The natural history of multiple sclerosis: a geographically based study


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Summary

Classifications of multiple sclerosis subtypes have been largely based on clinical phenomenology. Nevertheless, definitions of relapse, remission and progression have been imprecise. Recently an international consensus group, as part of a reclassification of disease subtypes, recommended dropping the term ‘relapsing–progressive’ (RP) and retaining the term ‘progressive–relapsing’ (PR) multiple sclerosis. The term ‘RP’ multiple sclerosis had been applied when the early course combined both relapses and progression and was believed to identify some patients with a worse than average outcome. The PR group consisted of patients with primary progressive disease who later in their course developed relapses. Since the terminology has been largely arbitrary, we have evaluated the validity of the terms ‘RP’ and ‘PR’ multiple sclerosis in the context of long-term outcome within a large population-based cohort of progressive multiple sclerosis patients seen at the London Multiple Sclerosis Clinic (Canada) between 1972 and 1984. Mean follow-up of the entire cohort was 25 years. Designation of RP multiple sclerosis did identify a more rapidly progressive subgroup. To realign these natural history data with consensus recommendations, these patients were reassigned to secondary progressive (SP) or to primary progressive (PP) multiple sclerosis, with progression defined as at least 1 year of progressive deterioration. PP multiple sclerosis patients with relapses after a year were designated as having PR multiple sclerosis. Relapses in primary progressive multiple sclerosis occurred in 27.8% of patients at some point even two to three decades after onset. In general these relapses were mild and remitting, but served to blur the distinction between progressive and relapsing–remitting disease. The long-term outcomes of time to Kurtzke disability scores (DSS) of 3, 6, 8 and 10 were compared among the progressive subtypes. Times to these disability end-points and to death were not different between PR and PP multiple sclerosis. Survival curves for progressive patients have been amended to incorporate the reassignment of PR multiple sclerosis patients into the PP group and the RP multiple sclerosis patients into the PP and SP subgroups. The time to reach DDS 3, 6, 8 and 10 for a population-based cohort of primary and secondary progressive patients resulting from the elimination of the categories of RP multiple sclerosis and PR multiple sclerosis has been established. These results provide justification for retaining only PP and SP multiple sclerosis as the subgroups of progressive disease.

Keywords: relapsing progressive multiple sclerosis; progressive relapsing multiple sclerosis

Abbreviations: DSS = Disability Status Score; PP = primary progressive; PR = progressive relapsing; RP = relapsing progressive; SP = secondary progressive

Introduction

Few observers of multiple sclerosis can fail to be struck by the degree of heterogeneity of this disease. Yet in the relative absence of biological understanding, classifications of the various types or categories of what we call multiple sclerosis have been largely based on clinical phenomenology (McAlpine et al., 1955). However, even though the clinical features have been well studied, consensus about widely used terms denoting individual clinical phenotypes has been slow to develop. The popularity of various descriptive terms has been variable over time and the lack of precise definition for
different clinical subsets has been placed into sharp focus by
the use of existing clinical classifications to categorize
patients for studies of genetic and immunological phenomena
(Madigand et al., 1982; Van Lambalgen et al., 1986; Olerup
et al., 1989; Hillert et al., 1992; Acarin et al., 1996) to
develop entry criteria for clinical trials (Schumacher, 1965;
Rose et al., 1976; Poser et al., 1983), and even to serve as
a kind of gating mechanism for determining eligibility for
drug benefits. However, relatively little comparative long-
term natural history information is available to support the
implication that these definitions entail different outcomes,
much less differences in specific biological mechanisms
(Confavreux et al., 1980; Runmaker et al., 1993).

Relapsing–remitting (RR) multiple sclerosis patients have
been studied intensively in recent years, especially in the
context of clinical trials. These studies have contributed
selected kinds of natural history data, which complement
those derived from the follow-up of untreated individuals.
Patients with progressive disease have been studied less
vigorously than those with the RR form, perhaps because
they are less likely to remit spontaneously and are therefore
commonly believed to be less likely to be ‘responders’ to
therapies. Recently, however, progressive disease has received
attention and some tentative progress has occurred (European
Study Group on Interferon β1-b in Secondary Progressive

Although the term ‘progressive’ is used in many contexts,
its has not been well defined. Historically, there have been
several different terms in use describing progressive multiple
sclerosis patients, the justification for which is little more
than descriptive. These include ‘chronically progressive’,
‘primary progressive’ (PP), ‘secondary progressive’ (SP),
‘transitional–progressive’, ‘relapsing–progressive’ (RP),
‘progressive–relapsing’ (PR), ‘progressive–cumulative’,
‘acute progressive’ and ‘malignant progressive’. This
proliferation of terms can be bewildering to newcomers to
the field, who are often surprised to find that even the term
‘progressive’ possesses a definition which is but qualitative
both for duration and degree.

