Objective: *To study if there are different patterns of clinical activity – measured by the annual exacerbation rate (AER) – among relapsing–remitting multiple sclerosis (RRMS), "early" secondary multiple sclerosis (SPMS) and "late" SPMS.* **Methods:** *A prospective 5-year follow-up study in 80 MS patients has been carried out, calculating the AER and the mean expanded disability status scale (EDSS) change rate (MCR).* **Results:** *A significant difference on the AER, among RRMS, early SPMS and late SPMS, has been found.* **Conclusions:** *The SPMS has a high clinical inflammatory activity before and during its transformation from a RRMS.*

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Introduction

Secondary progressive multiple sclerosis (SPMS) is the form of MS characterised by the presence of acute neurological symptoms (exacerbation) and the progressive decline in neurological functions without exacerbations.[1] Until now, only two prospective studies in the natural history of SPMS have been published.[2,3] Of them, only the work of Minderhoud *et al*[3] has studied the beginning of the progressive stage. They found a faster delta progression rate (DPR) early after the first progression year, with a slight decline in the following years. The DPR in this study was defined as the rate between the increase in expanded disability status scale (EDSS) and the disease duration in years. Unfortunately, the relapse rate was not reported in Miderhoud *et al*'s research, and its conclusion was that a significant relationship was found between the relapse rate and the DPR.

The purpose of our work has been to study if there are different patterns of clinical activity among patients with a recent conversion into SPMS, patients with a more evolved SPMS and patients with relapsing–remitting multiple sclerosis (RRMS).

Subjects and methods

Subjects

Eighty consecutive nonselected patients, with clinical definitive MS diagnosis according to the Poser criteria,[4] were included. A prospective study was carried out for 5 years, with an interim analysis of the clinical evolutive forms at year 3, followed by a 2-year follow-up for the confirmation of the clinical forms. The RRMS patients were distributed in two groups according to our criterion. One group included patients that remained in a RRMS form during the first 3 years, and the other group included patients that had evolved into a SPMS form during this time (Table 1).

Methods

Visits were scheduled every 3 months, and unscheduled visits occurred whenever patients felt a new symptom or a worsening of their previous condition. In each visit, the EDSS, the Kurtzke's functional systems and the Ambulatory index were recorded. *Progression* was defined as an increase of one point or more in the EDSS sustained in two scheduled visits, i.e., for 6 months, if EDSS was lower than 6.0, or an increase of 0.5 points if EDSS was equal or greater than 6.0. After a relapse, the basal EDSS employed to consider the progression was calculated 3 months after treatment with steroids, and the progression were considered if the aforementioned criteria were accomplished in the next scheduled visit 6 months after. Only patients who continued progressing in the following 2 years, after the SPMS diagnosis was made, were considered for the analysis in order to avoid cases of RRMS forms with high clinical activity and sequels. The *year of conversion* was set when the patients reached the defined progression criteria. Exacerbation was defined as the presentation of a new symptom which lasted more than 48 h plus an increase of one point in the EDSS or worsening of a previous symptom (except sphinterian worsening) without the presence of fever or another explanation for this worsening. Exacerbations were treated with 1 g of intravenous methyl prednisolone per day

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p**	0.2	0.14	0.09	0.55
Late SPMS	0.4	0.07	0.26	0.26

*Mean AER: mean annual exacerbation rate for the year of conversion and the previous year. **Probability was calculated only between RRMS and the early SPMS patients because no patients with the late SPMS form were on treatment with interferon-β.

