Transitional progressive multiple sclerosis: a clinical and imaging study

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Abstract

Objective—To study the prevalence and the natural course of transitional progressive multiple sclerosis (TPMS). This clinical form is defined by a progressive course beginning many years after an isolated bout.

Methods—214 consecutive outpatients with definite or probable multiple sclerosis were studied. The prevalence of TPMS was established. Patients with TPMS were compared with patients with other progressive forms of multiple sclerosis according to the clinical course. A prospective one year follow up study was performed in a subgroup of patients to compare progression of the disease using clinical indices and MRI.

Results—In this clinical population of 214 outpatients with multiple sclerosis, 55 had secondary progressive multiple sclerosis (SPMS), 38 primary progressive multiple sclerosis (PPMS), and 12 TPMS. Retrospective analysis of the clinical data of these patients shows that TPMS is very similar to SPMS at the beginning of the disease (age at onset, time before progression, clinical symptoms at onset, progression index). In addition a cohort of patients was prospectively followed up clinically and by MRI for one year. Conclusions—The results did not show any significant differences between the three forms during this follow up. However, all data showed a concordant trend suggesting that at this progressive stage, TPMS is closer to PPMS in terms of progression of disability and new MRI lesions.

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The distinction between clinical forms of multiple sclerosis has gained attention with the evidence that different pathophysiological mechanisms are involved at different stages of the disease, and therefore that different therapeutic goals have to be achieved. Recently, Lublin and Reingold published consensus definitions of these clinical forms. However, these definitions did not include transitional progressive multiple sclerosis (TPMS). This form was originally defined by McAlpine as a progressive course without superimposed relapse beginning many years after an isolated bout. Usually these patients are classified with patients with secondary progressive multiple sclerosis (SPMS). However, recently Filippi et al. presented evidence from MRI analysis of a case that TPMS may be closer to primary progressive multiple sclerosis (PPMS) than SPMS. This study was designed to determine the frequency of this clinical type in a specialised outpatient multiple sclerosis clinic and to compare it with other progressive forms of multiple sclerosis.

Methods

CLINICAL STUDY

All consecutive outpatients seen between 1 September 1993 and 20 March 1995 with a diagnosis of definite or probable multiple sclerosis were included in the study and included in our multiple sclerosis database. This database, the European database for multiple sclerosis (EDMUS) software, has been described elsewhere. To complete retrospective data, all information obtained from their medical files were checked by a neurologist during the consultation and compared with the history obtained from the patient interview. We obtained medical files for almost all the patients. From 214 patients with multiple sclerosis included in EDMUS during this period, 105 were in a progressive phase, defined as a steady increase in disability for more than six months measured by the expanded disability status scale (EDSS) or ambulatory index (AI).

 Patients were classified in three groups—PPMS, SPMS, and TPMS. PPMS and SPMS were defined according to EDMUS coordinating centre definitions. TPMS was defined by: steady progression occurring several years after an isolated bout with or without sequel. Retrospective data used in this study concerned sex, age at onset, age at onset of the progressive phase (SPMS and TPMS), symptoms of the initial bout (SPMS, TPMS),
The intervals between scans were strictly six months for all the patients: four with PPMS, eight with SPMS, and three with TPMS.

STATISTICS
Groups were compared using the \( \chi^2 \) test with Yates’ correction if applicable. Means were compared by Students \( t \) test and a distribution free test (Wilcoxon rank sum test) when conditions for the \( t \) test (normal distribution, similar variances) were not achieved.

Results

CLINICAL CHARACTERISTICS OF EACH GROUP
Twelve patients were diagnosed as having TPMS (11.4% of 105 patients with progressive multiple sclerosis; 5.6% of the multiple sclerosis population screened), 55 patients were diagnosed as having SPMS (52.4% and 25.7%), and 38 patients as having PPMS (36.2% and 17.8%). Three out of 38 patients with PPMS had a history of exacerbation at the onset of disease followed immediately by the progressive stage. Table 1 shows clinical characteristics. Several differences were found. The mean age at onset of patients with PPMS was significantly higher than that for patients with TPMS and SPMS. The age at onset of the progressive phase was, however, very similar in all groups in PPMS. The progression index of patients with PPMS was significantly higher.

