Making progress on the natural history of multiple sclerosis

Typically, the clinical course of multiple sclerosis is characterized by episodes, from which recovery may occur, and by progression. These phases usually evolve in sequence as part of the natural history. The number and frequency of episodes and the interval between first presentation and the often somewhat blurred transition to disease progression are generally held to be rather unpredictable. By definition, progression is not preceded by episodes in individuals with primary progressive multiple sclerosis. At one time, the essential pathological process in multiple sclerosis was thought to be loss of the myelin sheath that normally surrounds axons in the CNS, as a result of local inflammation, from which followed a cascade of secondary events culminating in development of the multifocal sclerotic lesions from which the disease gets its name. Thus, episodes were considered to be the critical component of the disease, and their reduction presented a natural and sufficient target for treatment.

That perspective changed with the rediscovery of axonal pathology as a significant additional component of the disease process and its correlation with the accumulation of disability, especially during the progressive phase. The concept of multiple sclerosis as a focal inflammatory demyelinating disorder took a further step backwards with the recognition that, in this disorder, normal appearing white matter is far from normal. The evidence is both histological and radiological, but the available observations do not resolve the ambiguous relationship between inflammation and neurodegeneration that remains central to understanding mechanisms of tissue injury in multiple sclerosis, and the relative contribution of each to clinical deficits occurring during different phases of the disease. Thus, magnetic resonance spectroscopic studies of whole brain white matter in multiple sclerosis show abnormalities indicating widespread axonal changes in the absence of apparent tissue inflammation (Filippi et al., 2003). But, while MRI and spectroscopy allow the whole brain and regions of interest to be examined serially, these techniques do not yet characterize each and every component of the pathological process, and they may lack resolution. Conversely, histological examination of tissue makes it possible to characterize the relative amounts of inflammation, demyelination and axonal loss in acute and chronic multiple sclerosis (Barnett and Prineas, 2004; Kutzelnigg et al., 2005) but, being confined to cross-sectional samples, does not directly reveal the sequence of pathological events. Here, the published evidence appears to be ambiguous but, in reality, the issue is more about the amount and type of inflammation rather than whether it is present or not.

A debate has therefore arisen as to whether the diffuse injury with axonal loss seen in multiple sclerosis is directly the consequence of widespread brain inflammation and microglial activation, beyond the present resolution of magnetic resonance techniques, or provides evidence for a primary degenerative disease process (Lassmann, 2003). Is inflammation the pivotal event from which all else follows; are inflammation and axonal loss fully independent processes; or does inflammation expose an intrinsic neurodegenerative susceptibility that renders axons vulnerable to coincidental immune mediated injury? Perhaps, the key observation is provided by clinical trials showing that substantial reduction in relapse frequency does not necessarily predict effects on disability and disease progression (Coles et al., 1999; Rice et al., 2000). Here, the suggestion is that relapse activity and disease progression are proceeding under independent momentum. Against this background, three papers in the current issue come at the problem from another direction—epidemiological studies of the natural history based on large and representative cohorts studied over prolonged periods.

Mark Kremenuchtzyk and colleagues use the London Multiple Sclerosis Clinic database to examine the relationship between relapse and disease progression (page 584). Their aim is to test the model that places episodic activity as the motor of subsequent progression and pari passu to inform the debates on whether demyelinating plaques are the essential pathological feature, and therapeutic reduction of relapse rate is a reliable predictor of long-term effects on disability and the dynamics of progression. They focus on three discrete groups: primary progressive multiple sclerosis, patients with a single attack followed at some later point by progression, and ‘regular’ secondary progressive disease. These are chosen to reflect extremes in relapse experience ranging from none, to one, to many. The single attack progression cases serve to isolate the characteristics of attack and later progression, thereby correcting for the confound of slow or incomplete recovery from an episode that may otherwise cloud the evaluation of what is driving disability in the many patients where intermittent and chronic disease activity overlap. Furthermore, in order to avoid contamination of short-term disability by slow recovery from the most recent episode, their registration of progression is conservative, requiring at
least 1 year of continuous deterioration. Cases are selected from 1043 patients representing an original cohort (generating 71 single attack progressive, 158 primary and 480 secondary progressive cases) and a second series of 1059 cases (69, 61 and 337 additional cases in each category, respectively). Follow-up is extensive (~26,000 patient-years, in total). The authors present three key findings. First, although the estimated age at disease onset differs between groups, and is later in those with primary progressive multiple sclerosis, there is no difference in the age at which disease progression begins [40.9 years for single attack progression cases, 38.6 years in primary progressive multiple sclerosis and 39.2 years in the secondary progressive group (here, there appears to be a slight discrepancy in tabulation either of age at onset, 29.8 years, or of the further interval to disease progression, 10.3 years)]. Secondly, time from onset of progression to Kurtzke disability status scores 6, 8 and 10 are 5.7, 13.6 and 32.9 years for single attack progressive; 6.4, 16.8 and 31.2 years for primary progressive multiple sclerosis and 6.6, 18.2 and ‘not available due to insufficient data points’ for the secondary progressive category. Thus, from the onset of progression, movement across these disability landmarks is even and uninfluenced by having previously had one, none or many previous episodes. Thirdly, the number of systems involved in the inaugural episode, but not the degree of recovery, amongst the single attack progressive category correlates with time to conversion. But, while sensory (37%) and motor (34%) sites may be involved at presentation in individuals who later develop secondary progressive multiple sclerosis, and in the single attack progression group (36 and 33%, respectively), progression almost always preferentially targets the corticospinal pathway (89%).