for 5 days followed by oral steroids tapering. The study was carried out between January 1996 and January 2001. In the beginning of the study, only the RRMS patients could be treated with interferon-β; thus, 39 patients (39 of 61 RRMS patients, 63.7%) fulfilled the criteria to receive this treatment during the first 2 years of the study, 30 in the group that remained in the RRMS phase and 9 in the "Early SPMS" group. The other 22 RRMS patients refused the treatment (four cases) or did not have clinical activity defined as the presence of two exacerbations in the previous 2 years (18 cases). We calculated the annual exacerbation rate (AER) and the annual medium change rate (MCR) for progression. MCR was calculated as the difference between the EDDS at the end of the years under observation and the basal EDSS divided by the number of years under observation; it has been established in 0.5 EDSS points for the progressive forms (SPMS or PPMS).[2]

We have studied the AER at the "year of conversion" into SPMS, in the previous year and in the following year after the transformation. For this purpose, we have studied two groups of patients – the group that evolved to SPMS in the second year (six patients) and the group that evolved to SPMS in the third year (seven patients). In these two, we have observed a high AER during the year of conversion and in the previous year, with a decrease in the following year (Table 1). We also have examined the effect of interferon-β in the evolution to SPMS, and we have not observed any difference (Table 2). We have compared the AER between the RRMS and the early SPMS, but not with the late SPMS, because in this group no patients were treated with interferon-β.

Finally, we have analysed the changes in the median change rate on the EDSS for all groups (RRMS, early SMPS, late SPMS and PPMS). A significant difference on the MCR, between early SPMS and late SPMS, was found at the third and fourth year and at the end of the study ($P<0.005$ in the three MCRs), but not between late SPMS and PPMS patients (Table 3).

Data were introduced in a database created for this purpose and were analysed with the SPSSPC v2.4 statistical package. Student's t-test was used for analysis of means. When the distribution was not normal, according to the Kolmogorov–Smirnov test or the Shapiro–Wilks test, Mann–Whitney's U-test was used.

Results

The initial distribution of the clinical forms according the criteria of Lublin *et al*[1] was: 61 RRMS (76.3%), 13 SPMS (16.3%) and 6 primary progressive MS – PPMS (7.5%). Clinical and demographical characteristics are described in Table 4. Along the time of this study, 13 patients (21.3%) changed from RRMS to SPMS, 6 patients at year 2 and 7 patients at year 3; this group of patients was designed as "Early SPMS". At the end of the study at the third year,

Table 2 Influence of interferon-β on the evolution to SPMS

	Remained as RRMS	*Evolved to SPMS*
(A) Evolution to SPMS in patients with or without interferon-β treatment on the second year; P=0.6 (Fisher's exact test)		
Patients under interferon-β treatment	35	4
Patients without treatment	19	2
(B) Evolution to SMPS in patient with or without interferon-β treatment on the third year; P=0.49 (Fisher's exact test)		
Patients under interferon-β treatment	30	5
Patients without treatment	17	2

Mean	3.19	3.11	4.23	5.38	5.76	6.27	0.73	0.64	0.60
Median	3.00	3.00	4.50	6.00	6.00	6.50	0.83	0.62	0.60
(C) EDSS for late SPMS patients									
Cases	13	13	13	13	13	10	13	13	10
Missing	0	0	0	0	0	3	0	0	3
Mean	6.00	6.30	6.73	7.03	7.11	7.14	0.34	0.27	0.24
Median	6.00	6.50	6.50	7.00	7.50	7.20	0.33	0.25	0.29
(D) EDSS for PPMS patients									
Cases	6	6	6	6	6	5	6	6	5
Missing	0	0	0	0	0	1	0	0	1
Mean	4.58	5.16	5.41	5.50	5.75	5.60	0.30	0.29	0.34
Median	3.75	4.75	5.00	5.25	5.75	6.00	0.33	0.31	0.40

[a]Delta rate (MCR) between basal EDSS and EDSS on the third year. [b]Delta rate (MCR) between basal EDSS and EDSS on the fourth year. [c]Delta rate (MCR) between basal EDSS and EDSS at the end of the study.

