Inflammatory-mediated demyelination of the central nervous system with well-recognized axonal injury has been described for over a hundred years. Yet, many pathologic aspects of multiple sclerosis remain poorly understood (Noseworthy et al., 2000). Clinically, a high proportion of patients with relapsing-remitting disease advance to the secondary progressive stage of the disease (Lublin and Reingold, 1996). In contrast, ~15% of patients never experience clinical relapses and demonstrate a steadily progressive phenotype from onset. The ability of available therapies, approved for the relapsing–remitting form of the illness, to modify the disease course in secondary or primary progressive multiple sclerosis is dismal (Compston and Coles, 2008). Paradoxically, success of the immunopathologic ‘line of thinking’ has revealed numerous deficiencies in our understanding of the neurobiology of the disease, including interdependence of the axon and oligodendrocyte (Piaton et al., 2010). At the heart of this broadening discussion of multiple sclerosis pathology is the question of what triggers disease progression and the mechanisms that lead to increased disability.

One area of research germane to this question is the expansion of focal inflammatory demyelinating lesions and the remyelinating capacity of the central nervous system in progressive phenotypes, i.e. secondary and primary progressive multiple sclerosis. Extensive cortical demyelination is a cardinal feature of progressive disease and presumably the cause of many symptoms of late-stage multiple sclerosis. Axonal injury and loss occur in association with activity of the adaptive immune response, thus leading to the question as to why this inflammation is resistant to the anti-inflammatory effects of existing therapies (Kutzelnigg et al., 2005; Frischer et al., 2009). The answer may partly lie in the slowly expanding demyelinating ‘front’ and the remyelinating capacity of focal lesions in the central nervous system, although much has yet to be learned about axonal-glial interactions and the state of virtual tissue hypoxia in the central nervous system that may ultimately determine the irreversible decline seen in progressive forms of multiple sclerosis (Trapp and Stys, 2009).

In this issue of Brain, Bramow and colleagues report findings from an autopsy study of 51 patients with progressive multiple sclerosis (34 secondary progressive and 17 primary progressive) and 12 matched controls (page 2983). Using planimetric analysis of paraffin-embedded archived brain and spinal cords from patients with multiple sclerosis, they performed an exhaustive histopathological study that focused on demyelination and remyelination. They examined demyelinating ‘frontlines’ as the border zone between areas of inflammatory demyelination and the surrounding white matter. However, they also describe a novel method for quantifying demyelinating plaques as ‘1st hit’ demyelination and ‘2nd hit’ demyelination. The former showed demyelinating frontlines affecting the white matter without evidence of prior de- or remyelination in the surrounding white matter, whereas the latter displayed demyelinating frontlines in previously demyelinated areas that had evidence for varying degrees of remyelination. This approach allowed estimation of vulnerability to inflammatory demyelination in remyelinated areas relative to the white matter area. They further validated this complex histopathological approach by quantifying ‘1st hit’ demyelination per cm² in the white matter and the number of ‘2nd hit’ demyelinating areas per cm² of remyelinating area. Based on this methodology, Bramow and colleagues make five key observations:

(i) Higher brain loads of active and total demyelination are seen in secondary progressive than primary progressive multiple sclerosis, showing similar degrees of spinal cord involvement.
(ii) Higher remyelination capacity in the brain is observed in primary than secondary progressive disease.
(iii) Remyelinated areas are more prone to inflammatory demyelination compared to the surrounding white matter.
(iv) Slowly expanding demyelination correlates with incomplete remyelination in both secondary and primary progressive multiple sclerosis.
(v) Incomplete remyelination in the spinal cord, but not the brain, correlates with severe clinical disability irrespective of the clinical phenotype.

