LETTER TO THE EDITOR

Age at disability milestones in multiple sclerosis and history of multiple sclerosis: a unifying concept

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On the basis of a reanalysis of the French natural history cohort of multiple sclerosis (MS) patients (Confavreux and Vukusic, 2006a, b), Confavreux and Vukusic put forth a unifying hypotheses that ‘the emergence of the progressive phase of [MS] might just be an effect of age, rather than the effect of a change in the pathogeny of the disease.’ These authors, thus, envision MS as a disease in which the ‘times to reach disability milestones, and the ages at which these landmarks are reached, follow a predefined schedule not obviously influenced by relapses, whenever they occur, or by the initial course of the disease (i.e. progressive or relapsing).’ If true, this observation has important implications with respect to both our understanding of the disease and our belief in the value of current treatments. Consequently, this hypothesis deserves careful consideration.

Two concerns come to mind. The first is really more of a disappointment. In the original description of this French cohort (Confavreux et al., 2000), the reported mean disease duration was 11 years. This is hardly different from the 11.3 years reported currently (Confavreux and Vukusic, 2006b). Thus, it seems that little, if any, new clinical data have been added over the intervening 6 years. The present analysis apparently only represents a reworking of the previously published data.

The second (and more important) concern relates to the methods used. To introduce this concern, two key observations deserve special emphasis (Confavreux and Vukusic, 2006a, b). First, patients with progressively earlier onset ages reach disability milestones significantly earlier (and progressively so) compared with patients with older onset ages (P < 0.0001; Table 1; Fig. 3). In other words, patients whose symptoms began before age 30 became disabled at a significantly younger age than patients whose symptoms began later in life. Secondly, in this study, the age at first symptom in progression-onset patients was significantly later compared with relapse-onset patients. Thus, 58% (906 out of 1562) of the relapse-onset patients had their first symptom this early (Figs 1A and B). This between-group difference is highly significant (P < 0.0001).

Indeed, the best test of the authors’ hypotheses that disability is just an effect of age is whether it applies to patients having a similar mode of presentation and, in the present cohort, the authors’ own data argue strongly against this notion.

Consequently, any comparison between relapse-onset patients and progressive-onset patients is significantly confounded by this difference in age at first symptom between groups. This creates a bias that must be corrected for in the analysis. Such a circumstance is well understood by epidemiologists. Because epidemiological studies are non-randomized, it is widely recognized that confounding variables of this type necessitate some statistical adjustment during the analysis stage.

In the present circumstance, because relapse-onset patients are significantly younger than progression-onset patients, they will reach their disability milestones artificially early compared with a cohort of relapse-onset patients with an age distribution similar to the progression-onset patients. Although the magnitude of this bias is not known precisely from the published data, it seems likely to be at least a decade, if not more (Table 1). Thus, the expected age to reach disability milestones in relapse-onset patients needs to be adjusted upward by this amount to compensate for the bias. Importantly, once the proper adjustment has been made, relapse onset will then be associated with an older age at reaching the various disability milestones compared with progression onset—a circumstance, which completely undermines the unifying hypothesis proposed by the authors.

References