Christian Confavreux and Sandra Vikusic (page 595) also stand back from the previous emphasis on time from onset to reach various milestones in the course of multiple sclerosis, categorized according to mode of presentation and subsequent clinical course, and build on their previous work showing that, once a certain threshold is reached, accumulation of disability progresses independently of prior relapse history, by considering ‘age’ at points of strategic disability (in their case, only verified over 6 months). They use the Lyon Multiple Sclerosis Cohort, maintained since 1957, registering 1844 cases reviewed annually through to 1997 classified as relapsing–remitting only and primary (with or without superimposed episodes) or secondary progressive multiple sclerosis. Ages at acquisition of landmark Kurtzke disability status scale scores 4, 6 and 7 are broadly similar across the groups, and uninfluenced by mode of onset or initial symptoms, but do correlate with age at onset. Thus, although individuals with secondary progression become disabled somewhat earlier than is seen in cases with primary progressive multiple sclerosis, the ages at which these milestones are reached in the entire cohort (44, 55 and 63 years, respectively) differ by <2.7 years between groups. The authors conclude that the mode of presentation does not influence age at disability landmarks in multiple sclerosis: relapses have very little influence on accumulation of disability or disease progression; and inflammation has only a limited effect on neurodegeneration—rather, this is pre-determined by an age-related process.

In a second paper, Confavreux and Vukusic (page 606) set out their stall with respect to the ambiguous relationship between relapse activity and progression (and hence inflammation and neurodegeneration) hoping to use the natural history data to address the issue of complexity and heterogeneity in multiple sclerosis. They categorize their 1844 cases as having relapsing–remitting multiple sclerosis (1066) and primary (282) or secondary progressive disease (496). Many of their descriptions seem intuitive. Given similarity in most other respects, the marked difference in the duration of relapsing–remitting and secondary progressive multiple sclerosis seems to reflect a maturation effect; primary progressive multiple sclerosis moves faster towards the initial disability milestone, and occurs at an earlier age, than relapsing–remitting disease but thereafter the dynamics are similar; transitional (progressive from onset with superimposed episodes) and primary progressive multiple sclerosis essentially behave in a similar manner; and other than a longer interval between onset and assignment of disability milestones and slightly more rapid subsequent course, the features of primary and secondary progressive multiple are similar.

Does this help? Both sets of investigators have interrogated powerful databases boasting large numbers of carefully evaluated cases, with prospective follow-up over prolonged periods, to ask simple questions. Although each group might have wished their predecessors to have anticipated details of the present enquiries, and gathered information directly relating to the questions now being considered, we should accept the observations and seek to place these in an overall framework of how the various disease mechanisms in multiple sclerosis contribute to clinical expression of episodes and progression. Kremenchutzky and colleagues conclude that the progressive phase of multiple sclerosis is an age-dependent degenerative process, at least in part, and that chronic axonal loss specific to the corticospinal tract is the pathological substrate for progression, beginning early in the disease course and long before clinical symptoms manifest. Confavreux and Vukusic also conclude that the clinical phenotype and course of multiple sclerosis are age-dependent. Times to reach disability milestones, and the ages at which these landmarks are reached, follow a predefined schedule not obviously influenced by relapses, whenever these may have occurred, or by the initial course of the disease, whatever its phenotype. They consider relapsing–remitting disease as multiple sclerosis in which insufficient time has elapsed for conversion to secondary progression; secondary progressive multiple sclerosis as relapsing–remitting disease that has now grown older; and progressive from onset disease as multiple sclerosis ‘amputated’ from its usual preceding relapsing–remitting phase. When a detectable threshold of irreversible disability is reached, the disease enters a final
common pathway where subsequent accumulation of disability becomes a self-perpetuating process, amnestic with respect to the prior history. Hence, the unifying concept embraced by their title.

Epidemiology can only suggest hypotheses that seek to illuminate disease mechanisms. It is not a discipline that can directly test these ideas. But, equally, neither does modelling the disease processes, in vivo or in vitro, nor obtaining imaging surrogates and snapshots of the neuro-pathology provide a definitive account. Perhaps the best test of how progression and episodic disease activity are entwined will be the demonstration, or not, that early effective suppression of inflammation not only eliminates new episodes but does also prevent the subsequent accumulation of disability and the onset of progression. Of course, how early is early and how complete is complete in this context are matters of detail but nonetheless of great importance. Trials that approximate to these aims are now in progress. My expectation is that, when all is finally known, people who develop multiple sclerosis will be shown to have a (genetically determined) diathesis that does indeed predispose to neurodegeneration, and hence disease progression, quite possibly in a specific pathway, but the exposure of that vulnerability requires an inflammatory insult without which the degenerative component does not manifest. Since this interplay is likely to depend on a number of additional variables influencing either component, the impact of which may differ between individuals, a strict relationship between inflammation and degeneration (or relapse activity and progression) is not to be expected. And the relationship may change with time: at first, a substantial amount of inflammation is needed to expose the degenerative tendency; later, as trophic and anti-inflammatory support normally provided by intact axon-glial arrangements is eroded, small amounts of inflammation take a greater toll. But both are necessary, and neither is sufficient for full expression of the natural history of this difficult disease.

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References