The natural history of multiple sclerosis: a geographically based study

9: Observations on the progressive phase of the disease

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The clinical features of relapses and progression largely define multiple sclerosis phenotypes. A relapsing course is followed by chronic progression in some 80% of cases within 2 decades. The relationship between these phases and long-term outcome remains uncertain. We have analysed these clinical features within a well-studied natural history cohort with mean follow-up of 25 years. For the entire cohort, median times to reach Disability Status Scale (DSS) 6, 8 and 10 were 12.7, 20.6 and 43.9 years, respectively. Among 824 attack-onset patients, the great majority entered a progressive phase with a mean time to progression of 10.4 years. The effects of relapses often cloud the clinical onset of progression. However, there are circumstances where onset of progression is early, relatively discrete and identifiable at DSS of 2 or less. Three subgroups allow for clarity of outcome comparison and they are (i) cases of primary progressive (PP) disease, (ii) attack-onset disease where only a single attack has occurred before onset of progression (SAP) and (iii) secondary progressive (SP) disease where recovery from relapses allows recognition of the earliest clinical stages when progression begins. Here we compare survival curves in these three groups. Among cohorts of SAP (n = 140), PP (n = 219) and SP (n = 146) where progression was stratified by DSS at its onset, there was no difference in time to DSS 6, 8 and 10. These findings demonstrate that the progressive course is independent of relapses either preceding the onset of relapse-free progression or subsequent to it. Among SAP patients, the degree of recovery from the single defining exacerbation had no significant effect on outcome. The site of the original attack was not usually where progression began. The relatively stereotyped nature of the progressive phase seen in all progressive phenotypes suggests regional and/or functional differential susceptibility to a process that appears degenerative in nature. The highly prevalent distal corticospinal tract dysfunction in progressive disease and the pathologically demonstrated selective axonal loss seen in this tract raises the possibility of a dying back central axonopathy, at least in part independent of plaque location or burden. Despite considerable individual variation, the progressive course of disability seen in groups of PP, SAP and SP-DSS2 is similarly stereotyped in quality and pace and may entail mechanisms common to all forms of progressive multiple sclerosis. The possibility that this is the primary process in some cases must be considered.

Keywords: multiple sclerosis; natural history; progressive clinical course

Abbreviations: DSS = Disability Status Scale; PP = primary progressive; RR = relapsing–remitting; SP = secondary progressive; SAP = single-attack progressive

Received October 19, 2005. Revised November 15, 2005. Accepted November 15, 2005

Introduction

Multiple sclerosis is often divided into relapsing–remitting (RR), secondary progressive (SP) and primary progressive (PP) forms. These terms are only clinical descriptors and it remains uncertain whether they serve to distinguish among potentially different disease mechanisms. In the case of SP multiple sclerosis, a progressive phase follows an exacerbating...
and remitting course in the same individual by consensus definition (Lublin and Reingold, 1996). This occurs in some 80% of relapsing patients within 2 decades (Weinshenker et al., 1989a), and few clinically recognized multiple sclerosis patients escape this evolution if they survive long enough. However, those who have relapses only and those with progression only serve as anchor points for further study of the relationships between relapse and progression. The relationships are especially important since the development of progression is the key determinant of prognosis yet relapses are what can be partially suppressed with currently available treatments.

Mechanisms related to exacerbation, recovery and remission probably differ from those associated with unremitting progression. This duality has long been considered and has recently been supported by an apparent dissociation between the effects of therapies on relapse frequency or MRI activity versus effects on delaying progression. This has been striking in several double-blind multi-centre trials, probably first seen in the type 1 interferon studies (INFβ multiple sclerosis Study Group 1995; Jacobs et al., 1996; European Study Group, 1998; PRISMS Study Group, 1998), and more clearly in the studies of Campath (Coles et al., 1998, 1999) and cladribine (Rice et al., 1997, 2000). In the cladribine trial of over 150 progressive patients, prolonged suppression of lymphocyte counts to levels seen in symptomatic HIV infection was produced in the treated group. Although there was prominent reduction of relapse frequency and MRI activity, progression continued as in untreated patients (Rice et al., 2000). Dissociation between progression on one hand and both relapses and MRI activity on the other has also been reported in studies of sulphasalazine (Noseworthy et al., 1998), glatiramer acetate (Bornstein et al., 1991; Johnson et al., 1995) and anti-CD4 antibodies (van Oosten et al., 1996). The dissociation in some of these studies has become increasingly apparent with time (Rice et al., 2001).

The relationship between relapse and progression is often confounded in the short term as disability data can be contaminated by relapses. This is especially problematic in treatment trials of relapsing–remitting disease. Here few studies remain intact past 24 months and definitions for progression have been shown to be unstable. Recent analyses of published trials have demonstrated heavy contamination of disability scores by recoverable relapse related influences (Rudick et al., 1997; Liu and Blumhardt, 2000) as was feared (Rice and Ebers, 1998). We have found it difficult to be confident of unremitting changes in disability scores with less than a year of confirmation. Certainly, the availability of relapse prevention therapy has placed the relationship between relapses and progressive disability in focus.