Several limitations of the study warrant careful interpretation of the findings. The archival autopsy material was obtained, in some cases, more than three decades ago. Histopathological observations, particularly autopsy studies, only provide an ultimate examination of pathology. The ‘snapshot’ nature of these observations necessitates careful deliberation when extrapolating to clinical correlations. Clinical ratings performed in this study were
Despite the limitation of the Multiple Sclerosis Severity Score estimation in this study, there was a positive correlation between spinal cord demyelination and severity, and a negative correlation with spinal cord remyelination capacity. Other studies have shown relatively weak correlations between spinal cord T2 lesion load and the Expanded Disability Status Scale (Stevenson et al., 1999). However, this study exemplifies why distinguishing demyelinated from remyelinated lesions and the balance between spinal cord demyelination and remyelination, may be necessary to determine resultant clinical disability. It would have been of great interest if the authors had examined the extent of demyelination in different tracts in the spinal cord. Equally interesting was the observation that the vulnerability of remyelinated areas to active demyelination is greater in secondary progressive disease and that there is a significant correlation between the ‘inactive’ lesion load and incomplete remyelination. These observations are strongly supported by a prior publication describing the so-called ‘Chari-Blakemore’ hypothesis, which suggests that cells of oligodendrocyte lineage may migrate and differentiate only in areas with a sufficient drive from inflammatory mediators, and that large demyelinating areas may expose remyelinating cells to these mediators (Chari and Blakemore, 2002). Others have shown that maturation of oligodendrocytes is seen in active but not inactive plaques (Kuhlmann et al., 2008). These observations also raise an important clinical question: is highly potent anti-inflammatory intervention counter-intuitive to reparative strategies, as suggested by a study of autologous hematopoietic stem cell transplantation in multiple sclerosis (Metz et al., 2007)? At the same time, increased vulnerability of remyelinated areas to active demyelination (‘2nd hit’ demyelination) in secondary progressive multiple sclerosis, supports the clinical observation of similar clinical relapses seen in patients with long-standing relapsing–remitting or secondary progressive multiple sclerosis with superimposed relapses. Recovery from these relapses is often incomplete, indicating ongoing or expanding active demyelination relative to complete remyelination (Lublin et al., 2003). Bramow and colleagues show that slowly expanding demyelination may have a predilection for remyelinated areas in secondary progressive than primary progressive disease. The slowly expanding plaque load correlated more strongly with incomplete remyelination than the plaque load of active demyelination. This points towards remyelination failure in secondary, relative to primary progressive multiple sclerosis. It would be interesting to reproduce these findings in a study involving a larger number of samples from primary progressive multiple sclerosis and in cases where the brain lesion load of patients with primary and secondary progressive disease are comparable. It has been shown that the brain MRI lesion load tends to be higher in patients with primary progressive disease having higher Expanded Disability Status Scale scores (Wolinsky et al., 2007). Nonetheless, it still remains unclear why remyelination predominantly fails in secondary progressive disease. Another issue that remains unresolved is difference in the ability of subcortical and periventricular plaques to remyelinate, as previously reported (Goldschmidt et al., 2009). However, the location of plaques and how this affects remyelination in the brain was not assessed by these investigators. An important finding of the present study, having direct clinical relevance, is the
correlation between incomplete spinal cord remyelination and disease severity. This also indirectly supports the observation that slowly expanding demyelinating plaques are a pathological correlate of disease progression. This highlights the need to focus on ‘remyelinating’ and neuroprotective therapeutic strategies in progressive phenotypes of multiple sclerosis, since these may offer greater potential to improve clinical outcomes in place of the predominantly immunomodulating anti-inflammatory approach, which is largely ineffective in both secondary and primary progressive multiple sclerosis (Fancy et al., 2010).

