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ORIGINAL COMMUNICATION

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Multiple sclerosis with a progressive course from onset in Lorraine-Eastern France

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Abstract To investigate the patient characteristics, disease progression, and associated risk factors in patients with multiple sclerosis (MS) with a progressive onset, we conducted a longitudinal population-based study of 359 patients (252 with primary progressive MS (PPMS) and 107 with progressive relapsing MS (PRMS)) in Lorraine, France. As outcome measures, we assessed the time from MS onset to reaching disability status scale (DSS) scores of 4, 6 and 7 and the time from assignment of DSS score of 6 to assignment of DSS score of 7. We studied the influence on these outcomes of sex, age of onset and symptoms of onset. We also studied the influence of the time from MS onset to assignment of DSS 6 on the time from MS onset to assignment of DSS 7.

There were no significant differences in the demographic data (gender and age at onset of MS) and clinical data (median time to DSS scores of 4, 6 and 7) between the patients with PPMS and PRMS suggesting such a distinction may be unnecessary. The male/female ratio in all 359 patients with MS with a progressive onset was 1/1.36. The median age at onset was 42.7 years (25 % Q1 = 34.7; 75 % Q3 = 50.0), was lower for male (40.5 years) than for female patients (44.2 years; p = 0.002). The median time to DSS scores of 4, 6 and 7 were (in years) 3.0 (95 % CI = 2.8 to 3.7), 9.9 (95 % CI = 9.0 to 10.6), and 17.0 (95 % CI = 14.9 to 19.0). A cane was required in 25 % of patients 5 years after onset and in 75 % 15 years after onset. We did not find any significant unfluence of sex, age at onset, or symptoms at onset on the time from MS onset to assignment of scores 6 or 7 or on the time from the assignment of a score of 6 to the assignment of a score of 7.

Key words multiple sclerosis · primary progressive course · sex · disability

Introduction

Approximately 10 % to 20 % of patients with multiple sclerosis (MS) run a primary progressive course characterized by the continuous accumulation of neurological deficits from the onset of symptoms without relapse or remission [15–24]. Patients with Primary Progressive MS (PPMS) have distinctive clinical features including a greater mean age of presentation, approximately 40 years compared with 30 years with Relapsing Remitting MS (RRMS), and affecting relatively more men with a loss of the usual female preponderance [18–23]. Prognosis has been considered poorer in PPMS as time from disease onset to advanced disability is shorter than with RRMS [4, 5, 8]. However, compared with the progressive phase in Secondary Progressive MS, both the age of onset and rate of progression are similar [5]. From MRI

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studies, lesion loads were lower and there was a reduced frequency of both new lesion formation and of gadolinium-enhancement lesions [10].

To date, there is no proven disease-modifying treatment for patients with PPMS [14]. Designing therapeutic trials for this group of patients has presented several problems [27]. Patient recruitment may be difficult because of the relative rarity of PPMS and historically has been hindered by the lack of specific diagnostic criteria [27]. The randomized number of patients in clinical trials is calculated from natural history studies. However, there have been few longitudinal natural history studies of PPMS [6, 8, 22, 25, 26]. Recent studies indicate that the progression of disability in PPMS is slower than that found in previous natural history studies [25]. Progressive relapsing MS (PRMS) and PPMS are not different when comparing these two forms according to demographic and disease-related clinical characteristics such as age at the time of assigning a disability, gender or initial symptoms of the disease [5].

Here, we describe the characteristics, disease progression, and predictors of progression in MS patients with a progressive onset from a longitudinal population-based study in Lorraine, France.