Recently a consensus group has attempted to simplify and
further define the terminology used to describe the clinical
phenotypes of multiple sclerosis (Lublin and Reingold, 1996).
Although the recommendations made were based on
considerable collective experience, unanimity of opinion was
not possible. This was influenced by the fact that there has
been no differential outcome validation for either
recommended or discarded subtypes derived from this
reclassification of progressive multiple sclerosis. In this paper
we evaluate the validity of the terms ‘relapsing–progressive’
and ‘progressive–relapsing’ multiple sclerosis in the context
of the long-term outcome of a large population-based cohort
of multiple sclerosis patients.

Methods

The Multiple Sclerosis Clinic

The Multiple Sclerosis Clinic at the London Health Sciences
Centre, University Campus, London, Ontario, Canada, was
established in 1972 to provide long-term care for multiple
sclerosis patients from its referral area of Southwestern
Ontario. The characteristics of our original population of
1099 patients have been outlined in six previous papers in
this series (Weinshenker et al., 1989a, b, 1991a, b; Cottrell
et al., 1999a, b). In general, primary care is delivered to
patients in the immediate area and secondary care to patients
in the surrounding area. Tertiary referral is provided for
patients with multiple sclerosis from Northern and Southern
Ontario and to a lesser extent for patients from adjacent
provinces and US states. The subgroup from Middlesex
County, which represented 90% of Middlesex County
multiple sclerosis patients at the time of a formal prevalence
study in 1988, has served as a strictly geographically based
standard population against which less strictly defined
subgroups of patients can be compared (Hader et al., 1988).
This subgroup serves to validate the pooling of groups for
total population analysis. In the mid-1980s, patients in the
multiple sclerosis clinic were seen on a yearly basis and an
effort was made to continue this for the natural history cohort
described in detail in this paper. This was not possible for
all patients, many of whom became severely disabled, and it
was particularly difficult for those who became
institutionalized. However, for this latter group, advanced
disability end-points had already been reached. Information
on physical status in the most severely disabled patients has
often been derived from telephone follow-up with physicians,
family and, as much as possible, from the patients themselves.
This has included visits to patients in local nursing homes.

Patients excluded from the analysis

If patients having a clear relapsing–remitting phase in the
first or subsequent years of clinical disease are excluded, there
were 367 multiple sclerosis patients labelled as progressives
(primary and/or relapsing progressives) in the original cohort
at the time of the initial detailed analysis (Weinshenker et al.,
1989). We excluded 25 cases because in eight the course of
the disease was not progressive in long-term follow-up (they
had relapsing disease with unremitting cumulative disability
but not progression between relapses early in the course).
In 14 individuals the diagnosis proved not to be multiple
sclerosis on follow-up, and in three patients there was less
than 1 year of follow-up (too short to contribute to the natural
history study). As a result of this revision we arrived at a
total number of 342 multiple sclerosis patients included in
any of the progressive subgroups. Patients who were difficult
to trace most often resulted from a change of name consequent
to a change of marital status. They were not different from
the population which was easily found in either demographics
or clinical outcome measures (unpublished data).

Population

The present report describes the clinical course of the 342
individuals included in the RP and PP subgroups from the
Table 1 Demographic characteristics of the original PP and RP multiple sclerosis patients and the reclassified PP, PR and SP multiple sclerosis group

