A function of myelin is to protect axons from subsequent injury: implications for deficits in multiple sclerosis

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Editorial

A function of myelin is to protect axons from subsequent injury: implications for deficits in multiple sclerosis

Once it was thought that the mechanism for development of permanent neurological deficits in multiple sclerosis was understood. Demyelination, the pathological hallmark of the multiple sclerosis lesion, was the culprit. Elegant physiological studies demonstrated that demyelination results in conduction slowing and, in particular, conduction block (McDonald and Sears, 1969). These observations appeared sufficient to explain the majority of deficits in multiple sclerosis. However, clinical observations began to challenge this hypothesis. With the development of MRI, clinicians saw patients with extensive white matter lesion load with minimal or no neurological deficits. Pathological studies demonstrated that lesions observed by MRI were indeed demyelinated and frequently involved eloquent areas of CNS that should have resulted in neurological deficits. Autopsy series made it clear that substantial demyelination, sufficient to make the pathological diagnosis of multiple sclerosis, can be observed in individuals who during life remained normal in neurological function (Mews *et al*., 1998). Patients with essentially normal vision have been documented in which the optic nerve and its tracts were completely demyelinated.

The hypothesis that I favour is that demyelination is necessary, but not sufficient, for development of permanent deficits in multiple sclerosis. Demyelination predisposes axons to subsequent secondary injury. This secondary injury to the axon may be the result of either (i) T cell cytotoxicity, or (ii) the failure of local target-derived neurotrophic support from death of myelinating oligodendrocytes. This hypothesis implies that one of the primary functions of myelin is to protect the axon from injury. The corollary of this hypothesis is that any strategy that promotes remyelination will be neuroprotective. Unknown is how long an axon can remain demyelinated in the human CNS. This hypothesis would predict only two possible outcomes for the demyelinated axon: (i) degeneration and death of parent neuron, and (ii) remyelination with associated axonal protection (Fig. 1).

How does this hypothesis reconcile with the progression of clinical deficits in a large cohort of multiple sclerosis patients? In this issue of *Brain*, Confavreux *et al*. (2003) tell us that clinical variables such as gender, age, course, number of relapses, and recovery from relapses predict the course of early disease. However, once the patient reaches a certain threshold of disability, the course is progressive and these variables are not predictive. A plausible explanation is that the early phase of disease is primarily explained by the influx of inflammatory cells and associated demyelination. In contrast, once demyelination is established and repair mechanisms exhausted, axonal degeneration ensues in a predictable manner. Thus the factors that contribute to the early events of the disease do not contribute to the second (axonal) phase of disease (Fig. 1).

What are the implications of this hypothesis to treatment and management? All current treatments have focused on controlling the early phase of disease. The hope has been that if inflammation is controlled, then demyelination will not take place; and therefore permanent deficits will be prevented. The study by Confavreux *et al*. (2003) raises major concerns as to the basis of this supposition. All our current treatments have been approved based primarily on the fact that they decrease relapse rate and decrease gadolinium enhancing MRI lesions (a surrogate for preventing inflammation). The clinical trials, as well as the predictions from Confavreux *et al.*, tell us clearly that our current treatment approaches are having no effect on permanent and accumulating deficits. Demyelination and inflammation are possibly independent contributors to the development of lesions. The mounting evidence that inflammation is necessary for myelin repair confounds the problem (Hammarberg *et al*., 2000; Bieber *et al*., 2001). The primary conclusion from this hypothesis is that the major therapeutic focus should be on early and rapid remyelination. This will turn out to be the most effective neuroprotective strategy. The ultimate goal of our therapies has to be to prevent axonal dysfunction, injury and loss.

Animal experiments began to cast doubt on the hypothesis that demyelination is sufficient to explain permanent deficits in multiple sclerosis. Using a viral murine model of multiple sclerosis, investigators at the Mayo Clinic showed that in mice with deletion of the MHC Class I arm of the immune response, profound demyelination of the spinal cord can occur despite normal neurological function (Rivera-Quiñones *et al*., 1998). Even physiological function was preserved, likely due to the up-regulation and redistribution of sodium