Methods

Patient sampling and data collection

Patients were identified through the Lorraine Multiple Sclerosis (LORSEP) Cohort, which was created in the Department of Neurology of Nancy, France in 1996. The cohort includes all patients with a diagnosis of MS who were examined at least once at the Department of Neurology since 1996 or by the regional network of neurologists in Lorraine since May 2003. The Lorraine Multiple Sclerosis Regional Network comprises neurologists (office-based practice and hospitals), MS centers, radiologists, biologists, nurses, physiotherapists, and the MS Association. Together they account for nearly all of the diagnoses of MS in the Lorraine region. The data were entered into the European Database for Multiple Sclerosis (EDMUS) [2]. Individual case reports included the following: identification and demographic data; medical history; key episodes in the course of MS, including date of disease onset, date of diagnosis, date of onset of the progressive course, Expanded Disability Status Scale (EDSS) evaluation [13], times to assignment of the successive scores of irreversible disability; biological, electrophysiological, magnetic resonance imaging data, and type and dates of treatment. For patients seen at the Department of Neurology in Nancy, data were entered retrospectively if the onset of MS was before 1996, and for patients seen by other neurologists in the Lorraine region, data were entered retrospectively if the onset of MS was before May 2003. The first neurological episode, clinical course, disability, CSF data, and magnetic resonance imaging data were collected from the primary medical files. Other data were collected prospectively after each visit to a neurologist, and they were checked by a clinical research assistant and by the neurologists in charge of the study (M. D. and S. P. V.) for consistency with previous information.

Definition of cases and assessment of patients

Prior to 2002, diagnosis of MS was established according to Poser's classification [21] and, since 2002, by McDonald's classification [16, 20]. Only the cases with definite or probable MS according to Poser's classification were included in the cohort. The clinical onset of MS and clinical variables, including gender, age at onset, and initial symptoms (isolated optic neuritis, isolated brainstem dysfunction, isolated dysfunction of long tracts, and combinations of these symptoms) were assessed in each patient. The progressive phase was defined as the steady worsening of symptoms and signs for at least six months, irrespective of whether there were concurrent relapses. Following onset, patients with a progressive course from onset progresses continuously, although there may be occasional plateaus or temporary improvements in symptoms [15]. If after progressive onset, there are one or more relapses, then the Progressive Relapsing form of MS (PRMS) is diagnosed [15]. To determine the extent of neurological disability, the EDSS score (0 to 10) was recorded at each visit to the neurologist.The DSS score is based on the results of neurological examinations and the ability of the patient to walk. Disability was defined as irreversible when the score was maintained for at least 6 months. By definition, when a given score of irreversible disability was assigned, subsequent scores or disability assessments were equal or worse. Thus, patients were excluded from analysis if the time since the onset of MS was less than 6 months.

Statistical analysis

End points were the time from the onset of MS to assignment of DSS scores of 4, 6, and 7. Demographic data (gender and age at onset of MS) and clinical data (initial symptoms and PPMS vs PRMS) with occurrence of scores of 4, 6, and 7 were analyzed by Kaplan-Meier estimates. The survival curves were compared using the log-rank test to define the predictive value of these criteria. The median time to assignment of the DSS score was given with the 95 % confidence interval (CI) and with quartiles (25 % and 75 % of the population assigned a DSS score of 6 or 7. In addition, the time from onset to assignment of a DSS score of 6 and the time between assignment of DSS scores of 6 and 7 were compared. Multivariate analysis was performed using a Cox regression model. Categorical characteristics were compared using the Pearson χ^2 test, and continuous comparisons were made by Student's independent t-test. Differences were considered significant at $p < 0.05$. All computations were performed using SAS for Windows version 8.2.

Results

In September 2005, there were 2871 patients in the LORSEP cohort. Of these MS patients, 359 (12.5 %) were classified as MS with a progressive onset (252 with PPMS and 107 with PRMS). The mean duration of disease at the last follow-up (onset to last DSS) was 13.6 ± 8.4 years (mean ± SD; range, 1.7 to 53.6 years). Of the 359 patients with MS with a progressive onset, 207 (58 %) were women, whereas women represented 1874 (74 %) of the relapsing-remitting (RR) MS population ($p < 0.0001$). The mean age at onset was 42.7 ± 11.3 years for MS with a progressive onset and 31.4 ± 9.6 years in the RR population ($p < 0.0001$). The median age at onset in the MS with a progressive onset was 41.7 years (25 %Q1 = 34.7 years; 75 %Q3 = 50.0 years).

