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## Pathophysiology of disability in multiple sclerosis

**Abstract** Acute symptoms in multiple sclerosis are attributable to physiological conduction block from inflammatory mediators, demyelination and axonal transection. Remission is achieved through release from conduction block, remyelination and functional adaptation. Persistent disability is due to axonal transection and demyelination. Intact demyelinated axons may conduct normally on

remission, but degenerate slowly over time, possibly through non-inflammatory mechanisms. This decay in function of individual tracts accumulates to cause the delayed emergence of the secondary progressive phase of the illness.

**Key words** Axonal degeneration • Multiple sclerosis • Cerebral atrophy • Nitric oxide

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### Introduction

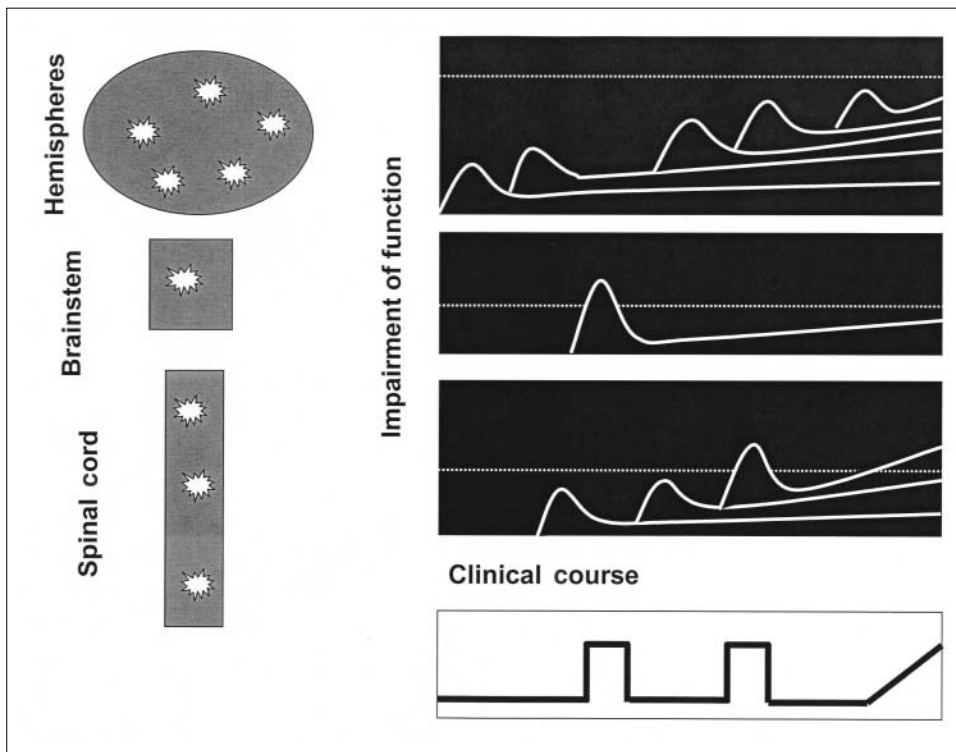
Patients with multiple sclerosis fear persistent and progressive disability more than anything. Understanding its pathophysiology leads to novel therapeutic strategies, such as the recent promotion of Na<sup>+</sup> channel blockade in multiple sclerosis [1]. Normal function of the nervous system depends upon “saltatory conduction”: the passive propagation of action potentials down stretches of myelinated nerve with sufficient depolarisation of the neighbouring unmyelinated node of Ranvier to trigger the active generation of an action potential. The structures underpinning this process are the axon, voltage-gated sodium channels at the nodes of Ranvier and compact myelin, made by the oligodendrocyte, a cell which maintains the myelin sheath of up to 40 neighbouring nerve axons in the central nervous system.

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### The lottery of anatomy

Through damage to one or other components of saltatory conduction, the multiple sclerosis plaque either slows or blocks conduction down a specific tract. The extent of impairment this causes depends upon the site of the lesion and the degree of adaptive responses. A single lesion of

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**Fig. 1** Each lesion of multiple sclerosis disrupts function in a tract acutely, resolves partly but then causes long-term attrition of function. This only expresses itself clinically if it crosses a threshold of functional reserve, which is different in different neuronal systems

the same size is likely to cause greater disability in the brainstem than the cerebral cortex, for instance, due to the greater clinical eloquence of the functions subserved by the brainstem and its lesser capacity for adaptation. Hence the greater “functional reserve” of the three sites illustrated in the figure (Fig. 1).

### The acute consequences of demyelination

Disruption of myelin slows conduction of the impulse or blocks it altogether. Partially demyelinated axons conduct impulses at reduced velocity – explaining the characteristic delays in conduction of evoked potentials. Demyelinated axons may discharge spontaneously and show increased mechanical sensitivity – accounting for the flashes of light on eye movement (phosphenes) and electrical sensation running down the spine or limbs on neck flexion (Lhermitte’s symptom and sign). Ephaptic transmission may occur between neighbouring demyelinated axons giving rise to paroxysmal symptoms – trigeminal neuralgia, ataxia and dysarthria, or painful tetanic posturing of the limbs lasting one or two minutes and often triggered by touch or movement. When axons become demyelinated, sodium channels, which normally cluster at nodes of Ranvier, redistribute themselves along the length of the axons [2]. This may be an adaptive response to restore conduction, but it does leave the axon vulnerable to excessive sodium loading.

