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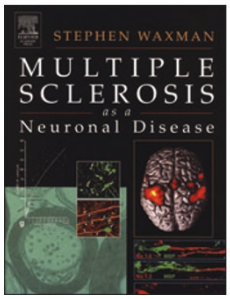
How are neurons damaged in multiple sclerosis?



Multiple Sclerosis as a Neuronal Disease

Edited by Stephen Waxman

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Reviewed by Monique Dubois-Dalcq and Bernard Zalc

Multiple sclerosis, the prototype of demyelinating disease in man, is a relapsing-remitting or progressively disabling disease of unknown cause. The first pathological descriptions of the disease 150 years ago already showed that demyelinated axons could degenerate. Recent evidence suggests that multiple sclerosis also affects neurons, as cortical atrophy is detected early in the disease, axon transection can occur in inflammatory lesions, and axonal loss is closely correlated with disease severity. Thus the timing of this book is most appropriate: it gathers evidence of neuronal and axonal dysfunction that offers neurologists, neurobiologists and neuroscience PhD students an opportunity to reflect on whether multiple sclerosis is both a neuronal and demyelinating disease.

The editor has contributed to 5 of the 30 chapters of this well-illustrated book. After a comprehensive introduction to myelin structure, myelination and the molecular assembly of nodes of Ranvier, the book covers the physiology of nerve impulse propagation before and after CNS demyelination. This emphasis on neurophysiological analysis of nerve conduction changes underlying disease is an original and valuable feature, as books on multiple sclerosis often focus heavily on the autoimmune process. The recent identification of ion-channel subtypes and ion transporters on the myelinated axon has allowed the characterization of changes in their distribution and density after demyelination. This has led to new pharmacological approaches to neuroprotection, which are thoroughly covered. The clinical effects of therapeutic interventions and the pathophysiological consequences of demyelination are followed in patients by magnetic resonance imaging (MRI), which reveals cortical atrophy and the development of inflammatory and demyelinating lesions. When combined with spectroscopy, MRI allows axonal damage to be quantified, whereas functional MRI reveals how the patient's brain partially compensates for the damage by recruiting other pathways. From this sophisticated appraisal of the disease process and from the evidence that large axons need myelin to survive and to maintain axonal flow and synapses, there is no doubt that multiple sclerosis affects both myelin and axons. The discovery that the ubiquitin proteasome pathway is involved in Wallerian degeneration suggests that an autodestruction pathway could be activated in demyelinated axons by membrane-bound or secreted products of inflammatory cells.

Is multiple sclerosis truly a "neuronal disease" as the book title boldly announces? The editor's preface rightly tempers this by stating that "it is not meant to imply that MS is a primary neuronal disease" but rather "to stimulate research on neuronal injury in MS." Such research is important, given that little is known about the molecular basis of cortical atrophy and lesions, which are detected with increasing frequency by high-resolution MRI. Neuropathological analysis of such lesions revealed apoptotic neurons and inflammatory cells as well as neurons with transected axons surrounded by activated microglia. Chronic inflammation indeed can cause neuronal apoptosis, as observed in rat retinal neurons during optic neuritis induced by immunization with myelin oligodendrocyte glycoprotein. One possible mediator of neuronal death is the tumor necrosis factor–related apoptosis-inducing ligand, an immunoregulatory molecule whose expression is elevated in peripheral T cells of multiple sclerosis patients and which induces neuronal death in mouse brain slices. One possibility is that inflammatory mediators may affect specific populations of neurons that express Toll receptors involved in innate immunity. This could account for the distribution of multiple sclerosis plaques. Alternatively, a random distribution of the plaques may occur because oligodendrocyte subsets of different embryological origins have distinct sensitivities to toxic insults.

This very informative book starts out tightly organized but becomes less so in the middle, as some chapters partially overlap earlier ones. Later, it takes some detours from the main theme to discuss factors involved in acute axonal neuropathy and demyelinating neuropathies, such as autoantibodies following microbial infection, whose involvement in multiple sclerosis has not been shown so far. Toward the end, however, the main subject takes center stage again, with a comprehensive appraisal of myelin repair in animal models, where it can be enhanced by antibodies or transplantation, reminding us that promoting remyelination is the best way to maintain axon survival. Although neuroprotective drugs have immediate therapeutic potential in multiple sclerosis, strategies to enhance remyelination are still far from reaching patients and therefore should be a high research priority.

The editor and many excellent contributors present abundant evidence for the importance of the neuronal component of multiple sclerosis. There is an immediate need for a reappraisal of experimental models that more closely mimic the human disease and for multidisciplinary clinical research addressing how neuroinflammation leads to such devastating lesions. Clearly the idea that multiple sclerosis is a purely demyelinating disease has to be abandoned. There is no doubt that Steve Waxman's forceful book will substantially influence the field by providing a strong impetus to research on the neuronal question in multiple sclerosis.

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