It might be expected a priori that relapse frequency and severity would have some impact on the development and rate of progression of unremitting disability. Indeed they were associated in our studies of the early clinical course (Weinshenker et al., 1991a) but only in the first 2 years. The great majority of this effect came in the first year. Although there are some patients in whom recovery from initial or subsequent exacerbations does not occur, this ordinarily cannot be determined with confidence with less than a year of follow-up. Where recovery has not occurred in this time period, the contribution to disability is unambiguous and most clearly seen in the Devic’s phenotype (Wingerchuk et al., 1999). However, it is well recognized that regardless of lesion location, the great majority of initial attacks are associated with full or partial recovery. In patients who may have begun to progress and continue to relapse, the progression of disability is not discretely attributable either to lack of recovery from the relapse or to the underlying progression. The differentiation between the relative impact of relapse and progression on disability is especially clear in those cases in which attacks and progression are separated by sufficient time such that destined recovery has occurred prior to the onset of progression. If the early phase of progression is uncontaminated by relapse, a clearer picture of progression onset is possible. Both of these features characterize patients whom we have termed single-attack progressive (SAP). This patient group serves to usefully isolate the characteristics of attack, recovery and later progression.

We report here a detailed longitudinal study of the progressive course in several population-based series of patients with progressive disease. These include 140 SAP patients derived from two consecutive natural history cohorts of 1043 and 1059 multiple sclerosis patients. In an effort to answer questions aimed at understanding the relationship between exacerbations, progression and long-term disability, long-term outcome in SAP was compared with SP and PP multiple sclerosis where relapses are common or largely absent.

The following hypotheses were posed:

(i) When only the original exacerbation is examined, incomplete or lack of recovery in SAP patients will shorten the time to onset of progressive deficit. Complete recovery from the original attack (OA) is a positive feature.

(ii) Latency to onset of progression is greater in SAP than in those whose progressive phase begins following multiple relapses.

(iii) The rate of progression from onset of the progressive phase in SAP, PP and SP will be closely similar, in cases where onset of progression is relatively discrete [e.g. Disability Status Scale 2 (DSS2)]. If progression begins, it is a phenomenon that is independent of relapses, implying that the key target in multiple sclerosis should be the delay in onset or prevention of the progressive phase.

(iv) Progression does not begin at a ‘locus minoris resistentiae’ at the site of the OA. Progression evolves gradually and encompasses a bilateral ascending focal loss of motor corticospinal tract functions as a stereotyped and cardinal feature.
Methods
Population and patients
The London Multiple Sclerosis Clinic (London Health Sciences Centre, Canada) was established in 1972 to provide long-term care for multiple sclerosis patients from its referral area of Southwestern Ontario. The characteristics of this clinic have been outlined in numerous previous studies based on its patient population (Weinshenker et al., 1989a, b; Cottrell et al., 1999a, b; Kremenchtzky et al. 1999; Ebers et al., 2000). We reviewed the clinical course of 1043 multiple sclerosis patients from the original natural history cohort (Weinshenker et al., 1989a). Subgroups of the population strictly defined by population-based epidemiological studies (Hader et al., 1988) served as an internal control and may be viewed as the core of a concentric design.

Second series
A second independent more contemporary cohort of 1059 multiple sclerosis patients seen consecutive to the original cohort between 1984 and 1991 was also evaluated. The same criteria were applied and a second similarly sized series of 69 SAP patients were evaluated to test some hypotheses generated from analysis of the original sample. This cohort necessarily had different (shorter) follow-up and disease duration times. The size of the SP cohort was enlarged from the original sample by accepting progressive onset dating to DSS3, a criterion that added an additional 188 patients. There were 128 SP patients with progression dated from DSS2 and an additional 209 from DSS3 giving a total of 337 SP patients. Additional cohorts of SP and PP were not sought since sample sizes were already large.

Definitions
Onset and exacerbations
Exacerbations and remissions were defined as already described by Schumacher et al. (1965) and Poser et al. (1983). The date (year) for the likely first symptom of the disease was considered to mark the clinical onset of multiple sclerosis. The occurrence of exacerbations and disability scores were enumerated by yearly follow-up, but all interim contacts regarding exacerbation and steroid use were systematically recorded in the records.

Clinical course
Patients were reclassified according to recent consensus definitions for clinical course patterns of multiple sclerosis (Lublin and Reingold, 1996). However progressive-relapsing patients (Weinshenker et al., 1989a) were incorporated into the PP category given the fact that no significant differences in demographics, clinical characteristics and long-term outcome were found between these two subgroups (Andersson et al., 1999; Kremenchtzky et al., 1999). Progressive disease was defined by at least 1 year of continuous deterioration, regardless of the rate of worsening. Transitory plateaus and trivial temporary improvements in the relentlessly progressive course were allowed in the long term, although steady progression was the rule given the evaluations at yearly intervals with the distinct advantage of longer retrospect than is available in treatment trials.

SP, PP, SAP
Some patients were seen within the first year after onset. For those patients not seen at onset, DSS (Kurtzke, 1961) prior to being seen by the multiple sclerosis clinic specialists were determined retrospectively. For hard endpoints such as cane and wheelchair dependency, which are the focus of this study, there was clear documentation, almost always prospective. Since the follow-up was long and additional later outcomes were available, only unambiguous data were entered in such circumstances. Accordingly, specific DSS levels were ‘censored’ (left blank) if it was not documented when they were reached. For SAP, the interval between the ‘OA’ and the ‘onset of the progressive phase’ (OPP) had to be attack-free and of a minimum duration of one year, parallel to the definition of PP, although it was characteristically very much longer in each of these.

