course of multiple sclerosis, be it exacerbating-remitting or progressive. This is further evidence that neurological relapses, whenever they may occur, have only a limited influence on the accumulation of irreversible disability in the long-term (Confavreux *et al.*, 2000, 2003). This age-dependency of the accumulation of irreversible disability, whatever the initial course of the disease, finds preliminary support in brain imaging studies of patients with multiple sclerosis (Filippi *et al.*, 2001; Kassubek *et al.*, 2003) and in clinico-pathological studies of experimental models of the disease (Smith *et al.*, 1999). However, it would be an oversimplification to consider that accumulation of irreversible disability in multiple sclerosis is strictly age-dependent. As shown in this paper, age at clinical onset of multiple sclerosis is also influential: the younger the onset, the younger the age at assignment of disability milestones. Similarly, the younger the onset, the longer the survival time for converting from an exacerbating-remitting onset of the disease to secondary progression (Vukusic and Confavreux, 2003) and therefore the lower the rate of patients converting per year (S Vulusic and C Confavreux, unpublished personal data). This confirms the complex interaction existing between age at clinical onset of multiple sclerosis and current age, which has already been observed in the Lyon cohort (Confavreux, 1977; Confavreux *et al.*, 1980) and in an Italian study (Trojano *et al.*, 2002). Furthermore, gender is also influential, females reaching disability milestones at an older age than males. By contrast, initial symptomatology of multiple sclerosis was essentially not influential in our series.

The statistical results we have obtained at the level of a large and representative population of patients with multiple sclerosis depict a very homogeneous prognosis of the disease. However, it is important to realize that this does not preclude the considerable inter-individual variability in age at disability milestones in multiple sclerosis. This can be observed in Table 1 by comparing the 25th and 75th percentiles to the median age at disability steps. The age-dependency phenomenon described here surmounts this however, with an absence of influence of the type of the initial course of the disease on the age at disability milestones.

At the pathophysiological level, these clinical results suggest that acute multifocal recurrent inflammation, namely the substratum of clinically detectable relapses (Youl *et al.*, 1991), has only a limited effect on the early diffuse chronic neurodegeneration, which is likely to be the substratum of clinical progression in multiple sclerosis (Confavreux and Vukusic, 2002). They also suggest that, at least to some extent, ageing-related processes might play a role in the chronic diffuse neurodegeneration of multiple sclerosis. Physiological age-related decrease in remyelinating capacity, immunological reactivity or adaptative response to oxidative stress are well-demonstrated (Sohal and Weindruch, 1996; Sim *et al.*, 2002; Chari *et al.*, 2003; Fraker and Lill-Elghanian, 2004). It may therefore be hypothesized that chronic inflammation in multiple sclerosis could elicit an accelerated ageing of the central nervous system. This suggests that, apart from acute focal recurrent inflammation and diffuse chronic neurodegeneration, accelerated ageing-related mechanisms might be taken into account in therapeutic strategies for the control of multiple sclerosis.

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