### The consequences of partial demyelination

The safety factor for conduction in partially demyelinated axons is compromised. Whilst conduction may be normal under best conditions, environmental changes reveal the vulnerability of partially demyelinated tracts. For instance, they cannot contain the fall in membrane capacitance induced by a rise in temperature and conduction fails – leading to the characteristic appearance of symptoms and signs following exercise or a hot bath (Uhthoff’s phenomenon). Components of the acute inflammatory response also impair conduction; as shown by the rehearsal of previous symptoms with the cytokine storm induced by the therapeutic antibody, Campath-1H. In the laboratory, nitric oxide transiently and reversibly blocks conduction of normal, and especially demyelinated axons [3].

### The consequences of acute axonal loss

Immunohistochemical staining for amyloid precursor protein confirms that axonal injury occurs as part of the acute demyelinating lesion [4]. This acute axonal damage mainly occurs early in the course of multiple sclerosis and is correlated with the degree of inflammation. The inflammatory culprit is probably nitric oxide which, when compounded by high axonal firing frequency, causes axonal loss [5]. The underlying mechanism for this may be a rise in intracellular  $\text{Ca}^{2+}$  through the reversal of the normal  $\text{Na}^+-\text{Ca}^{2+}$  exchanger

in energy-starved and Na<sup>+</sup>-overloaded demyelinated axons [1]. Acute transection of axons causes irreversible dysfunction in that tract. Although Wallerian degeneration may be imaged over the subsequent eighteen months, this does not cause any further clinical deficit.

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### Physiology of remission

After the initial inflammatory insult, and the release of pathways from nitric oxide-induced physiological conduction block, functional pathways are re-organised [6]. These processes account for the initial recovery from a relapse. The presence of shadow plaques attests to the possibility of remyelination to further restore function. But endogenous remyelination is limited by gliosis, a physical barrier induced by astrocyte activation. Incomplete recovery from a relapse suggests insufficient adaptive responses to acute axonal transection or demyelination.

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### Progressive accumulation of disability

The accumulation of disability between discernible relapses, which marks the secondary progressive phase, is not associated on MRI with new lesion formation, but rather with progressive cerebral atrophy, which proceeds even after suppression of cerebral inflammation [7, 8]. However a high load of early inflammatory lesions on MRI predicts subsequent clinical disability and cerebral atrophy [9, 10]. A hypothesis that explains these findings is that progressive disability is due to axonal degeneration, which is itself a late consequence of inflammatory demyelination. One mechanism for this may be loss of trophic support normally provided for axons by myelin or glia, acting directly and/or through the maintenance of electrical activity [11, 12]. This is illustrated in the figure by a slow decay in function of compromised pathways over time. These accumulate to cause the secondary progressive phase of the illness.

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### Balance of pathologies in multiple sclerosis

Currently the only therapies available to treat multiple sclerosis are anti-inflammatory. Under the model described here, and supported by the clinical trial evidence, there is little logic for their use in the secondary progressive phase of the illness. The model's prediction would however be that effective anti-inflammatory therapy much earlier in the disease course would reduce or delay the proportion of patients who enter the secondary progressive phase. It is simplistic to suppose that the

inflammatory and post-inflammatory phases are distinct and always clearly distinguishable. Rarely, patients with an apparently progressive course may benefit from immunotherapies; such was the case for subgroup of patients with relapses in the MIMS mitoxantrone trial of worsening multiple sclerosis [13]. The clinician needs to weigh the balance of pathologies in each patient. In the difficult group of rapidly worsening multiple sclerosis, it can be helpful to measure the amount of enhancement on MRI, brain volume and the response to corticosteroids.

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### References

1. Bechtold DA, Kapoor R, Smith KJ (2004) Axonal protection using flecainide in experimental autoimmune encephalomyelitis. *Ann Neurol* 55:607–616
2. England JD, Gamboni F, Levinson SR et al (1990) Changed distribution of sodium channels along demyelinated axons. *Proc Natl Acad Sci U S A* 87:6777–6780
3. Redford EJ, Kapoor R, Smith KJ (1997) Nitric oxide donors reversibly block axonal conduction: demyelinated axons are especially susceptible. *Brain* 120:2149–2157
4. Ferguson B, Matyszak MK, Esiri MM et al (1997) Axonal damage in acute multiple sclerosis lesions. *Brain* 120:393–399
5. Smith KJ, Kapoor R, Hall SM et al (2001) Electrically active axons degenerate when exposed to nitric oxide. *Ann Neurol* 49:470–476
6. Werring DJ, Bullmore ET, Toosy AT et al (2000) Recovery from optic neuritis is associated with a change in the distribution of cerebral response to visual stimulation: a functional magnetic resonance imaging study. *J Neurol Neurosurg Psychiatry* 68:441–449
7. Filippi M, Rovaris M, Iannucci G et al (2000) Whole brain volume changes in patients with progressive MS treated with cladribine. *Neurology* 55:1714–1718
8. Coles AJ, Wing M, Molyneux P et al (1999) Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol* 46:296–304
9. Brex PA, Ciccarelli O, O'Riordan JI et al (2002) A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. *N Engl J Med* 346:158–164.
10. Chard DT, Brex PA, Ciccarelli O et al (2003) The longitudinal relation between brain lesion load and atrophy in multiple sclerosis: a 14 year follow up study. *J Neurol Neurosurg Psychiatry* 74:1551–1554
11. Barres BA, Raff MC (1993) Proliferation of oligodendrocyte precursor cells depends on electrical activity in axons. *Nature* 361:258–260
12. Wilkins A, Majed H, Layfield R et al (2003) Oligodendrocytes promote neuronal survival and axonal length by distinct intracellular mechanisms: a novel role for oligodendrocyte-derived glial cell line-derived neurotrophic factor. *J Neurosci* 23:4967–4974
13. Hartung HP, Gonsette R, Konig N et al (2002) Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 360:2018–2025