For comparison, SP patients where the progressive phase was recognized at or rarely before DSS2 was reached were identified. Such patients may have had multiple relapses but had recovered such that the insidious onset of progression could be identified at an early stage.

Variables
We investigated the influences of gender, age of onset, type(s) of symptom(s) involved at onset of disease, type(s) of symptom(s) involved at onset of progressive disease, the influence of the OA and the interval between the OA and the onset of the progressive disease on the long-term outcome. Specifically, median times for DSS 6, 8 and 10 were calculated for each of the patient subgroups. In addition, comparisons were made between distinct multiple sclerosis categories according to different clinical courses and characteristics of the attacks.

The symptom(s) characterizing both the onset of the OA and the onset of the progressive phase were used to determine the types of systems involved. Although times to initial examination and diagnosis could be some years after onset of symptoms, findings on initial examination were used to confirm the systems suggested by the history. These were categorized following the Functional Systems classification (Kurtzke, 1961, 1983) and then regrouped into motor (pyramidal), sensory, cerebellar, brainstem, visual (optic nerve) and others (bladder/bowel, mental or others) given the paucity of the numbers for the specific subgroups.

The period of time (measured in years) between the onset of OA and onset of the progressive phase was examined. The occurrence of symptoms or improvements during this interval was also documented and the degree of recovery (if any) after the OA was catalogued simply as ‘full recovery’, ‘partial recovery’ or ‘no recovery’.

Statistical analysis
All analyses were performed using SAS (SAS Institute Inc., Cary, NC, USA). Survival analysis was performed with SAS/LIFETEST 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-up 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. Multivariable accelerated failure-time models for time to onset of progressive phase were fitted to the data from the SAP patients using SAS/LIFEREG.

Results
Population and patients
Among the 1099 individuals from the original natural history cohort (Weinshenker et al., 1989a, b) 15 were seen only once
and we excluded both these and the 41 cases felt either to have ‘possible’ multiple sclerosis or to have a different diagnosis in long-term follow-up (Cottrell et al., 1999a). All were seen in the clinic for variable intervals. After 25 years mean follow-up, there was 96.3% accuracy in the diagnosis of multiple sclerosis based on clinical grounds even including cases originally designated as ‘possible’. This entire cohort accrued before the advent of the MRI technology. No case of treatable disease emerged in follow-up of those ultimately deemed not to have multiple sclerosis.

The characteristics of the remaining 1043 multiple sclerosis patients have been recently collected and updated (Cottrell et al., 1999a; b; Kremenchutzky et al., 1999; Ebers et al., 2000). We found 219 cases progressive from onset (PP) and 824 attack-onset cases (RR and SP). In 71 of 551 SP cases (12.9%) there was only a single identified attack before the beginning of progressive disease and these cases constitute the first series of SAP patients. Among the remaining 480 SP individuals (551–71) the onset of progression was identified in the records and DSS-specific onsets are given in Appendix B. These include 126 whose progression could be dated to DSS2 or less and 276 to DSS3 or less together comprising 76% of the SP total. In all of these there were two or more attacks with the great majority having had many attacks. The SAP patients constituted 71/824 (8.61%) of attack-onset patients and 6.81% of the total multiple sclerosis population.

The ‘second series’ of SAP multiple sclerosis

In the 7 years consecutive to the end of accrual in 1984 for the first cohort, some additional 69 SAP cases were identified among the 1059 patients seen. The demographic and clinical course characteristics of the more contemporary series of 69 SAP patients are tabulated alongside those from the original cohort in Table 1. The two groups were almost identical. Necessarily, follow-up and disease duration times were shorter among patients in this second series (20.0 years mean) than among those in the original cohort (27.6 years mean). We have used the original cohort for subsequent comparison to other subgroups also derived from this cohort. The results given below refer to this ‘second series’ exclusively only where specifically mentioned.

Demographic characteristics including age of onset

The demographics for the SAP patients are compared with PP, SP ≤ DSS2 and SP ≤ DSS3 in Table 2. The mean age of onset was 33.3 years, intermediate between the 29.8 years for all SP and the 38.6 years for PP patients. The male:female ratio was 1:1.8 (similar to 1:1.7 for other SP and different from 1:1.3 for PP patients). The mean follow-up time was 27.7 years (25 years on average for the entire cohort) and 31 individuals (43.6%) were followed-up until they were deceased.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparative descriptive statistics for the two SAP cohorts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Time from OA to OPP (years)</td>
<td>7.61 (6.14)</td>
</tr>
<tr>
<td>Recovery after OA</td>
<td></td>
</tr>
<tr>
<td>Full</td>
<td>46 (64.80%)</td>
</tr>
<tr>
<td>Partial</td>
<td>20 (28.20%)</td>
</tr>
<tr>
<td>None</td>
<td>5 (7.00%)</td>
</tr>
<tr>
<td>Symptoms at OA</td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>0.33</td>
</tr>
<tr>
<td>Sensory</td>
<td>0.36</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>0.08</td>
</tr>
<tr>
<td>Brainstem</td>
<td>0.15</td>
</tr>
<tr>
<td>Visual</td>
<td>0.22</td>
</tr>
<tr>
<td>Others</td>
<td>0.03</td>
</tr>
<tr>
<td>Symptoms at onset of progressive phase</td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>0.88</td>
</tr>
<tr>
<td>Sensory</td>
<td>0.23</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>0.11</td>
</tr>
<tr>
<td>Brainstem</td>
<td>0.04</td>
</tr>
<tr>
<td>Visual</td>
<td>0.07</td>
</tr>
<tr>
<td>Others</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Symptoms

