Early Relapses, Onset of Progression, and Late Outcome in Multiple Sclerosis

Antonio Scalfari, MD; Anneke Neuhaus, MSc; Martin Daumer, PhD; Gabriele C. DeLuca, MD, PhD; Paolo A. Muraro, MD, PhD; George C. Ebers, MD

Objectives: To investigate the relationship among attacks in the first 2 years (early relapses), secondary progression (SP), and late disability in multiple sclerosis (MS).

Design: Cohort study with follow-up of 28 years.

Setting: Referral MS center.

Patients: Patients (N = 730) with relapsing-remitting MS diagnosed according to Poser criteria, from the database of the London Multiple Sclerosis Clinic, London, Ontario, Canada.

Main Outcome Measure: Long-term evolution of patients with high (≥3 attacks) and early (within the first 2 years of the disease) frequency of relapses. In the total SP population and in patients grouped by numbers of early relapses, we assessed the predictive effect of latency to progression (time to SP) on times to attain cane requirement (Disability Status Scale score of 6 [DSS 6]) and bedridden status (DSS 8).

Results: Among the group with frequent early relapses (n = 158), outcomes were variable. Although 103 (65.2%) experienced rapid conversion to SP MS (median duration, 5 years) and rapidly attained DSS 6 and DSS 8 scores (7 and 17 years, respectively), the remainder (n = 55) did not enter the SP phase, despite adverse early relapse features. Among the total SP population, longer latency to progression was associated with lower probability of attaining DSS 6 (odds ratio, 0.76 [95% CI, 0.69-0.84] and 0.44 [95% CI, 0.37-0.52] for 5- and 15-year latency, respectively) and longer times to severe disability. The same association between time to onset of SP and late outcomes was observed even in patients matched by number of early attacks. However, duration of the relapsing-remitting phase did not influence the times from SP onset to DSS levels.

Conclusions: Our results indicate dissociation between early inflammatory attacks and onset of the SP phase and further question the validity of relapse frequency as a surrogate marker for late disability. Among the group with frequent early relapses, we observed a large variability of outcomes, ranging from one extreme to the opposite.


Although the disease evolution of multiple sclerosis (MS) is largely unpredictable, disability accumulation during the progressive phase has been reported to be homogeneous among patient groups and independent of factors preceding its onset. Therefore, late outcome likely relates to mechanisms leading to the onset of secondary progression (SP), clearly the key determinant of long-term prognosis. Relapses are infrequently a direct cause of severe disability, especially when cases of neuromyelitis optica are excluded. Despite the lack of correlation between relapse and severe disability, attack frequency is used for monitoring disease activity, is considered by some to be a valid surrogate marker for disability progression, and represents a ubiquitous target of disease-modifying therapies. Indeed, therapeutic relapse suppression still has no proven effect on the probability of becoming severely disabled, even in the long term.

The predictive value of relapses is seen for the first 5 years (early relapses) from disease onset, but this effect appears to be derived from the first 2 years. This influence is primarily exerted by increasing the probability of conversion to SP MS and particularly by shortening the latency to progression onset. However, causality between early relapses and long-term outcome could not
be established, and simple association remains likely. Indeed, total attacks during the relapsing-remitting (RR) phase were shown not to influence the times to SP onset and to hard end points (Disability Status Scale [DSS] 6-8-10), contradicting the widespread belief that unremitting disability results from cumulative relapses. These results imply dissociation between inflammatory attacks and the mechanisms driving disability accumulation, already suggested by findings from neuropathological studies. In addition, they further question the validity of relapse frequency as the clinical end point in randomized controlled trials.

In this context, we sought to elucidate further the relationship among early relapses, onset of progression, and severe disability accumulation. By analyzing the London, Ontario, Canada database, we focused on the long-term disease evolution of patients with high (≥3) attack frequency during the first 2 years, which has been shown to drive the association between early relapse frequency and late outcomes. In addition, we evaluated the independent predictive value of latency to SP.

METHODS

The characteristics of the patients database have been described extensively in previous reports. In brief, the London Multiple Sclerosis Clinic (London Health Sciences Centre, Ontario, Canada), established in 1972, provides long-term care for MS patients from southwestern Ontario. Accrual ended in 1984, and the observation period was extended to 28 years (1972-2000). The shortest follow-up was 16 years. Patients underwent annual or semiannual evaluation, regardless of clinical course. At each visit, new information was collected and data previously recorded were confirmed. Disability was scored using the DSS. No patient received disease-modifying therapies. The database was subjected to a rigorous data quality check process in 2009.