<table>
<thead>
<tr>
<th></th>
<th>Original PP</th>
<th>Original RP</th>
<th>Current PP</th>
<th>Current PR</th>
<th>Current SP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>190</td>
<td>148</td>
<td>218</td>
<td>61</td>
<td>538</td>
</tr>
<tr>
<td>Males</td>
<td>76</td>
<td>63</td>
<td>94</td>
<td>24</td>
<td>195</td>
</tr>
<tr>
<td>Females</td>
<td>114</td>
<td>85</td>
<td>124</td>
<td>37</td>
<td>343</td>
</tr>
<tr>
<td>Ratio of males : females</td>
<td>1 : 1.50</td>
<td>1 : 1.35</td>
<td>1 : 1.32</td>
<td>1 : 1.58</td>
<td>1 : 1.76</td>
</tr>
<tr>
<td>Disease duration in years (mean ± SD)</td>
<td>23.0 ± 9.0</td>
<td>24.3 ± 9.8</td>
<td>23.7 ± 9.2</td>
<td>25.2 ± 7.3</td>
<td>25.9 ± 10.2</td>
</tr>
<tr>
<td>Age of onset in years (mean ± SD)</td>
<td>39.0 ± 10.0</td>
<td>31.3 ± 9.9</td>
<td>38.6 ± 10.4</td>
<td>36.7 ± 9.0</td>
<td>29.4 ± 9.0</td>
</tr>
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Fig. 1 The survival curves (time to DSS 10) for the original cohort of PP, SP, RP and RR multiple sclerosis patients.

original cohort of 1044 multiple sclerosis patients consecutively evaluated at the Multiple Sclerosis Clinic at the London Health Sciences Centre between 1972 and 1984, and includes follow-up data gathered for these data sets until 1997.

Definitions
At the first analysis, the clinical course of the multiple sclerosis patients was empirically classified into relapsing from onset (including RR and SP) or progressive from onset, with (RP) or without (PP) superimposed episodes of worsening (Weinshenker et al., 1989a). At that time we had arbitrarily defined RP multiple sclerosis as ‘predominantly progressive disease from onset with superimposed episodes of acute worsening’. This was an attempt to identify a group of patients we had expected to do poorly in which the early course encompassed both relapses and progression. The early development of unremitting disability was often a feature. Following the international consensus recently reached (Lublin and Reingold, 1996), in which it was decided to drop the RP category of the disease, we reclassified our RP patients into retained consensus subtypes. (i) PP multiple sclerosis: disease progression from onset with occasional plateaux and temporary minor improvements allowed, but not distinct relapses. (ii) SP multiple sclerosis: initial RR disease course followed by progression with or without occasional relapses, minor remissions, and plateaux. (iii) PR multiple sclerosis: progressive disease from onset, with clear acute relapses, with or without full recovery. The criterion for progressive

Fig. 2 The survival distribution of the original PP group of patients compared with those reclassified as PP. (A) Time to DSS 8. (B) Time to DSS 10.
disease was continuing deterioration (for at least 1 year) without substantial remission or exacerbation, regardless of the rate of deterioration.

**Variables**

To compare rates of progression we examined the DSS (Disability Status Score) survival curves (time to reach each one of the DSS levels of 3, 6, 8 and 10) of patients from the original natural history series, with data updated to 1997. We also documented the year and DSS level at which the SP patients became progressive, an assessment that is more easily and reliably determined in retrospect. Yearly evaluations eliminated much of the instability that characterizes disability end-points over short-term periods of observation. We compared the rates of survival of PP and SP patients both
from the onset of multiple sclerosis and from the onset of the progressive phase.

**Statistical analysis**
All analyses were done using SAS (SAS Institute, Cary, NC, USA). Survival analysis was performed with SAS/LIFE TEST using the life table (actuarial) method with intervals of 1 year. In this analysis patients who had not yet reached the given DSS level but who had been followed for a known period of time were included as right-censored. The log-rank statistic was used for significance tests of the equality of survival distributions. Missing data points, i.e. DSS scores flanked by times to adjacent DSS strata, were not used in the calculations, resulting in numbers in the denominators that were different from the numbers of patients known to have passed through that level.

**Results**

**Patient populations: characteristics and reassignments**
The 342 multiple sclerosis patients with progressive disease from onset were previously subdivided into two groups, RP and PP. When RP was collapsed into PP and SP using the criterion of 1 year of progressive onset for PP, the PP multiple sclerosis category encompassed some 218 patients, as defined by consensus criteria. The remaining 124 patients had had unambiguous relapses (although usually with partial remission), producing the initial symptoms of the disease, before the progressive stage of their multiple sclerosis. Accordingly, they were reclassified as having SP multiple sclerosis and have been added to the original SP multiple sclerosis subpopulation of the total multiple sclerosis population cohort. The demographic characteristics of the original PP and RP multiple sclerosis patients, and the characteristics of the reclassified PP, PR and SP multiple sclerosis groups compared with the original sets, are shown in Table 1.