Symptoms (at onset of disease and/or at onset of the progressive phase) were regrouped according to functional systems (Kurtzke, 1961) and then analysed. The systems most commonly involved at onset of disease were sensory (36.6%) and pyramidal (33.8%). As is usually seen among patients with PP multiple sclerosis (Matthews, 1998), SAP patients’ clinical onset appears heralded by sensory-motor involvement more often than that in the general multiple sclerosis population (Koch-Henriksen, 1999) (Appendix A). In contrast, the presenting system involved at onset of progression was overwhelmingly pyramidal (88.7%). Table 1 lists all systems involved in either circumstance. The number of systems affected at disease onset and recovery from the attack was also studied as a potentially independent prognostic factor using a multivariate analysis (see below).

Disability level at onset of progression

The mean time to onset of progression was 7.6 and 10.3 years from onset of multiple sclerosis for SAP and for SP patients, respectively (Table 2). In consequence, the mean age of onset of progression was calculated to be 40.9 years for SAP patients and 39.2 years for SP cases. These can be compared with the mean 38.6 years for PP patients.

Development of the progressive phase in the great majority (84.8%) of SAP patients had been identified to occur at DSS levels of 2 or less. While the substantial majority (76%) of the other SP cases is recognized at DSS3 or less, many were
Years from OA to OPP (mean) 9.76
6
6
DSS at conversion to progression (mean) 1.90
6
6
Age of onset Mean (years
6
6
Table 2 Demographics (*original cohort, **two cohorts combined)

<table>
<thead>
<tr>
<th></th>
<th>SP OPP ≤ DSS 2*</th>
<th>SP OPP ≤ DSS 3*</th>
<th>SAP**</th>
<th>PP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>114†</td>
<td>302†</td>
<td>140</td>
<td>219</td>
</tr>
<tr>
<td>Males</td>
<td>49</td>
<td>116</td>
<td>49</td>
<td>94</td>
</tr>
<tr>
<td>Females</td>
<td>65</td>
<td>186</td>
<td>91</td>
<td>125</td>
</tr>
<tr>
<td>Ratio M : F</td>
<td>1 : 1.33</td>
<td>1 : 1.60</td>
<td>1 : 1.85</td>
<td>1 : 1.33</td>
</tr>
<tr>
<td>Duration of follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (years ± SD)</td>
<td>28.46 ± 11.63</td>
<td>27.10 ± 10.74</td>
<td>27.75 ± 10.7</td>
<td>23.75 ± 9.2</td>
</tr>
<tr>
<td>Age of onset Mean (years ± SD)</td>
<td>30.42 ± 8.91</td>
<td>29.77 ± 9.59</td>
<td>33.30 ± 10.7</td>
<td>38.56 ± 10.2</td>
</tr>
<tr>
<td>DSS at conversion to progression (mean)</td>
<td>1.90 ± 0.31</td>
<td>2.56 ± 0.56</td>
<td>1.92 ± 0.83</td>
<td>n/a</td>
</tr>
<tr>
<td>Years from OA to OPP (mean)</td>
<td>9.76 ± 7.82</td>
<td>10.27 ± 7.32</td>
<td>7.61 ± 6.14</td>
<td>n/a</td>
</tr>
</tbody>
</table>

n/a = not applicable; OA = original attack; OPP = onset of progressive phase. †Number of patients with available data.

Table 3 Median time from disease onset to DSS 6/8/10: (years—SE)

<table>
<thead>
<tr>
<th>Multiple sclerosis subgroup</th>
<th>SAP (n = 71)</th>
<th>PP (n = 219)</th>
<th>P-value: SP and PP*</th>
<th>P-value: SAP and SP*</th>
<th>P-value: SAP and PP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSS6</td>
<td>12.73 (0.67)</td>
<td>8.03 (0.55)</td>
<td>0.0001</td>
<td>0.6925</td>
<td>0.0003</td>
</tr>
<tr>
<td>DSS8</td>
<td>20.64 (0.9)</td>
<td>18.59 (0.63)</td>
<td>0.0001</td>
<td>0.2758</td>
<td>0.1144</td>
</tr>
<tr>
<td>DSS10</td>
<td>43.87 (0.59)</td>
<td>33.32 (0.41)</td>
<td>0.0001</td>
<td>0.4691</td>
<td>0.0171</td>
</tr>
</tbody>
</table>

*P-value for testing the equality of the survival curves.

deemed to occur at higher levels (Appendix B). In retrospect, the higher levels were in general those in which the greatest difficulty separating the effects of relapses occurred.

Survival curves and times to DSS 6, 8 and 10

For the SAP cohort, the median times from onset of disease to reach DSS 6, 8 and 10 were 12.7, 20.6 and 43.9 years, respectively (Table 3). Figure 1 shows the survival curves for the three cohorts including SAP, measured from the onset of multiple sclerosis for times to DSS 6, 8 and 10 demonstrating the worse outcome for PP taken from disease onset. We then measured the progressive phase independently of the previous relapses to the extent possible on clinical grounds. The survival curves from OPP were compared for SAP, SP and PP, all from DSS2 (Fig. 2). The median times to DSS 6, 8 and 10 from OPP at DSS2 for SAP cases were 5.7, 13.6 and 32.9 years, respectively (Table 4). In Fig. 2A–C can be seen a comparison of survival curves in terms of time from DSS2 to DSS6, 8 and 10 for the different subgroups of multiple sclerosis in this study. The results show no statistically significant difference in any pairwise comparison within these groups (P = 0.08, 0.47 and 0.86, respectively).