Table 2 shows the symptoms reported at onset in the patients with progressive multiple sclerosis according to the EDMUS classification. Patients with PPMS began their disease less often by an optic neuritis but more often by lower limb motor impairment than patients with TPMS. By contrast, patients with SPMS did not differ from patients with TPMS for the clinical symptoms reported at onset.

IMAGING STUDY
Fifty nine MRI scans obtained at different intervals in 19 patients (five PPMS, 11 SPMS, and three TPMS), all included in the clinical study, on the same 1.5 T magnet (Siemens) according to the following protocol: proton density weighted and T2 weighted spin echo sequence (TR=2400, TE=30/80) and T1 weighted spin echo sequence (TR=600, TE=20) five minutes after intravenous injection of 0.2 mg/kg gadolinium-DTPA. Careful attention was paid to obtain good repositioning of patients for serial studies using the recommendations of Miller et al.1

The analysis was performed to detect activity of the disease during the observation period. The mean number of enhanced lesions—that is, the number of enhanced lesions on post-gadolinium T1 weighted sequences plotted against the number of MRI examinations—was counted (16 from five patients with PPMS, 33 from 11 patients with SPMS, and 10 from three patients with TPMS). The mean number of new lesions, not present on a first scan and measured at least 5 mm on a T2 weighted scan performed six months after the first, were counted. T2 lesions less than 5 mm were not measured to avoid partial volume averaging.

The mean number of new lesions on T2 weighted images in six months was not significantly different between groups (0.75 (0.8) in PPMS, 0.6 (0.5) in TPMS, and 1.1 (1.1) in SPMS).

The mean number of enhanced lesions—on post-gadolinium scans
The mean number of enhanced lesions by scan was not significantly different between groups (0.1 (0.3) in PPMS, 0.1 (0.3) in TPMS, and 0.3 (0.8) in SPMS).

New T2 lesions
The mean number of new lesions on T2 weighted images in six months was not significantly different between groups (0.75 (0.8) in PPMS, 0.6 (0.5) in TPMS, and 1.1 (1.1) in SPMS).
TPMS is not rare. In our multiple sclerosis outpatient clinic it represents 5.6% of the patients and 11.4% of progressive patients. However, our multiple sclerosis clinic is a tertiary referral clinic, probably with an overrepresentation of patients at the progressive stage (49.1%) compared with the general multiple sclerosis population. Patients at the progressive stage are more severely affected by their disease and therefore more likely to be referred to a specialised multiple sclerosis clinic. However, referring physicians were not aware of the study or of a special interest of our team in progressive stage patients. The mean number of enhanced lesions on MRI, which reflect the damage to the blood-brain barrier usually associated with the inflammatory stage of the lesion, was, as expected, low in these patients at a progressive stage. However, this number seems to be very low in TPMS, as in PPMS. Similarly, although not significant, the mean number of new T2 lesions was lower in PPMS and TPMS than in SPMS. We did not include small lesions in our analysis to avoid partial volume averaging. However, it is known that small lesions are common in patients with primary progressive multiple sclerosis. To solve this problem it would be interesting to measure lesion loads in these patients and to compare these with secondary and primary patients. A larger cohort, in a multicentre study, is necessary to compare patients with the same duration of disease and the same duration of progression phase. However, our results confirm the findings of Filippi et al. These results suggest that TPMS is associated with a low activity of disease in terms of the appearance of new lesions at this stage; the situation is similar in PPMS. The precise mechanisms of the pathological process at the progressive stage of TPMS may be closer to those of PPMS than those of SPMS. This has to be taken into account in clinical trials when new drugs are tested.

In conclusion, this study gives some evidence that TPMS is very similar to SPMS from a clinical point of view at the beginning, but suggests that at the progressive stage it shares similar features with PPMS in terms of pathological activity and increase in disability.