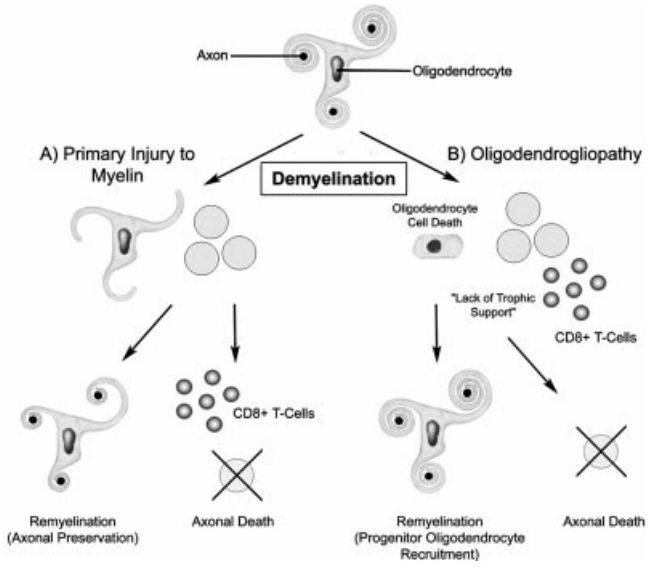

Fig. 1 Demyelination in multiple sclerosis occurs by two major mechanisms: (**A**) primary injury to the myelin sheath with relative preservation of oligodendrocytes, or (**B**) direct injury to oligodendrocytes (oligodendrogliopathy). Following demyelination of the axon there is either (i) remyelination with axonal preservation, or (ii) axonal death. Remyelination can take place by either surviving mature oligodendrocytes, or more likely by the recruitment of progenitor oligodendrocytes that mature into myelinating cells. Axonal death occurs as a result of either the inflammatory response, in particular MHC Class I restricted CD8 positive T cells, or by the failure of local neurotrophic support as a result of injury to glial cells.

channels along demyelinated axons. Retrograde labelling experiments demonstrated failure of axonal transport in mice with demyelination and functional deficits. However, axonal transport was preserved in demyelinated mice with deletion of MHC Class I (Ure and Rodriguez, 2002). Depletion of antigen-specific cytotoxic T cells restricted to an immunodominant peptide resulted in preservation of neurological function (Johnson *et al*., 2001). This was the first demonstration that CD8 positive T cells restricted to Class I MHC alleles may be the main players in axonal injury and permanent deficits. Of interest, recent pathological studies show that CD8 positive T cells are the most common subset of T cells in the multiple sclerosis brain (Babbe *et al*., 2000). CD8 T cells are statistically associated with axonal injury in multiple sclerosis (Bitsch *et al*., 2000). In addition, CD8 T cells have been shown to injure neurons and transect axons *in vitro* (Medana *et al*., 2001).

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References

Babbe H, Roers A, Waisman A, Lassmann H, Goebels N, Hohlfeld R, et al. Clonal expansions of CD8(+) T cells dominate the T cell infiltrate in active multiple sclerosis lesions as shown by micromanipulation and single cell polymerase chain reaction. J Exp Medicine 2000; 192: 393–404.

Bieber AJ, Warrington A, Pease LR, Rodriguez M. Humoral autoimmunity as a mediator of CNS repair. Trends Neurosci 2001; 24 (11 Suppl): S39–44.

Bitsch A, Schuchardt J, Bunkowski S, Kuhlmann T, Bruck W. Acute axonal injury in multiple sclerosis. Correlation with demyelination and inflammation. Brain 2000; 123: 1174–83.

Confavreux C, S. Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 2003; 126: 770–82.

Hammarberg H, Lidman O, Lundberg C, Eltayeb SY, Gielen AW, Muhallab S, et al. Neuroprotection by encephalomyelitis: rescue of mechanically injured neurons and neurotrophin production by CNS-infiltrating T and natural killer cells. J Neurosci 2000; 20: 5283–91.

Johnson AJ, Upshaw J, Pavelko KP, Rodriguez M, Pease LR. Preservation of motor function by inhibition of CD8(+) virus peptide-specific T cells in Theiler's virus infection. FASEB J 2001; 15: 2760–2.

McDonald WI, Sears TA. Effect of demyelination on conduction in the central nervous system. Nature 1969; 221: 182–3.

Medana I, Martinic MA, Wekerle H, Neumann H. Transection of major histocompatibility complex class I-induced neurites by cytotoxic T lymphocytes. Am J Pathol 2001; 159: 809–15.

Mews I, Bergmann M, Bunkowski S, Gullota F, Bruck W. Oligodendrocyte and axon pathology in clinically silent multiple sclerosis lesions. Mult Scler 1998; 4: 55–62.

Rivera-Quiñones C, McGavern D, Schmelzer JD, Hunter S, Low PA, Rodriguez M. Absence of neurological deficits following extensive demyelination in a class I-deficient murine model of multiple sclerosis. Nat Med 1998; 4: 187–93.

Ure DR, Rodriguez M. Preservation of neurologic function during inflammatory demyelination correlates with axon sparing in a mouse model of multiple sclerosis. Neuroscience 2002; 111: 399–411.