Multivariate analysis

Given the potential importance of time to onset of progressive deficit as an untested but attractive endpoint, a multivariate analysis of original exacerbation features as predictive of time to OPP was carried out in the SAP group. Thus, the number of systems involved at the clinical presentation or onset of multiple sclerosis has a highly significant effect on the time to conversion for SAP patients (P = 0.003). These results are very similar to those for PPMS. The negative regression coefficient indicates that patients with more systems involved at onset have a reduced time to conversion to the progressive phase even when only a single attack could be identified.

The degree of recovery after the OA was also investigated here in the SAP group. This was rated only as full, partial (function abnormal) and absent. Recovery was full in 64.8% and partial in 29.5% of patients, while 5.6% showed no recovery. Regardless of the degree, the occurrence of recovery had no significant effect on the time to conversion to progressive disease (P = 0.2736) and even when compared with those with no recovery at all, no difference was evident (P = 0.6884).

Discussion

There has been a widespread but poorly documented belief that the most visually striking features of multiple sclerosis, the demyelinating plaques, are the pathology of the disease. Even the presence of atrophy has initially been interpreted in the context of myelin loss. The chronic progression of the disease then is seen as the cumulative disability resultant from a succession of attacks amalgamating into a chronic progressive deterioration of function. The more rapid deterioration said to characterize primary progressive disease when found to occur in the context of relatively few MRI lesions was therefore considered surprising in these terms (Thompson et al., 1997). Indeed this view seems to have been supported by the embrace of MRI surrogate markers as targets for therapeutic trials leading to the surmise that reaching this target, i.e. suppression of MRI lesions and their clinical correlates of relapses, logically would translate into long-term efficacy. The poor correlation between conventional MRI measures and progressive disability was seen as related to the discrepancy between lesion site and function.
However, there have always been uncertainties with both these premises and conclusions for both practical and conceptual reasons. A practical reason is that available treatment studies have been short-term and neither designed nor executed to evaluate impact on unambiguous long-term outcome measures. This largely reflects the nature of the disease, its age of onset and the emergence of a variety of interests, which make long-term trials unfeasible. Noteworthy among the conceptual uncertainties are the relationships between the presence of relapses and/or their frequency.
and the subsequent development of a progressive course. Although these are largely unknown, a close relationship is expected.

Less comfortably, unproven assumptions of correlations between relapse frequency over the course of the disease and disability outcomes have been influential in determining clinical trial design and interpretation. The absence of convincing data indicating that slowing of the chronic progressive course or the frequency of its occurrence has been achieved is disturbing given the number of patient-years of treatment under available observation. Relapse suppression ranked last when clinical trialists in multiple sclerosis were asked to list outcome measures in order of importance as targets for clinical trials (Noseworthy et al., 1989). No additional information has materially elucidated these relationships since then. Few experienced in the long-term management of this disease would disagree that the development of unremitting progression in multiple sclerosis represents the major adverse event in the course of the illness.

Undeniably, recovery from relapses can be incomplete or absent; in occasional patients with the Devic’s phenotype, deterioration occurs in the setting of relapses. This happened by relapses to unremitting disability for most patients is relatively minor, although with occasional dramatic exceptions. Furthermore, even where a relapse leaves permanent loss, the overall effect would be blunted if not eliminated if the degree of disability it entailed were soon to be inevitably incurred as part of the progressive course. Accordingly, we have taken the opportunity presented by the availability of a large natural history cohort encompassing some 26 000 years of observation to study some of these clinical features of multiple sclerosis.

The relationship between relapses and progression has not been systematically analysed previously in a large longitudinally followed-up population-based cohort. The studies reported here represent the third analysis of the impact of relapses on multiple sclerosis subgroups. In sequence, we have previously shown that there is no relationship between outcome and the presence of relapses in the 28% of primary progressive cases who eventually have them (Kremenhubzky et al., 1999). Here we extend these findings to a comparison of the progressive phases of four clinical categories of multiple sclerosis including (i) primary progressive, (ii) SAP, (iii) SP recognizable ≤DSS2, which means with the initial symptom of progression and (iv) SP cases ≤DSS-3 and then all SP cases. These groups encompass (i) patients with few or no attacks in which progression is the main or only feature, (ii) those with a single exacerbation and later relapse-free progression and (iii) those in whom frequent relapses often precede and also cloud the onset of the chronic progressive phase.

### The initial exacerbation

We have previously shown that polysymptomatic onset is associated with shorter time to unremitting disability (Weinshenker et al., 1989b). With an additional 15 years mean follow-up, we have re-examined this prognostic variable in those with SAP and find a significantly shorter time to onset of the progressive phase than in those with monosymptomatic onset. These findings in the specific subgroup of attack-onset patients in whom identification of early progression would be expected to be the most accurate are consistent with our previous results. They further suggest that this attack related feature might operate indirectly by interacting with the mechanisms involved in subsequent progression.