SUBJECTS AND OUTCOMES

The analyses included 730 patients with RR onset for whom information on the number of attacks during the first 2 years (early relapses) was available (389 patients had 1 attack; 183, 2; and 158, ≥3). We focused on those patients with high (≥3) attack frequency (ie, frequent early relapses). Within the total SP population (n = 534), information on the time to onset of the progressive phase was available for 509 patients. Exacerbations were defined as acute development of new symptoms or worsening of existing symptoms lasting more than 24 hours (ie, Poser and Lublin criteria). Onset attacks were counted as the first relapse. Progressive disease (the SP phase) 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 recorded in the long term, although steady progression was the rule. Documentation collected for the onset of the SP phase and for the hard disability end points of moderate disability (DSS 3), required aid for walking (DSS 6), and restriction to bed with preserved use of the arms (DSS 8), the focus of this study, were rechecked repeatedly during the observation period, thus resolving ambiguities over time. A minority of unrecorded DSS scores or SP onset information were derived from the description of the neurological findings only when unambiguous. Otherwise, the database was left blank for that specific visit.

STATISTICAL METHODS

We used binary logistic regression analysis to investigate the effect of increasing time from disease onset to onset of the SP phase (ie, latency to progression) on the probability of developing severe disability, expressed by odds ratios (ORs). Kaplan-Meier analysis estimated times to disability end points from disease onset and from onset of progression in SP patients grouped by duration of the RR phase (time to onset of SP phase) as short (1-5 years; n = 143), intermediate (6-12 years; n = 176), and long (≥13 years; n = 188). The same analysis was performed in the subgroup of patients with 1, 2, and 3 or more early relapses. Grouping aimed for similar numbers in each category; additional stratifications provided internal controls to confirm results. We used the log-rank test to investigate differences observed among groups; survival was compared against the group with a longer time to SP (≥13 years). When assessing the predictive effect of time to conversion to SP MS, times for attaining disability end points were adjusted to the interval from onset of progression to make variables independent from each other. Information on time to every DSS level was not always available, resulting in slightly different numbers of patients contributing at each DSS level when estimating the survival curves for time to disability. Patients not reaching given DSS levels but observed for known periods were right-censored. Cox proportional hazards regression analysis investigated the risk of accumulating disability, expressed by hazard ratios, according to increasing number of relapses during the first 2 years in patients grouped by duration of the RR phase (short indicates 1-5 years; intermediate, 6-12 years; and long, ≥13 years). We checked the proportional hazards assumption by visual inspection of Schoenfeld residual plots and corresponding statistical tests. The χ² and Wilcoxon signed rank tests were used for the comparisons of categorical and quantitative data, respectively.

We set up and agreed on a statistical analysis plan. All statistical analyses were performed using commercially available software (SPSS, version 15; SPSS Inc) by one of us (A.S.) and subsequently independently recalculated at the Sylvia Lawry Centre for Multiple Sclerosis Research, where R software was used.

RESULTS

At the end of the observation period, among the total RR population, 657 patients (90.0%) had attained DSS 3, 543 (74.4%) had attained DSS 6, and 390 (53.4%) had attained DSS 8 in a median of 10, 18, and 28 years, respectively. Table 1 presents clinical and demographic characteristics of the 730 patients with low (1-2 attacks; n = 572) and high (≥3 attacks; n = 158) frequency of early relapses: a total of 1363 attacks was recorded. In both subpopulations, women predominated, and the mean age at disease onset differed very little (28.8 vs 27.4 years; P = .11). However, patients with frequent early relapses (≥3 attacks) were significantly younger when entering the SP phase (mean age, 35.3 vs 41.5 years; P < .001).
secondary to a shorter RR phase (mean duration, 6.9 vs 11.7 years; *P* < .001). Among those with low (1-2 attacks) relapse frequency, 84.2% had attained DSS 3, 70.6% had attained DSS 6, and 46.3% had attained DSS 8 in 11, 19, and 31 estimated median years, respectively, by the end of the observation period, which is significantly slower than those with frequent early relapses (Table 1).

### FREQUENT EARLY RELAPSES

We assessed the long-term disease evolution of the 158 patients with 3 or more attacks in the first 2 years, because these drove the association between early relapses and times to disability endpoint. The Kaplan-Meier estimated time to onset of the SP phase among all patients with frequent early relapses was 14.2 mean years (95% CI, 12.0-16.5); 79 (50.0%) converted to SP MS by 9 years after disease onset, increasing to 103 (65.2%) at 24 years (Figure 1). The remaining 55 patients (34.8%), despite the high frequency of early relapses, did not enter the progressive phase (Figure 1). Within the RR subgroup, less than half (43%) had attained DSS 3 in an estimated 16.2 mean years, 11 years longer than among those who converted to SP MS (Table 2), and very few (8 patients) advanced to DSS 6 through relapses. We did not exclude neuromyelitis optica in this subgroup because the cohort ended accrual in 1984 but, based on current data (G.C.E., unpublished data), the condition could have accounted for less than 1% of the total. Among the 103 patients who entered the SP phase, 50% had attained progression by 5 years from disease onset and 75% by 9 years (Figure 1). At the end of the observation period, 100% had attained DSS 3, 94% had attained DSS 6, and 75% had attained DSS 8 in 4.5, 9.1, and 17.2 estimated mean years, respectively (Table 2).