There is no significant difference on the demo-

Table 1 Comparative demographic and disease-related characteristics of progressive relapsing cases and primary progressive cases among 359 patients with a progressive onset of multiple sclerosis

Factor	Overall	Progressive Relapsing Multiple Sclerosis* (n = 107)	Primary Progressive Multiple Sclerosis* (n = 252)	P value
Sex: no (%)				0.22
Female	207 (58)	67	140	
Male	152 (42)	40	112	
Age at onset, years				
Median	41.7 (17–66)	41.0 (17–58)	42.0 (17–66)	
Mean (SD)	42.7 (11.3)	41.1 (11.4)	43.3 (11.2)	0.10
Kaplan-Meier estimates of the time [median (95 % CI)]: (years)				
From onset of MS to assignment of a disability of				
DSS 4	3.0 [2.8–3.7]	3.1 [2.7–4.3]	3.0 [2.6–3.8]	0.80
DSS 6	9.9 [9.0–10.6]	10.0 [8.1–10.9]	9.8 [8.9–11.6]	0.75
DSS 7	17.0 [14.9–19.0]	15.9 [13.8–21.8]	17.8 [15.4–20.0]	0.72

* Defined according to the Lublin and Reingold classification [15]
CI confidence intervals; *DSS* Disability Status Scale; *SD* standard deviation

graphic data (gender and age at onset of MS) and clinical data (median time to DSS scores of 4, 6 and 7) between the patients with PPMS and PRMS (Table 1). During the follow-up of the 359 MS with a progressive onset patients, a total of 326 (91 %), 219 (61 %), and 124 (35 %) patients reached DSS scores of 4, 6, and 7, respectively. Only 37 (10 %) reached a DSS score of 8.

Kaplan-Meier analysis showed that the median times to DSS 4, 6 and 7 in the MS with a progressive onset population were (in years) 3.0, 9.9 and 17.0 respectively. Five years after onset, 25 % of MS patients with a progressive onset required a cane. After 15 years, this increased to 75 %. In addition, 11 years after onset, 25 % were assigned DSS scores of 7, and this increased to 75 % after 25 years (Table 2).

The median age at onset was significantly lower for male (40.5 ± 10.6 years) than for female patients (44.2 ± 11.6 years; $p = 0.002$); however, the median time to DSS scores of 4, 6, and 7 were similar for both male and female patients.

We attempted to identify predictors of time to DSS scores of 6 or 7 using Kaplan-Meier curves. We found that there was no effect of sex, age at onset (< 35, 35 to 45, and > 45 years), or symptoms at onset (Table 3). There was no significant variation in time to DSS scores of 6 or 7 according to age of onset ($p = 0.13$ and $p = 0.08$). None of the onset symptoms (isolated brainstem dysfunction, isolated dysfunction of long tracts, or combination of these symptoms) predicted the time to DSS scores of 6 or 7 ($p = 0.21$). Univariate analysis showed that the time from the onset of MS to assignment of a

Table 2 Kaplan-Meier estimates of the time (years) from onset of multiple sclerosis to assignment of disability scores (DSS)

	Time to DSS 4 (95 % CI)	Time to DSS 6 (95 % CI)	Time to DSS 7 (95 % CI)
For 25 % of patients	0.8 (0–1.0)	5.1 (4.6–6.3)	11.0 (9.5–12.0)
For 50 % of patients	3.0 (2.8–3.7)	9.9 (9.0–10.6)	17.0 (14.9–19.0)
For 75 % of patients	6.4 (5.8–7.3)	15.2 (13.0–18.2)	25.0 (22.0–38.6)