We thought that the degree of recovery from the initial attack might influence the likelihood of developing unremitting disability. Since SAP patients typically progressed in a system other than the one in which their initial attack occurred they shed novel light on this question. In our sample, the great majority of SAP patients experienced recovery with minimal (28% of cases) or no disability (65% of cases) after the first attack and only some 7% did not recover and exhibited fixed disability subsequent to the initial episode. The development and rate of progression seem to be largely independent of the degree of recovery from the initial exacerbation. This is consistent with clinical experience, which indicates that relapses with poor recovery often occur in patients who have had full recovery from other attacks.

### Subsequent exacerbations in the clinical course

The clinic population was followed-up with yearly visits and patients were asked yearly about interim attacks. Since the clinic delivered care for multiple sclerosis related issues, exacerbations were usually reported but we are sure that some mild exacerbations went unreported. However we are confident that most moderate and all severe attacks were probably captured in the records as there was an attempt to do so. The SAP subgroup was repeatedly questioned for

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Survival times (medians in years) to DSS 6, 8 and 10 from onset of progressive phase for SAP, SP and PP</th>
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</thead>
<tbody>
<tr>
<td>SP with OPP at DSS2 or less</td>
<td>SAP with OPP at DSS2 or less</td>
</tr>
<tr>
<td>DSS6</td>
<td>6.63 (0.60)</td>
</tr>
<tr>
<td>DSS8</td>
<td>18.20 (0.73)</td>
</tr>
<tr>
<td>DSS10</td>
<td>NA</td>
</tr>
</tbody>
</table>

OPP = onset of progressive phase; NA = insufficient data points for analysis. *P-value for testing the equality of the survival curves.
the occurrence of any other attacks and a small number of exclusions based on later recall of inevitable forgotten or unrecorded attacks were placed in the SP group. The validity of this approach is supported by the nearly identical results in the second series both for frequency of this phenotype and for its outcome.

Onset of progression

Many observers have viewed the development of a progressive course as the single most adverse factor influencing prognosis (Leibowitz and Alter, 1970; Kurtzke et al., 1977; Confavreux et al., 1980; Poser et al., 1983; Verjans et al., 1983; Runmarker and Andersen, 1993; Hawkins and McDonnell et al., Cottrell et al., 1999a). However, none of these studies have been able to independently assess the relative roles of relapse and relapse-free progression. This is largely because of inability to overcome the problem of overlap between these phases, a problem exacerbated in trials where follow-ups are short, patients are selected for relapse frequency and attempts are made to make some assessment of disability, regardless of validation of the measure used.

To try to circumvent this problem and to address the relationship between relapses and progression, we have used cohorts with SAP multiple sclerosis to help consider the nature of onset and evolution of the progressive phase of the disease. In this group the onset of progression is more easily identified and commonly occurs many years after the initial exacerbation. Here progression is typically identified at DSS2 when patients are routinely followed-up yearly. Since time to disability accumulation, i.e. reaching DSS 3 and 6 was influenced by the exacerbation rate in the first 1–2 years (Weinshenker et al., 1989b), we had hypothesized that SAP patients would have a longer time to onset of progression than those with multiple preceding relapses. This proved erroneous. The converse was true, as latency to onset of progression was actually shorter in SAP (mean 7.6 years) than in those who had multiple preceding relapses. This proved erroneous. The converse was true, as latency to onset of progression was actually shorter in SAP (mean 7.6 years) than in those whose progressive phase begins preceded by multiple relapses. This probably reflects the later onset of SAP when compared with SP. These data also belie a causal relationship between relapses and outcome and imply that age is an important factor in determining the progressive phenotype. The absence of further clinical exacerbations in the SAP group provided no attenuation in latency for onset of progression. Although this may seem at odds with the previous data showing a strong association of early relapses and late outcomes, it must be remembered that early relapse rate could influence the likelihood of later progression, time to onset of progression and the slope of progression. There remain no data indicating a relationship between early and late relapses and we find none in this data set (GC Ebers, unpublished data).

Age of onset of the progressive course

The conspicuous fact that the mean age of onset of progression is not significantly different for all kinds of progressive patients (PP, SP, SP-DSS2, SAP), regardless of their initial clinical course (Table 5) warrants comment. The ages of onset of the progressive course differed by only 2.3 years among the four progressive phenotypes and the two extremes of phenotype in the context of relapse, SP (most often many) and PP (most often none) each had a mean onset of 39 years, despite a 10 year span in mean age of disease onset. Comparing SP (where onset of progression was often clouded by relapses) with SP-DSS2 or SP-DSS3 where this was not the case, ages of onset of disease and of progression were virtually identical. For age of onset of progression the presence of one, many or no relapses did not differentiate among these progressive groups. Hence, age of onset and age at observation seem to be important determinants of clinical phenotype in multiple sclerosis as they are for so many other diseases with relapses and remission, i.e. rheumatoid arthritis (Lynn et al., 1995), psoriasis (Swanbeck et al., 1995), neuro-Behçet’s disease (Serdaroglu, 1998), etc. These results would be in keeping with the view that the progressive phase of multiple sclerosis is an age-dependent degenerative process, at least in part (Trojano et al., 2002).

The timing of onset of progression may be important to identify accurately. Delaying its development seems a much more worthwhile target outcome for future therapeutic trials. The recognition that the clinical onset is relatively uniform regardless of previous clinical behaviour may be helpful in this context. However, it seems reasonable to point out that if tract-specific chronic axonal loss is the pathological correlate of progression, it probably begins long before clinical symptoms develop (Lumsden, 1970; Lassmann, 1983; Ferguson et al., 1997; Trapp et al., 1998).