47 patients remained in the RRMS group, but the SPMS group ("Early SPMS" and "Late SPMS") had increased to 26 patients – 6 patients remained in the PPMS group and 1 patient had been lost to follow-up. Therefore, 13 patients had evolved from RRMS to SPMS (21.3% of the RRMS patients), 6 patients in the second year and 7 in the third year.

In the group of the "Early SPMS", we found an AER of 1.23 in the first year, 1.0 in the second year and 0.76 in the third year, the mean AER for the 3 years being 1.0; whereas the AER in the RRMS group was 0.59 in the first year, 0.51 in the second year and 0.34 in the third year (mean AER for the 3 years was 0.4). Differences were significant in each year, and also in the mean AER for the 3 years ($P=0.01$, $P=0.05$, $P=0.05$ and $P=0.01$, respectively). When we compared the AER in these years between early SPMS and late SMPS, we found that AER in late SPMS was 0.6 in the first year, 0.4 in the second year and 0.07 in the third year, the mean AER for the 3 years being 0.3. There were no differences between RRMS patients and late SPMS except at the third year. Nevertheless, a trend for the first year, and significant differences on the third year and on the mean AER for the 3 years, between the early SPMS and late SPMS were reached ($P=0.06$, $P=0.01$, $P=0.01$, respectively). In all cases, Mann–Whitney's *U*-test was used (Table 5).

The demographic and clinical characteristics in the RRMS group and the early SPMS were comparable on the age and on the mean evolution time since diagnosis, but there was a significant difference on the EDSS at the beginning of the study ($P=0.02$, Student's *t*-test). Differences in the mean evolution time since diagnosis were significant between early SPMS group and late SPMS group ($P=0.04$) (Table 6).

After 5 years of follow-up, five more patients have evolved into SPMS in the last 2 years. However, these patients have still been analysed in the RRMS group until confirmation of progression. These patients are responsible

Table 4 Clinical and demographic characteristics of patient at baseline

	n *(%)*	*Mean age*	*Sex (M/F)*	*Mean age at diagnosis*	*Mean evolution time*	*Mean time since progression*	*Median EDSS (range)*
RRMS	61 (76.3)	35.8	20/41	28.5	7.1*	–	3 (0–5.5)
SPMS	13 (16.3)	46.5	0/13	33.4	12*	5	6 (4–8)
PPMS	6 (7.5)	49	3/3	42.3	5.1	–	3.7 (4–8)

*$P=0.04$.

for the increase of the MCR in the last 2 years in the RRMS group (Table 1).

Discussion

We herein report a prospective study on a cohort of 80 consecutive, nonselected MS patients. We have studied the clinical inflammatory activity of the disease along these years and we have found a significant increase in the AER in patients during the year of conversion into SPMS. Diagnosis of SPMS is very difficult because there is not a moment in which one can determine that a patient "is" in a secondary progression, e.g., it may be that a rapid increase in the disability be due to an exacerbation or its sequelae, and if there are many exacerbations, it is impossible to consider progression between bouts. The EDSS was measured 3 months after steroid treatment for an exacerbation and each 6 months, in order to avoiding a possible factor of confusion for a result being secondary to a sequel to an exacerbation and not due to real progression. Also, we extended the study for 2 years, and considered patients with an SPMS form only if the patient would continue progressing in the last 2 years of the study. Then the diagnosis of SPMS was made in agreement with the criteria of impairment of one point or more sustained in two visits separated by 6 months, and 3 months after an exacerbation.

We assume that this is not a natural history study because many patients (but not all) with initial RRMS, and no patients with late SPMS, are in treatment with interferon-β. In the case of the late SPMS patient, treatment was not available for this indication, and recently, interferon-β action over exacerbations in both RRMS and SPMS has been shown. For this reason, we cannot compare the AER between early SPMS and late SPMS; nevertheless, the patients under interferon-β treatment were those who presented more accounts of exacerbations ($P=0.01$).

