Transitional progressive multiple sclerosis: a clinical and imaging study

Annick Gayou, Bruno Brochet, Vincent Dousset

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.

Keywords: multiple sclerosis; magnetic resonance imaging; progressive multiple sclerosis; transitional multiple sclerosis

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 specialized 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 used in this study, 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 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.

PROSPECTIVE ASSESSMENT
Sixty five patients were seen at least twice at a mean 0.98 (SD 0.20) year interval during the study: nine with TPMS, 36 with SPMS, and 20 with PPMS. The patients included in this follow up did not differ from the whole population according to sex ratio, age at onset, duration of disease, or EDSS at the first visit in the study (data not shown). The mean increases for EDSS scores were 0.18 (0.47) for PPMS, 0.28 (0.36) for TPMS, and 0.39 (0.61) for SPMS. Comparison of EDSS changes by the Wilcoxon rank sum test shows that the differences did not reach significance.

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 measuring 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 numbers of new lesions (measured to avoid partial volume averaging) were not significantly different between groups (0.1 (0.3) in PPMS, 0.1 (0.3) in TPMS, and 0.3 (0.8) in SPMS).

MII STUDY
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).

### Table 1  Clinical characteristics of 105 patients with progressive multiple sclerosis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>TPMS (n=12)</th>
<th>SPMS (n=55)</th>
<th>PPMS (n=37)</th>
<th>P value TP/SP</th>
<th>P value TP/PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Women</td>
<td>58.3</td>
<td>60.0</td>
<td>52.6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Mean age at onset (y)</td>
<td>30.5 (10.9)</td>
<td>29.9 (8.9)</td>
<td>38.7 (7.9)</td>
<td>NS</td>
<td>&lt;0.01†</td>
</tr>
<tr>
<td>Mean age at onset of progression (y)</td>
<td>39.1 (9.4)</td>
<td>40.4 (8.6)</td>
<td>38.7 (7.9)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Duration of the remitting phase (y)</td>
<td>10.5 (6.0)</td>
<td>8.5 (8.0)</td>
<td>—</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Total remission after onset bout (% patients)</td>
<td>66.7</td>
<td>69.1</td>
<td>—</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>% With bouts during the progression</td>
<td>16.7</td>
<td>25.5</td>
<td>13.2</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Progression index (EDSS/nt)</td>
<td>0.48 (0.4)</td>
<td>0.50 (0.3)</td>
<td>0.83 (1.2)</td>
<td>NS*</td>
<td>P&lt;0.05†</td>
</tr>
</tbody>
</table>

* $\chi^2$ test comparing patients with PPMS and TPMS; † $t$ test comparing patients with PPMS and SPMS. Values in parentheses are SD. TPMS = transitional multiple sclerosis; APMS = secondary progressive multiple sclerosis; PPMS = primary multiple sclerosis.

### Table 2  Symptoms at onset in 105 patients with progressive multiple sclerosis (n (%) )

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>TPMS (n=12)</th>
<th>SPMS (n=55)</th>
<th>PPMS (n=37)</th>
<th>P value TP/SP</th>
<th>P value TP/PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>LL</td>
<td>7 (58.3)</td>
<td>29 (52.7)</td>
<td>32 (86.5)</td>
<td>NS</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>UL</td>
<td>0</td>
<td>7 (12.7)</td>
<td>4 (10.8)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SS</td>
<td>4 (33.3)</td>
<td>18 (32.7)</td>
<td>7 (18.9)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>ON</td>
<td>4 (33.3)</td>
<td>11 (20.0)</td>
<td>2 (5.4)</td>
<td>NS</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>OM</td>
<td>2 (16.7)</td>
<td>8 (14.5)</td>
<td>3 (8.1)</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>FS/FM/VE</td>
<td>1 (8.3)</td>
<td>5 (9.1)</td>
<td>0</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>SP/SX</td>
<td>0</td>
<td>3 (5.4)</td>
<td>7 (18.9)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

P value established by Yates corrected $\chi^2$ test; LL = lower limb impairment; UL = upper limb impairment; SS = sensory symptoms; ON = optic neuritis; OM = oculomotor impairment; FS/FM/VE = facial sensory, motor, or vestibular impairment; SP/SX = sphincter or sexual impairment. For other abbreviations see table 1.
Discussion

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 multiple sclerosis. In a survey of 1055 patients in north-east Scotland, Phadke found 31% of patients with a progressive disease (22% with SPMS and 9% with PPMS). Therefore, TPMS is likely to be less frequent in the general multiple sclerosis population.

The main purpose of this study was to know if the distinction between TPMS and PPMS and SPMS is justified. We studied retrospective clinical data to compare the early stage of the disease in these three groups and prospective clinical and imaging data to compare the ongoing progressive stage. The limited number of patients with TPMS obviously limits the statistical value of the present study. However, some significant results and concordant trends point to certain conclusions.

All retrospective data were concordant. Clinically, TPMS began like an SPMS form with only one initial bout. Several clinical characteristics were very similar between TPMS and SPMS but differed significantly between TPMS and PPMS: age at onset was about 30 years old for TPMS and SPMS and 39 for PPMS, a similar duration of the remission period and the relapsing-remitting phase respectively for TPMS and SPMS (about nine years), lower limb motor involvement was very common in PPMS and less frequent in TPMS and SPMS, the opposite for optic nerve involvement and a progression index greater in PPMS than in the other two forms. Some other characteristics did not reach significance but showed a similar trend: the proportion of women was greater in SPMS and TPMS than in PPMS, sensory symptoms and brainstem involvement were more common in TPMS and SPMS and the proportion of totally remitting bouts at onset was very similar in the two forms. All these data suggest that TPMS is very similar to SPMS, from a clinical point of view, at least at the beginning of the disease.

However we found different results when we looked prospectively by clinical and MRI assessment at the progressive stage in these patients. The limited number of patients may explain the absence of significant results in this part of the study dispute concordant trends with limited dispersion of values. In the progressive stage the rate of progression assessed by change in EDSS rating in patients with TPMS was intermediary between PPMS and SPMS. Patients with PPMS who had the greatest progression index at entry because of the longest duration of their progression phase had a lower progression rate for one year at this stage. Patients with TPMS had a greater progression rate, but this was not as great as in patients with PPMS. A small 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.10 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.11 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 pathological 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.

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