Evolution of the progressive course

Latency

Since time to disability accumulation, i.e. reaching DSS 3 and 6 was influenced by the exacerbation rate in the first 1–2 years (Weinshenker et al., 1989b), we had hypothesized that SAP patients would have a longer time to onset of progression than those with multiple preceding relapses. This proved erroneous. The converse was true, as latency to onset of progression was actually shorter in SAP (mean 7.6 years) than in those whose progressive phase begins preceded by multiple relapses (mean 10.3 years). This probably reflects the later onset of SAP when compared with SP. These data also belie a causal relationship between relapses and outcome and imply that age is an important factor in determining the progressive phenotype. The absence of further clinical exacerbations in the SAP group provided no attenuation in latency for onset of progression. Although this may seem at odds with the previous data showing a strong association of early relapses and late outcomes, it must be remembered that early relapse rate could influence the likelihood of later progression, time to onset of progression and the slope of progression. There remain no data indicating a relationship between early and late relapses and we find none in this data set (GC Ebers, unpublished data).

Table 5 Age of onset of progression (OPP) for subgroups of multiple sclerosis

<table>
<thead>
<tr>
<th>Multiple sclerosis subgroup</th>
<th>Age of onset of progression (OPP) mean [±]</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP—excluding SAP</td>
<td>39.2 [10.0]</td>
</tr>
<tr>
<td>SP DSS ≤ 2</td>
<td>40.2 [8.3]</td>
</tr>
<tr>
<td>SP DSS ≤ 3</td>
<td>40.1 [8.4]</td>
</tr>
<tr>
<td>SP—all</td>
<td>39.4 [9.8]</td>
</tr>
<tr>
<td>SAP—original cohort</td>
<td>40.9 [9.4]</td>
</tr>
<tr>
<td>PP</td>
<td>38.6 [10.0]</td>
</tr>
</tbody>
</table>
Site of progression

The site of the OA has been suspected of becoming a 'locus minoris resistentiae' where progression begins (Fog, 1950). However, there was no demonstrable relationship between the site of the initial clinically evident expression of disease and the location of the progressive deficit. Patients with optic neuritis, brainstem and sensory onsets were all characterized by an overwhelming predominance of distal central motor dysfunction. On one hand, the distribution of sites of initial manifestations paralleled those of the general population of multiple sclerosis patients. On the other, the progressive deficit was almost exclusively localized to distal lower extremity corticospinal tract fibres. This then may be the 'locus minoris'.

Course of progression

Comparison of the progressive phase of the disease from onset of progression in SAP, PP and SP allowed a more appropriate correlation of their progressive courses and removed the effects of early-attack related events. Here, the course of progression can be evaluated often independent of relapses. The results indicate that survival curves for PP with or without relapses are very similar to those for SAP and SP DSS ≤ 2 from onset of progression. This holds true despite the fact that the SP DSS ≤ 2 group contained many patients with the kind of relapses from which excellent recovery usually occurs. Although we have only emphasized the data where onset of progression could be taken back to DSS2 because this allowed the most discrete comparison, the survival curves were examined in several additional ways including those with SP DSS2, SP DSS ≤ 2, SP DSS ≤ 3 (the latter including some 76% of all SP patients). No differences were found either among SP groups or among similarly divided SAP groups or when compared with PP.

We find no basis for the claim and apparently widespread belief that PP has a poor prognosis unless this is broadened to all progressive patients. Accordingly it might be deduced that the contribution to long-term disability from relapses is minimal, given the virtually uniform survival curves seen for progression following one, multiple or no exacerbations. This was true for a variety of definitions of progression onset. It would seem in this population-based sample that once progression has begun, its rate is largely independent of factors that have preceded it as originally suggested by Patzold some 20 years ago (Patzold and Pocklington, 1982) and more recently by Confavreux in a patient group treated with immunosuppressive (Confavreux et al., 2000; Confavreux, 2003). It is entirely possible that the process of progression begins well before clinical features indicating the onset of the progressive course and that this phenomenon is predestined to occur for reasons unconnected to relapses. However the factors involved are not clear.

It is important to emphasize that the clinical courses within each progressive group have considerable variation and that the outcomes although relatively predictable within a group are not readily applicable to the individual. We have given here survival curves for DSS 6, 8 and 10 although we are aware of the potential usefulness of more detailed survival information.

Most patients with SP multiple sclerosis go through a phase where the onset of progression is confounded by concomitant relapses. The ambiguity in such patients is only partly related to the incompletely validated definitions used to identify the onset of the chronic progressive phase and 'significant worsening'. Further difficulty has arisen from the fact that it is often hard to determine if serial relapses are associated with relapse-related permanent deficits, or with progression or both. This is more difficult when relapse intervals are short, recovery is slow and transient improvement or worsening is observed with symptomatic therapy, fatigue and concomitant illness. As ambulation is increasingly impaired, disability scales become more sensitive to these phenomena. It becomes difficult to judge the relative influence of relapses on lack of recovery from accumulated deficit compared with effects on the onset of chronic progressive disease. The difficulty with clinical overlap of the relapsing–remitting and SP phases that is observed in most patients is illustrated in a practical way by the many relapse suppression studies, which have included patients with disability as high as Expanded Disability Status Scale (Kurtzke, 1983) 5 or 5.5. This implies that these patients have not yet entered the chronic progressive phase (Achiron et al., 1992; INFB Multiple Sclerosis Study Group, 1993; Durelli et al., 1994; Johnson et al. 1995; PRISMS Study Group, 1998). An alternative explanation that seems worth exploring is that progression, when so destined, occurs much earlier but that relapses are superimposed, much as diagrammed by McAlpine (1955). In his Schematic A, he shrewdly diagrammed the early features of an incipiently progressive course beginning with the earliest relapses in such individuals.