We compared clinical and demographic features of RR (n = 55) and SP patients (n = 103) with frequent early relapses (Table 2). Clinical onset in both subgroups was similar; most patients presented with sensory symptoms and monosymptomatic attack. Those who remained in the RR phase had a larger percentage of women (81.8% vs 63.1%; *P* = .02) and a younger age at disease onset (25.5 vs 28.4 years; *P* = .01) (Table 2). Mean disease duration was slightly shorter (*P* = .003) in the RR subgroup (17.2 years [95% CI, 15.4-18.8]) compared with the SP subgroup (20.3 years [18.8-21.7]). However, more than 80% of the RR patients were observed for longer than 10 years and more than 70% for longer than 15 years (Figure 2).

### TIME TO ONSET OF PROGRESSION

Among the total SP population, we assessed the association between the time to onset of the progressive phase and late outcomes. Binary logistic regression analysis demonstrated that longer latency to the SP phase correlates with a proportionally lower probability of attaining DSS 6 (regression coefficient, −0.055; OR, 0.95 [95% CI, 0.90-0.98]; *P* = .01) and DSS 8 (regression coefficient, −0.055; OR, 0.95 [0.92-0.97]; *P* < .001) scores. Among those free from progression for 5, 10, or 15 years, the probability of requiring a walking aid (DSS 6) was reduced by 24% (OR, 0.76; [95% CI, 0.69-0.84]), 42% (OR, 0.58 [0.51-0.67]), and 56% (OR, 0.44 [0.37-0.52]), respectively (Figure 3). Kaplan-Meier analysis demonstrated that groups with shorter duration of the RR phase attained disability end points from disease onset in significantly shorter times. We found a difference of 15.6 and 16.4 mean years for attaining DSS 6 and DSS 8 scores, respectively, between those with short (1-5 years) and long (≥13 years) latency to progression (Figure 4A). This effect largely disappeared once the SP phase supervened. Times from onset of SP to DSS 6 and DSS 8 scores were similar between groups, without a significant effect by the duration of the RR phase (Figure 4B).

### EARLY RELAPSES AND LATENCY TO PROGRESSION

We observed the same association between the time to onset of SP and late outcomes, even when patients were grouped by number of early relapses. Short duration of the RR phase was associated with shorter times from disease onset to DSS 6 and DSS 8 scores among those with 1, 2, or at least 3 attacks during the first 2 years (Table 3). Within the SP subgroup with frequent early relapses (≥3
attacks), mean differences of 11.9 and 15.6 years were found for attaining DSS 6 and DSS 8 scores, respectively, between those with short (1-5 years) and long (≥13 years) latency to the SP phase (Table 3), accounting for the large variability of the outcome despite the adverse clinical features. In addition, among SP patients grouped by duration of the RR phase, the probability of developing severe disability increased proportionally with the number of early relapses. However, the size of the predictive effect decreased proportionally with time to conversion to SP MS and became only marginally significant \( (P = .03) \) in those with long times to enter the progressive phase (≥13 years) (Table 4). Three attacks during the first 2 years yielded hazard ratios of 3.03, 2.27, and 2.02 for reaching DSS 6 scores in patients with short, intermediate, and long latency to progression, respectively (Table 4).

**COMMENT**

The general pattern of long-term evolution of MS can be predicted and described, but prognosis remains individually uncertain. The widespread and orthodox belief that progression and long-term disability result from cumulative inflammatory attacks cannot sufficiently explain the large variability of the outcome among patients. This study provides evidence that severe disability accumulation is induced by mechanisms tied to the onset and evolution of the progressive phase, which are largely independent of inflammatory attacks.

Faster conversion to SP MS in groups with more early relapses has been reported,\(^{15,22,33}\) however, causality was never demonstrated and the question whether inflammatory attacks have any relevant role in the development of the progressive course remains open.\(^{24,36}\) Most patients accumulate no more than moderate disability (DSS 3 score) during the RR phase\(^3\) and, therefore, the onset of the SP phase undoubtedly represents the key determinant of severe disability accumulation.\(^3,8,21\) Herein we showed that its latency dictates the tempo of long-term disease evolution and accounts for the variability of outcomes among patients. As widely evident in clinical practice, earlier conversion to SP MS is associated with higher probability of (Figure 3) and shorter times to severe disability (Figure 4A). However, we found that the slope of the progressive phase was only modestly affected by the duration of the RR phase (Figure 4B). This finding agrees with previous studies using DSS 3\(^2,3\) and DSS 4\(^1,5\) scores as landmark status and supports an amnestic nature of disease evolution, characterized by 2 independent stages.\(^1-3,5,37\) Our data support the notion that prognosis is largely determined before the onset of progression and that the RR phase, more likely its earliest stage, represents the only plausible but unproven window of therapeutic opportunity with available agents.\(^36,39\) Shorter latency to SP was associated with shorter times to disability end points, even in groups with the same number of early relapses (Table 3). In addition, the predictive effect of early relapses decreased proportionally with time to conversion to SP MS, becoming only marginally significant \( (P = .03) \) among those with long latency to progression (≥13 years) (Table 4). These data suggest dissociation between early inflammatory attacks and the mechanisms driving the evolution of the RR phase.