**Original cohort and progressive subgroups of PP multiple sclerosis patients: subpopulations and survival curves**
The survival curves for the original cohorts of PP, SP and RR multiple sclerosis patients, and the RP patients as categorized at the first evaluation when median follow-up was some 11 years, are shown in Fig. 1. Among the 218 patients having primary progressive disease as defined, the majority appeared not to have experienced an acute or subacute relapse during the follow-up period. In the remainder, exacerbations (commonly only one) occurred after a preceding progressive onset and following variable intervals. When the original group of PP patients was compared with those 218 reclassified as 'progressive from
onset’ (PP and PR together), no differences were found either in demographic characteristics or in the distribution of survival over time (Fig. 2). One hundred and fifty-seven patients (72.2%) had a ‘pure’ primarily progressive course of the disease (contributing to the PP group), while 61 (27.8%) had late superimposed relapses (and according to the consensus were reassigned to the PR definition). Survival curves of PP and PR subgroups were compared, and were almost identical both for the time from onset of multiple sclerosis and by definition from the onset of the progressive phase to DSS 6 ($P = 0.26$), DSS 8 ($P = 0.14$) or to DSS 10 ($P = 0.21$).

**The ‘late’ relapses**

Examination of the ‘late’ relapses in the PR patients showed that some 50% occurred within the first 10 years of progressive disease, ~40% between 10 and 20 years and ~10% after 20 years, to a maximum of 39 years. These exacerbations were generally mild, often discrete, in extraspinal locations and were characterized by good recovery, the degree of which seemed unrelated to the duration of disease. Although the power to detect an influence of relapses on outcome is limited by their relatively infrequent occurrences, it is enhanced by the long duration of follow-up and the high frequency with which advanced levels of disabilities were reached. Since it was demonstrated that the survival curves to DSS 6, 8 and 10 for PP and PR multiple sclerosis patients were superimposable (Fig. 3A–C), we pooled the PR patients with the PP group.

**The RP multiple sclerosis patients reclassified SP multiple sclerosis**

On the other hand, the original ‘RP multiple sclerosis’ patients, now reclassified as SP multiple sclerosis, did demonstrate a worse outcome than the original SP multiple sclerosis cohort. They reached DSS 8 and DSS 10 significantly sooner ($P = 0.0005$ and 0.03, respectively), reflecting selection for the known prognostic factors of short time to disability (Fig. 4), early progression, frequent relapse and incomplete recovery. We examined survival from the onset of the progressive phase of the SP multiple sclerosis patients compared with that for the PP and RP multiple sclerosis patients. Progression seemed to be more rapid for time to DSS 6 and DSS 8 but less clearly for DSS 10 (Fig. 5). An analysis of the entire SP multiple sclerosis population is beyond the scope of this study and

![Fig. 6 Distribution of time to DSS 6 (A), DSS 8 (B) and DSS 10 (C) for the progressive phase since DSS 2 level in SP patients compared with that for time from the onset of multiple sclerosis to DSS 10 (death from multiple sclerosis) in PP and RP patients.](image-url)
Discussion
The heterogeneity of the clinical course of multiple sclerosis is one of its most puzzling features and has led to many attempts to classify the disease. These attempts have often used the clinical features and particularly the phenomena of exacerbations, remission and relapse progression at points of departure. However, even within the same individual, different phenomena or phases are identifiable and are not always discretely separable. The use of clinical phenotypes has been enduring, although based more on tradition and convenience than on known mechanisms of disease. Under these circumstances, there has been a proliferation of terms used to describe patients with progressive multiple sclerosis and a recent attempt to create some order has been a welcome development. An international committee reviewed disease phenotypes and made specific recommendations for disease categories (Lublin and Reingold, 1996). Although unanimity was not reached for categories of progressive multiple sclerosis, there was a consensus to eliminate the term ‘relapsing–progressive’ (RP) and to preserve the term ‘secondary progressive’ (SP) multiple sclerosis. In order to facilitate categorization, qualitative descriptors were applied to the endorsed categories. However, in this report of the International Committee, the rate and duration of progression required to satisfy definitions, remained unspecified. It is generally true that these terms are more reliably applied to the long-term clinical course, especially when viewed in retrospect. Accordingly, they defined PP multiple sclerosis as ‘disease progression from onset with occasional plateaux and temporary improvements allowed’, but no distinct relapses. There was no consensus for RP (and the discontinuation of this terminology was recommended). The authors of the report suggested another category, namely ‘progressive–relapsing’ (PR), to denote those patients with ‘progressive disease from onset, with clear acute relapses, with or without full recovery’. These recommendations have presented a framework for future study even if the categories are not entirely distinct.