These studies then have shown in population-based cohorts (~26 000 patient-years) no difference in outcome in progressive patients stratified by the presence, frequency, or absence of relapses. Although we have focused here on the progressive subtypes where relapses can be more easily separated from progression, the results for all SP patients are indistinguishable. When we include those SP cases seen to have progressive disease at DSS ≤ 3, which encompasses some 76% of all SP patients or the entire SP population (data not shown), survival curves do not differ from that characterizing SAP. These results not only imply that relapses have no effect on long-term outcome in patients selected for the subsequent development of a chronic progressive course but also that this course is homogeneous among the progressive subtypes. This is supported by the strikingly similar age of onset of the progressive cases irrespective of age of onset of disease or prior relapse history. These features would be more consistent with a degenerative process than one in which outcome represented the cumulative effect of randomly determined relapses. It remains possible that progression results from a threshold effect of inflammation exceeded by all progressive

...
forms that we have studied. However, no dose-response has been shown. More than a century and a half has elapsed since Cruveilhier’s term ‘gray degeneration’ was coined in the original definitive description of multiple sclerosis (Cruveilhier, 1924). His terminology may turn out to be especially apt even if he was referring to the colour of the plaques.

The dissociation of relapses and progression seen in these studies has practical implications as well, implying that the most important outcome measures in the treatment of patients with early relapsing–remitting disease may be the prevention and/or attenuation of the progressive course. Finally these findings suggest that the predictability of the clinical course, always weak in the short term and in the individual, may be high in the long term in groups of patients, as is implied here at least for the progressive course.

Acknowledgements
These studies were supported by the authors’ own resources.

References
Ancelin PB, Waubant E, Gee L, Goodkin DE. Multiple sclerosis that is progressive from the time of onset: clinical characteristics and progression of disability. Arch Neurol 1999; 56: 1138–42.
Multiple sclerosis: the progressive phase


Appendix

Appendix A Comparison of symptoms at onset of disease for SAP and total population of multiple sclerosis patients

<table>
<thead>
<tr>
<th>Symptoms at OA</th>
<th>SAP Original cohort n = 71</th>
<th>PP population n = 219</th>
<th>Total multiple sclerosis population n = 1043</th>
<th>Total multiple sclerosis population [Danish reg.]* n = 8842</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>0.33</td>
<td>0.45</td>
<td>0.21</td>
<td>0.25</td>
</tr>
<tr>
<td>Sensory</td>
<td>0.36</td>
<td>0.35</td>
<td>0.45</td>
<td>0.34</td>
</tr>
<tr>
<td>Cerebellar</td>
<td>0.08</td>
<td>0.10</td>
<td>0.12</td>
<td>0.13</td>
</tr>
<tr>
<td>Brainstem</td>
<td>0.15</td>
<td>0.10</td>
<td>0.13</td>
<td>0.08</td>
</tr>
<tr>
<td>Visual–optic nerve</td>
<td>0.22</td>
<td>0.08</td>
<td>0.17</td>
<td>0.19</td>
</tr>
<tr>
<td>Others</td>
<td>0.03</td>
<td>0.06</td>
<td>0.06</td>
<td>0.16</td>
</tr>
</tbody>
</table>


Appendix B DSS level for onset of progressive phase for SP- and SAP-multiple sclerosis (multiple sclerosis)

<table>
<thead>
<tr>
<th>DSS level</th>
<th>SP</th>
<th>Cumulative</th>
<th>SAP</th>
<th>Cumulative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases</td>
<td>n = 435*</td>
<td>n = 66**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>8 (1.8%)</td>
<td>1.8%</td>
<td>18 (27.3%)</td>
<td>27.3%</td>
</tr>
<tr>
<td>2</td>
<td>120 (27.6%)</td>
<td>29.4%</td>
<td>38 (57.5%)</td>
<td>84.8%</td>
</tr>
<tr>
<td>3</td>
<td>209 (48.0%)</td>
<td>77.4%</td>
<td>9 (13.6%)</td>
<td>98.4%</td>
</tr>
<tr>
<td>4</td>
<td>59 (13.6%)</td>
<td>91.0%</td>
<td>–</td>
<td>98.4%</td>
</tr>
<tr>
<td>5</td>
<td>21 (4.8%)</td>
<td>95.8%</td>
<td>–</td>
<td>98.4%</td>
</tr>
<tr>
<td>6</td>
<td>17 (3.9%)</td>
<td>99.7%</td>
<td>1 (1.5%)</td>
<td>99.9%</td>
</tr>
<tr>
<td>7</td>
<td>1 (0.2%)</td>
<td>99.9%</td>
<td>–</td>
<td>99.9%</td>
</tr>
</tbody>
</table>

*SP: data available for 435/480 cases. **SAP: data available for 66/71 cases.