Predicting a window of therapeutic opportunity in multiple sclerosis

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Sir, The relationship between cumulative relapses and unremitting progressive disability is highly relevant to clinical practice and to randomized controlled trial design. Neuropathological studies unmentioned by Andersen (2010) have not been able to confirm the widespread belief that severe disability accumulates as a result of successive exacerbations. DeLuca et al. (2006), examining one of the largest reported pathological cohorts of multiple sclerosis cases, demonstrated lack of correlation between plaque load and axonal loss in the corticospinal tracts throughout the length of the spinal cord where the clinical phenomena characterizing the progressive phase typically localize. Disease progression and inflammatory attacks are probably driven by different mechanisms (Trapp and Nave, 2008). This became clear in the interferon and monoclonal antibody studies which showed no impact on disease evolution following relapse suppression, and MRI studies have provided but weak or non-existent correlations between lesion load and long-term disease evolution (Fisniku et al., 2008).

Previous natural history studies have demonstrated predictive value of early disease features, including early relapse rate (Weinshenker et al., 1989b; Eriksson et al., 2003). Nevertheless, this no longer reported to apply once permanent disability occurs (defined as 4 on the Disability Status Scale [DSS]; Confavreux et al., 2003). Outcome appears to be largely determined during the early stage of the disease, and once progression has begun, its rate seems independent of factors preceding it (Confavreux et al., 2003). It is unaffected by superimposed inflammatory attacks (Kremenchutzky et al., 1999) and it is homogeneous among progressive subtypes (Kremenchutzky et al., 2006). Number of relapses during the first 2 (Weinshenker et al., 1989b) and 5 years (Kantarci et al., 1998; Confavreux et al., 2003) had modest predictive value but the 5-year data did not show any additional effect beyond 2 years. Causality could not be assumed. Previous studies had examined neither the independent predictive role for long-term outcomes of relapses after the second year nor the relationship between inflammatory attacks and the onset of the progressive phase.

The London Ontario database, advantaged by geographical ascertainment and 28 years follow-up, provided opportunities to address in detail these aspects of disease course. The large number of patients reaching hard outcomes (67% at DSS 6 and 48% at DSS 8) and low percent of censored information warranted high reliability to the survival estimates.

In contrast to Andersen’s assertion, we have provided strong evidence that characteristics of the onset attack have little or no prognostic value. The degree of remission from first relapse had no significant impact on long-term disease evolution (Kremenchutzky et al., 2006) and the current study showed no independent effect exerted by type and number of neurological systems involved at onset. We did confirm modest predictive value of number of relapses during the first 2 years, driven by the minority (21%) having three or more attacks during this period. This appeared to operate by increasing the probability of entering the secondary progressive phase and by shortening the latency to progression, also unmentioned by Andersen (2010). Patients with more frequent early relapses seem unable to suppress mechanisms evolving into progressive disability accumulation, are more likely to convert to secondary progressive multiple sclerosis in shorter time and are therefore at higher risk of developing severe disability. The earlier onset of progression seems either to suppress or mask further relapses, explaining the inverse relationship between number of...
attacks during the Year 3-secondary progressive phase and times to disability levels. The 2-year watershed was not as stated by Andersen (2010) ‘arbitrarily chosen’, but was the natural division in the data observed by John Baskerville in the first analysis (Weinshenker et al., 1989b) and was confirmed in the recent analysis (Scalfari et al., 2010).

Because times for Year 3-secondary progressive phase are necessarily variable, we assessed variation in relapse frequency in serial 2-year intervals from Year 3 up to secondary progression, making comparisons within each time interval. For each 2-year interval beyond Years 1 and 2, no significant effect of relapse frequency on late outcomes could be found. We agree it cannot be concluded with certainty that relapses shortly after Year 2 are not predictive; however, it seems improbable or at best minor—indeed, the effect of even Year 1 and 2 relapses are minor when viewed among patients in general.

The most significant result in the paper went unmentioned by Andersen (2010). There was no correlation between total number of attacks during the entire relapsing–remitting phase and times to secondary progression or to severe disability levels. This is presented in Fig. 1D, which seems to have been misinterpreted. Kaplan–Meier survival analysis of patients stratified according to the total number of relapses before the onset of the progressive phase did not take into account any future event, as it might have been assumed. Only relapses experienced before the onset of the secondary progressive phase and therefore experienced before the attainment of the endpoints (DSS 6–8) were included in the analysis. No patient started to progress at or after DSS 6. These results invalidate relapses as prognostic factors for hard outcomes and it should not be overlooked that Year 3 and later relapse frequencies were associated with better outcomes. This period is the one in which most studies have enumerated relapses.

In mild contrast with the study from Leray et al. (2010), we confirmed that time to reach moderate disability (DSS 3) predicts times to higher disability levels (DSS 6–8–10), as observed after 12 years of follow-up (Weinshenker et al., 1989b). When adjusted for time to DSS 3, the impact of early relapses on outcomes lessened substantially, supporting the assumption that late disability is mainly determined early in the disease. More frequent attacks during the first 2 years are likely to be concomitant with, rather than causative of, faster disease progression. Similarly, we found an effect of early relapses on the slope of progression, but milder than the effect exerted on the probability of entering the progressive phase and on the latency to progression. The impact of relapses in Years 1 and 2 on the attainment of endpoints from progression was larger than the effect exerted from disease onset (Table 6).

The analysis from disease onset also included those who never entered the progressive phase and therefore might be less impacted by early relapses, confirming that the influence of attacks in Years 1 and 2 on the slope of progression is probably indirect, driven by increased probability of developing secondary progressive multiple sclerosis and by shortened latency of its onset. This was further supported by the large difference in the impact size of early relapses on times to disability from DSS 3 (five attacks yielded hazard ratio = 1.75 for reaching DSS 6), when still a minority (25%) had not entered the progressive phase, and on times to the same endpoints from onset of progressive phase (five attacks yielded hazard ratio = 5.15 for reaching DSS 6) when the predictive effect was already fully exerted (Table 6). These results further indicate that mechanisms leading to the onset of the progressive phase and driving the accumulation of severe disability are independent of inflammatory attacks and are already active during the early stage of the disease. Long-term prognosis seems to be largely determined during this period, representing therefore a potential window of opportunity relevant for future therapies, and on this we agree. However, the earlier the intervention, the less prognostic information is available and potentially the higher the risk–benefit ratio. Nevertheless, this should obscure neither the uncomfortable result that total relapses in the relapsing–remitting phase showed no relationship to hard outcomes nor the conclusion that preventing, delaying or attenuating the progressive phase is the key therapeutic target in multiple sclerosis.

Finally, as specified in the Methods section, outcomes in the London Ontario total population were exactly the same as in the Middlesex County and ‘seen at onset’ highly ascertained subgroup, indicating that data were not affected by ascertainment bias. There is no basis for the claim by Anderson (2010) that there was ‘varying ascertainment’. Andersen’s commentary did not mention that we found a lack of association of long term disability with (i) relapsing-remitting phase attack frequency, (ii) poly symptomatic onset, and (iii) with the degree of recovery from the first attack. Nor was it mentioned that the relapses used as therapeutic targets, the suppression of which many current treatments and trials rely, viz. those after Year 2, are associated with a better outcome. These findings seem conceptually and practically more important than the emphasis of the editorial, i.e. the deleterious effect of relapses in Years 1 and 2, modest overall and which Andersen also failed to point out, clearly operate via interaction with secondary progression.

**References**