In our analysis of the clinical activity at the year of conversion and on the previous year, results were consistent with the global results; and in the two groups of patients that evolved to SPMS on each year of observation, the behavior was similar, with an increase in the AER at this moment. The effect of interferon-β did not seem to influence the conversion into SPMS; these results are in line with the recent analysis on the natural history of the disease reported by Confavreux *et al*,[11] in which it was shown that the evolution to SPMS was not related to the number of exacerbations.

With respect to the analysis of the MCR, we consider that our results are not comparable between early and late SPMS because it has been demonstrated that the EDSS is not a lineal scale and the time that a patient is on the range between 3.5 and 6 is lower than at scores near both ends of the scale. We think that in our study, the similarity between the MCR in the late SPMS and PPMS is an important finding, but we do not conclude that a faster conversion of three to six EDSS is the expression of a more clinical activity, as occurs in the early SPMS.

The use of steroids did not seem to influence the conversion into SPMS since all exacerbations had been treated similarly (see Methods). Similarly, the use of β-interferon did not affect results because 35 patients were in treatment for almost 2 years, 7 of which developed SPMS, the difference on the AER between them being significant. At the end of the 3 years, 28 patients remained as RRMS and 7 evolved to SPMS; the AER were 0.6 and 1.2, respectively ($P=0.001$).

In summary, our results show that there exists an increase in the number of exacerbations compared to the RRMS and the late SPMS at the moment of conversion into SPMS, in line with the results of Minderhoud *et al*[3] We

Table 6 Evolutive characteristics of RRMS patients who remained in RRMS after 3 years, patients who changed their clinical form from RRMS to SPMS (early SPMS) and late SPMS patients

	n	*Mean age*	*Sex (M/F)*	*Mean age at diagnosis*	*Mean evolution time*	*Initial median EDSS*
RRMS	47	35.4	15/32	28.5	6.5	2.5*
Early SPMS	13	37.4	4/9	28.2	7.6**	3.5*†
Late SPMS	13	46.5	0/13	33.4	12**	6.0†

Statistical significant differences were reached in the initial EDSS between RRMS and early SPMS, the mean evolution time between early SPMS and late SPMS and in initial EDSS between early SPMS and late SPMS. *$P=0.03$, Mann–Whitney's *U*-test. **$P=0.04$. †$P<0.000$, Mann–Whitney's *U*-test.

above are the three studies of interferons in SPMS. The main difference between them was the time of evolution since the beginning of the progressive stage. In the European interferon beta-1b study,[5] it was 2.1 years, while in the USA interferon beta-1b study[6] and in the SPECTRIMS,[7] it was 4 years. In these trials, contradictory results were obtained apparently. While the European interferon beta-1b study showed a reduction in the progression of the disability, this objective was not reached at the SPECTRIMS and the USA interferon beta-1b studies. One possible explanation for these results is that in the European interferon beta-1b study, a higher number of patients with more inflammatory activity (exacerbations) were included. According to the results of several RRMS trials,[8,9] the significant lower MCR in the treatment group compared to placebo group had a relationship with the effect of interferon-β on the disability due to exacerbations, and not with a possible effect over the progression. A retrospective study of Hughes and SPECTRIMS Group[10] after the publication of the SPECTRIMS results has approached this issue. They classified the SPMS placebo patients in two groups: a "relapsing" SPMS group and a "nonrelapsing" SPMS group. They found more activity in the exacerbation rate and a faster progression in the first group.

On the other hand, our MCR results in the late SPMS and in PPMS (between 0.25 and 0.35) are lower than those in other published studies. This fact supports the hypothesis that there is a similar mechanism responsible for progression which is independent of the previous stage of the disease, as it has been pointed out by Confavreux *et al*[2,11] Thus, the main difference between the SPMS and the PPMS is the disability degree at the beginning of progression.

To conclude, we should take into account that there is a higher clinical inflammatory activity in "Early SPMS"; this is an important fact for the design of future trials, but it is

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