Relapses do not matter in relation to long-term disability: No (they do)

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It seems rather perverse to have to defend the most defining element of multiple sclerosis (MS), the relapse. And yet here we are…

The relapse is best defined as patient-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the central nervous system (CNS), current or historical, with duration of at least 24 hours, in the absence of fever or infection.1

The clinical, radiologic (as a measure of in vivo pathology) and pathologic evidence for a role of relapses in the long-term evolution of MS is considerable. The onset of a relapse is relatively easy to discern (although determining the end is more problematic). The neurologic deficits are obvious and the residual dysfunction is observable and measurable. Despite this, the role of relapses in production of long-term disability has been questioned in several natural history cohorts.

Relapses produce immediate and obvious neurologic dysfunction, frequently with MRI correlation. The early course of MS is most often dominated by exacerbations and remissions. The role of relapses in the accrual of disability has been most directly addressed in studies that have utilized well-characterized cohorts, frequently followed over a period of years. Studies of these groups have shown quantifiable residual neurologic dysfunction in 40–50% of subjects experiencing relapses.2–4 The degree of residual dysfunction from relapses may well be underestimated in these studies as they measured residual with changes in Expanded Disability Status Scale (EDSS), likely not the most sensitive measure of persistent deficit. These results nicely complement the earlier natural history studies that correlate early relapse frequency and residual with rapidity of reaching disability status scale (DSS) 6, 5, 6

The differences in the types of populations that have been utilized to study this problem highlight some of the methodological issues at play. Natural history cohorts and clinical trial studies differ markedly in their study populations, length of follow up, standardization of assessments (e.g. use of DSS or EDSS), frequency of assessments, rigor of data collection, consistency of examiners, data collection methods and other factors.7 Is the DSS or EDSS too insensitive to change in any functional system other than ambulation after one reaches a level of 4? If an exacerbation affected upper extremity or brain stem function, might the EDSS in the 4–7 range remain unchanged? These factors alone may explain the discrepancies. This issue can best be resolved through analysis of prospectively studied, well-controlled populations for longer duration than the usual MS clinical trial.

All pivotal clinical trials in relapsing–remitting MS have demonstrated the development of irreversible disability over time in a proportion of subjects. This is most likely produced by stepwise worsening from relapses, as development of secondary progressive MS has been uncommon in these studies of early MS patients.

Several more recent natural history cohorts have reported on the short- and long-term effects of early relapses on later disease course.8–11 Importantly, each has shown a significant effect of relapses in producing disability early in the disease course. As the disability levels obtained are permanent, it is curious that the authors do not fully acknowledge that the sooner one reaches a disability level, the longer they remain in a disabled state. That the subsequent time to more severe disability levels was found to be similar for those with or without relapses in these studies does not alter the fact that those with relapses developed disability at an earlier stage. This is best demonstrated in the analyses of Tremlett et al.10 They demonstrate that a higher relapse rate was associated with a shorter time to fixed disability (EDSS 6) and to onset of secondary progressive disease. They note that the effect of early relapses on the later development of disability diminishes with time. This finding is in keeping with the nature of a relapse, that it produces dysfunction over a short period and then one is left with residual deficits that remain stable until the next relapse or transition into a progressive phase.12 When Tremlett et al. and other natural history cohort studies refer to the effects of an early relapse as being transitory and without long-term consequences, they under-appreciate the
residual disability that they so carefully detail in their data; residual that is not transitory but rather remains with the patients through the rest of their lives. The parceling out of relapses into a period saying they matter early, but they do not matter later and are thus unimportant to long-term disability is a failure to consider the disease continuously.

Questioning the role of relapses after the onset of secondary progressive disease begs the primary question (what is the effect of relapses on the total disease course?), but does raise the possibility that once one enters a progressive phase, the relative role of any subsequent relapses on overall disability (as measured in natural history cohorts) may be overshadowed by the disability accrued by the underlying process of progression. This reasonably raises the question as to whether the underlying process has changed from inflammatory to degenerative. However, this observation does not negate the benefits derived from disease-modifying therapies that reduce the rate of relapses (and accrual of fixed disability) in patients with relapsing forms of MS. Also, it is important to remember that not all sufferers of MS enter a progressive phase.

Although some natural history studies suggest no significant effect of relapses on subsequent development of disability once patients enter a progressive phase, more recent data, collected prospectively, from clinical trials in progressive disease suggest otherwise. In both the clinical trial of glatiramer acetate in primary progressive MS (PROMISE Study) and rituximab in primary progressive MS (OLYMPUS Study), subjects with gadolinium-enhanced lesions (an MRI counterpart of a relapse) developed disability at a more rapid rate than those without, irrespective of treatment arm. A recent analysis of the subjects in the PROMISE trial who had on-study relapses (and thus switched from primary progressive to progressive relapsing MS) showed that those who had relapses developed disability faster than those who did not.

In the end, are we really disagreeing or rather looking at two different issues? I suspect the latter. Relapses have physical, emotional and economic consequences, leading to hospitalization, courses of high-dose corticosteroids, time away from work and family, and secondary medical complications from the neurologic deficits or the therapy such as infection, pain, skin breakdown, and falls. However, the relative role of the relapse has been demeaned in the natural history cohort rather than drawing the more reasonable conclusion, supported by most studies, that in early disease the relapse is responsible for the majority of the worsening seen and that once the progressive phase sets in, that process, as measured in natural history cohorts, becomes the dominant factor in worsening. This is not amnesia; no one using a cane years earlier is ignoring that event or the role of subsequent events that lead to earlier disability. Rather, the sooner one reaches a disability threshold, no matter what the mechanism, the longer they will have spent in a disabled state.

References