CI confidence intervals; *DSS* Disability Status Scale

Table 3 Demographic characteristics of 359 patients with a progressive onset of multiple sclerosis and time to assignment of a disability (DSS of 4, 6, and 7)

Factor	No. (%)	Median time (years) to DSS 4 (95 % CI)	Median time (years) to DSS 6 (95 % CI)	Median time (years) to DSS 7 (95 % CI)
Sex				
Female	207 (58)	3.3 (2.8–4.0)	10.2 (9.0–11.0)	18.0 (15.0–20.7)
Male	152 (42)	3.0 (2.4–3.8)	9.1 (8.0–10.8)	15.4 (13.4–20.0)
		$p = 0.43$	$p = 0.44$	$p = 0.80$
Age at onset (years)				
< 35	93 (26)	3.7 (2.8–4.3)	9.0 (8.0–11.1)	16.6 (13.7–20.0)
35–45	119 (33)	3.0 (2.0–4.6)	11.0 (8.7–14.0)	18.8 (15.6–25.0)
> 45	147 (41)	3.0 (2.4–3.7)	9.0 (7.7–10.0)	14.4 (11.0–21.6)
		$p = 0.21$	$p = 0.13$	$p = 0.08$

Kaplan-Meier analysis was used. Overall comparisons of groups were made using a log-rank (Mantel-Cox) test

DSS score of 7 correlated with the time from the onset of MS to assignment of a score of 6 ($p < 0.0001$). Also, the time from assignment of a score of 6 to the assignment of score of 7 correlated with the time from the onset of MS to assignment of a score of 6 ($p = 0.01$) (Table 4).

Only 23 % of this cohort of patients received a treatment which consisted of an immunosuppressor treatment (mainly cyclophosphamide) for the majority (87 %). There was no significant difference in the median time to EDSS 6 and 7 between treated and non-treated patients ($p = 0.55$ and 0.69 respectively).

Multivariate Cox regression analysis for simultaneously assessing the effects of sex, age at onset (continuous), and time to a DSS score of 6 (continuous) showed that only the time to a DSS score of 6 was a significant predictor of assignment of a score of 7. There was no significant predictor of time between assignment of a score of 6 and assignment of a score of 7 (Table 5). Neither did multivariate Cox regression analysis for simultaneously assessing the effects of sex, age at onset (continuous), and time to DSS score of 4 (continuous) show that the time to a DSS score of 4 was a significant predictor of assignment of a score of 6 ($p = 0.72, 0.43$ and 0.21 respectively).

Comment

The age at onset in our MS with a progressive onset population (42.7 years) was higher than that found in other studies (37 to 41 years) [6, 17, 25]. We found that male patients developed symptoms 3.7 years earlier than female patients, which is similar to some other reports [6, 17], although the age at onset of symptoms was the same for male and female patients in British Columbia [25]. The male/female ratio of our population (= 1:1.36) was very near to that in other studies (male/female ratio = 1:1.3) [6, 17, 19].

Our MS with a progressive onset population in Lorraine, France (n = 359) represents a lower proportion of the total MS cohort (12.5 %) than in London, Ontario, Canada (20 %) [6] but is close to that in Lyon, France (15 %) [3] and Goteborg, Sweden (14 %) [22] and equal to that of British Columbia, Canada (12.4 %) [25]. Our population took a median of 9.9 years to reach a sustained DSS score of 6 (i. e., requiring a cane), which was somewhat longer than reported in Goteborg, Sweden (6 years; n = 36) [22], London, Ontario (8.5 years; n = 216) [6], and Lyon, France (7.1 years; n = 282) [3] but shorter than reported in British Columbia, Canada (13.3 yr; n = 352) [25].