This finding was further supported by the analysis of frequent early relapsers. Although the disease course is unpredictable at the individual level, we expected to char-
acterize a rather homogeneous subgroup of patients with poor prognosis. Nevertheless, despite sharing the adverse features of high early-relapse frequency \((\geq 3 \text{ attacks})\), patients at the end of the observation period were distributed from one extreme of the disability spectrum to the opposite. This large variability of clinical outcomes was accounted for by the onset of progression and its latency. Fifty-five patients (34.8%) did not enter the SP phase and less than half (43.6%) of these accumulated even moderate disability (DSS 3), showing a remarkably benign disease course (Figure 1). The remaining 103 patients (65.2%) rapidly attained SP (median, 5 years), and most of them experienced the expected aggressive disease course (Figure 1). However, even among this subgroup the outcome largely varied, accounted for by the latency to progression; those with a longer time to SP \((\geq 13 \text{ years})\) attained DSS 6 score 11.9 mean years later than those with a short time to SP \((1-5 \text{ years})\) (Table 3). The RR and SP groups with frequent early relapses differed little in features that might explain such a different long-term evolution \((43.6\% \text{ vs } 100\% \text{ reaching DSS 3 score in } 16.2 \text{ and } 4.5 \text{ mean years, respectively})\) (Table 2). The type of onset attack was similar, and age at onset, known to have a strong effect on the probability of developing a progressive course,\(^{4,20,40-42}\) was only slightly younger \((25.5 \text{ vs } 28.4 \text{ years}; \text{P} = .01)\) among those who remained in the RR group. This subgroup did not experience a progressive course despite a mean disease duration of 17.2 years \((95\% \text{ CI}, 15.4-18.8)\); more than 80% were observed for longer than 10 years. Relapsing-remitting patients \((n = 55)\) had 3 or more attacks in the first 2 years.
Figure 4. Kaplan-Meier survival analysis in the total population with secondary progression (SP) multiple sclerosis. A, Times from disease onset to attainment of Disability Status Scale (DSS) scores of 6 (walking aid requirement) (left) and 8 (bed-bound status) (right). B, Time from onset of secondary progression to DSS 6 (left) and DSS 8 (right). Patients were stratified by duration of the relapsing-remitting phase (latency to SP). Tabular material in parts A and B display the numbers of patients in each category, mean times to end points, and percentiles. RR indicates relapsing remitting; Reference categories are 13 years or more. P values were calculated using the log-rank test.
of the follow-up, and we acknowledge that, among those still in the RR phase at the end of the observation period, progression presumably supervened eventually in most as long as 5 decades after onset, albeit at a low rate and with no significant effect on the ultimate outcome.

The lack of association between inflammatory attacks and mechanisms leading to the onset of progression suggests that axonal vulnerability or resistance to degeneration could be influenced by an independent genetic control, promoting a more aggressive outcome by facilitating conversion to SP MS. Whether this facilitation is related to interaction with inflammation remains ambiguous. The HLA-DRB1*01 allele clearly affects outcome, but no axonal relevance is obvious. Further genetic studies may better clarify its protective effect.

This study follows previous analyses of the London Multiple Sclerosis Clinic database showing no effect on long-term evolution from relapses occurring during the progressive course and no effect of late (from year 3 to SP onset) and total (during the RR phase) relapses on the time to SP onset and to hard disability end points (cane requirement and bed-bound status). Together, our data diverge from previous results supporting surrogacy of relapse numbers for disease progression in the short term. We provide strong evidence that relapse frequency cannot be validated as a surrogate marker for late disability accumulation, questioning the current practice of using relapse rate as the primary end point in trials. Our results discourage any causal relationship between inflammatory attacks and mechanisms driving the evolution of the RR phase and highlight the prevention or the delay of the progressive phase as the ideal target of future treatment. Research aimed at understanding the biological reasons underlying different long-term outcomes in frequent early relapers is warranted.

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Correspondence: George C. Ebers, MD, Department of Clinical Neurology, Level 3, West Wing, John Radcliffe Hospital, University of Oxford, Oxford OX3 9DU, England (george.ebers@ndcn.ox.ac.uk).

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