Several important pathological aspects of progressive multiple sclerosis not examined in this study, but which may potentially correlate with the findings, deserve mention. The presence of ectopic lymph follicles in patients with multiple sclerosis may perpetuate an inflammatory response within the central nervous system and have particular bearing on disease progression (Aloisi and Pujol-Borrrell, 2006). Mitochondrial injury is a major effector mechanism of demyelination and neurodegeneration. Attempts to reduce mitochondrial and consequently axonal metabolic injury may be critical to the concept of ‘neuroprotection’ (Dutta et al., 2006; Kalman, 2006; Mahad et al., 2009). Mitochondrial injury has been induced in mixed glial cultures when exposed to a mixture of pro-inflammatory cytokines (Lisak et al., 2009). This may have potential histopathological implications for the development of slowly expanding plaques. The role of microglial cells and of activated macrophages is also critical in understanding disease progression (Rotshenker et al., 2008; Gandhi et al., 2010). Based on the presence of microglial nodules in the peri-plaque white matter (Prineas et al., 2001), it has been speculated that myelin loss may be progressive in chronic lesions. Regulatory pathways influencing remyelination, including ‘notch’ and ‘wnt’, may be important targets of therapeutic intervention in remyelinating strategies (Fancy et al., 2010). Axonal injury, a critical correlate of permanent disability in multiple sclerosis, was not examined by Bramow and colleagues. Besides the well known massive axonal transection that occurs in acute demyelinating plaques, axonal injury is also linked to inflammation seen in the chronic stages of the illness possibly due to CD8 T-cell-mediated attack or collateral bystander injury (Fletcher et al., 2010). The evolving concept of a state of ‘virtual hypoxia’, leading to chronic injury of demyelinated axons has considerable merit. The increased energy demand needed for electrical conduction in viable demyelinated axons combined with reduced axonal ATP production leads to a state of virtual hypoxia in chronic lesions (Trapp and Stys, 2010). Consequently this leads to aberrant function in the mitochondria, Na+ influx through voltage-gated Na+ channels and axonal AMPA receptors, and release of toxic Ca2+ from the axoplasmic reticulum. In turn, overactivation of axonal glutamate receptors as well as activation of voltage-gated Ca2+ channels leading to excessive stimulation of Ca2+-dependent pathways, causes irreversible cell injury (Matute, 2010). Equally important as a determinant of permanent injury, is the reciprocal communication between neurons and oligodendrocytes that is vital to myelin biogenesis and remyelination in pathologic states (Nave and Trapp, 2008).

Taken together, Bramow and colleagues highlight several new findings in their quantitative histopathological study of demyelination and remyelination in progressive forms of multiple sclerosis. Almost two decades after the approval of the first ‘disease-modifying’ therapy for this illness, it is becoming increasingly evident that tissue repair, especially remyelination in the central nervous system, is dependent on complex mechanisms, and may occur differentially in the brain and spinal cord in multiple sclerosis. These complex, yet sobering observations are likely to enhance our understanding of multiple sclerosis disease pathology in the progressive phenotype. Furthermore, they shift the focus from present immunomodulatory approach towards remyelinating and neuroprotective strategies based on improved understanding of the complex pathology of progressive multiple sclerosis (Khan, 2007; Weiner, 2009; Tselis et al., 2010). Effective treatment for progressive disease remains the biggest unmet need in people with multiple sclerosis.

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References


Expanding the concept of inflammatory neuropathies

Inflammatory neuropathies include several clinical entities and constitute a major portion of peripheral neuropathies. Inflammatory neuropathies may be caused by immune-mediated mechanisms initiated by constituents of the peripheral nervous system. Among these neuropathies, Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy are especially well known. Although Guillain–Barré syndrome had been considered to be identical to acute inflammatory demyelinating polyradiculoneuropathy (Asbury, 1981), recent studies have added acute motor axonal neuropathy as a component of Guillain–Barré syndrome (Griffin et al., 1995; Hughes et al., 2005; Yuki and Kuwabara, 2007). In addition, investigations for anti-ganglioside antibodies have further widened the concept of Guillain–Barré syndrome (Kusunoki et al., 1999; Willison and Yuki, 2002; Kaida et al., 2008). Although chronic inflammatory demyelinating polyneuropathy usually manifests as a motor sensory neuropathy, a pure motor form, designated as multifocal motor neuropathy, and a pure sensory form, which is termed chronic immune sensory polyradiculopathy, may occur (Pestronk et al., 1988; Sinnreich et al., 2004). In addition to these mainly somatic neuropathies, the discovery of anti-ganglionic acetylcholine receptor antibodies has shed light on autonomic neuropathies in the field of immune-mediated neuropathies (Vernino et al., 2000). These immune-mediated neuropathies are caused by an abnormal