In this study, we did not identify any predictors of disease progression in the MS with a progressive onset population. The times to DSS scores of 6 and 7 were not consistently affected by sex, age at onset, or onset symptoms. The sole finding was that a more rapid progression to DSS 6 predicted a more rapid progression to DSS 7 [25]. Some studies have similarly found that the rate of progression is set early in the course of the disease, although this is controversial [5, 6]. In addition, some studies have found that the disease progresses more slowly in female than male patients [4], whereas we and others have not observed these findings [6, 25]. Overall,

Table 4 Influence of the time from onset of multiple sclerosis to assignment of a score of 6 on the Kaplan Meier estimates of the median time (years) from onset of multiple sclerosis to assignment of disability score (DSS) of 7 and the median time from assignment of disability score (DSS) of 6 to assignment of a score of 7

(Mantel-Cox) test	Time (years) from assignment of an DSS score of 6 (95 % CI)			
	< 5 years	5–10 years	> 10 years	p value
Median time from onset of MS to assignment of an DSS score of 7	6.7 (6.0–7.7)	11.0 (10.5–12.1)	23.0 (21.6–26.9)	< 0.0001
Median time between assignment of an DSS score of 6 to a score of 7	3.3 (2.3–5.1)	4.1 (3.1–6.1)	5.6 (4.0–6.4)	0.01

Kaplan-Meier analysis was used. Overall group comparisons were made using the log-rank

Table 5 Hazard ration (95 % CI) for demographic and disease-related characteristics in the time from the onset of MS to assignment of a disability (DSS) score of 7 and the time from assignment of disability score (DSS) of 6 to assignment of a score of 7

		Sex	Age at onset of MS	Time from assignment of score of 6 (years)
Time from onset of MS to assignment of score of 7		1.09 (0.76–1.59)	1.00 (0.98–1.02)	0.78 (0.75–0.82)
	p value	0.63	0.81	< 0.0001
Time from assignment of score of 6 to assignment of a score of 7		1.10 (0.77–1.58)	1.00 (0.98–1.02)	0.99 (0.96–1.03)
	p value	0.61	0.97	0.74

Multivariate analysis was performed using a Cox regression model. *CI* confidence intervals

this provides the working clinician with limited clinical or demographic indicators for the disease progression within the PPMS population [8, 9, 12, 25].

Our study included a minority of patients classified as PRMS because they had experience of an acute relapse during follow-up despite a typical progressive course of onset [15]. Disease progression has previously been shown to be nearly identical between PPMS and PRMS [1, 11] and we confirm these data.

There are some limitations to our study, however. First, not only is the diagnosis of PPMS difficult but differences between published studies are unavoidable as the classification of PPMS has changed over the years [16, 20, 23]. Recently, in three MS centres, we compared diagnostic criteria of PPMS between Thompson (definite, probable and possible MS), McDonald and revised Mc Donald criteria. We demonstrated that PPMS could be diagnosed in only 69 % of the patients according to the McDonald criteria, 74 % with revised criteria and 97 % with probable or definite PPMS according to Thompson criteria [7]. Second, because PPMS is a more aggressive form of MS than RRMS, there is a higher proportion of PPMS patients followed in specialized MS clinics than represented in the general population of MS patients. This could introduce a bias in natural history studies of PPMS populations [4]. However, this risk of bias is greatly reduced in our study because the LORSEP cohort is a geographical population-based study with more than 50 % of the patients being seen by neurologists working outside the reference hospital center.

Longitudinal studies demonstrate a similar course of progression and outcome for PPMS and Secondary Progressive MS (SPMS) indicating that PPMS resembles SPMS with the relapsing course removed [4]. Nevertheless, the two forms differ in the sex ratio. Although a sex influence in patients with RRMS and SPMS but not in patients with PPMS has already been described, our study suggests that male PPMS patients developed symptoms earlier than females. A better knowledge of hormonal influence on PPMS is therefore necessary.

The only predictive factor of disease progression in the PPMS population seems to be the progression time to DSS 6 which was predictive of progression time to DSS 7. None of the other assessed factors (sex, age of onset, symptoms at onset) are predictors of disease progression in these patients. In view of these results, only DSS need be used as covariates in the statistical analysis when investigating treatment effect in trials in PPMS or PRMS.

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