A pragmatic classification would be based on a difference in long-term outcome among subgroups defined by clinical features. However, these characteristics would need to be recognizable relatively early in the course for them to be of practical value. There are distinct general advantages...
of long-term natural history studies for disease classification. Phenomena used to differentiate subgroups have had a greater opportunity to develop, a range of disabilities has occurred, they have become unambiguously unremitting, and substantial numbers of patients will have reached final end-points. For SP multiple sclerosis the interval between clinical onset and onset of progression is highly variable. Furthermore, the beginning of the progressive phase can be indistinct, especially when relapses are prolonged but eventually remit. We have suggested here that 1 year of unremitting progression be required for the designation of progressive multiple sclerosis. The likelihood of remission after such an interval is low, and such a duration of follow-up makes improvement unlikely even in RR multiple sclerosis patients, although plateaux, sometimes quite prolonged, can occur (Rice and Ebers, 1998).

The extension of the follow-up of our population-based natural history cohort to nearly 25 years has meant that a large proportion of patients have reached the hard end-points of wheelchair or bed-bound status and many have died of their disease. In this population of 1044 individuals, the clinical course of 342 multiple sclerosis patients was originally classified as progressive from onset (including PP and RP). By reviewing the updated clinical data of these patients, we have differentiated subgroups to conform to the recent consensus terminology (Lublin and Reingold, 1996), with the minor modification of requiring 1 year of relapse-free progression at onset for the progressive categories. We found that 61 patients fulfilled the suggested category of PR multiple sclerosis while 157 showed a purely progressive course of the disease (PP multiple sclerosis) and were relapse-free. The remaining 124 patients were reclassified as having SP multiple sclerosis and amalgamated into the main SP multiple sclerosis group.

Relapses are used to differentiate PR from PP multiple sclerosis. Relapses occurred in primary progressive patients in the first 10 years in half the cases, but in the other half they occurred at intervals from onset of up to 20 years or longer. In no patients were relapses frequent—most had but a single episode but they were discrete and usually extraspinal, although this may be dependent on ascertainment. Relapses were usually mild and followed by good recovery. There were no differences in terms of the distribution of survival in time to reach DSS 3, 6, 8 and 10 when comparing PP and PR patients (Fig. 3). Accordingly, there appears to be no good reason to preserve the category of PR multiple sclerosis or to consider any differently those with relapses following at best 1 year of PP disease. Although pathology may show some differences between PP and SP multiple sclerosis (Revesz et al., 1994), data are limited so far and are not well controlled for age and duration of disease, not to mention potential ascertainment biases. Although often cited to support the view that PP multiple sclerosis is fundamentally different from SP multiple sclerosis, Revesz commented in his paper that ‘their observation that inflammation is present in primary as well as secondary progressive disease does, however, provide further evidence for similarity in the pathological process in the two forms of the disease’.

From a practical point of view it seems useful to drop the terms ‘relapsing–progressive’ and ‘progressive–relapsing’ multiple sclerosis. For the former, imprecise definition and the ability to re-accommodate such cases in the PP and SP multiple sclerosis groups supports such a condensation. For the latter, the fact that prognosis is unaltered by the occasional relapses makes it supportable to include such cases with PP multiple sclerosis and to avoid their exclusion from PP multiple sclerosis trials. The phenomenon and mechanisms of chronic progression seem less clearly established than those of relapses. Whereas the anatomical correlates of acute relapse can often be visualized by MRI scanning by localization, or implied by the determination of concomitant activities (e.g. new and enlarging lesions), this is not the case for progression (Thompson et al., 1990). If chronic progression singly represents the accumulation of new lesions or the enlargement or worsening of the pathology of old ones, it is not easily reconciled with the clinical patterns of disease in the progressive population. The rediscovery (Lassmann, 1998; Trapp et al., 1998) of axonal degeneration in multiple sclerosis (Charcot, 1868, 1877; Huber, 1895; Redlich, 1897) warrants re-evaluation in the context of glial–axonal interactions. In a subsequent paper in this series we will examine in detail the qualitative and quantitative clinical phenomena surrounding the development of progressive disease. The findings presented here may be helpful in simplifying nosology for the present, and may provide some empirical outcome results arising from a reclassification of progressive forms of multiple sclerosis, which should have some practical value for prognostics and for therapeutic trails.

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