

# Pathophysiology of conduction block in multifocal motor neuropathy

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## Summary

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Multifocal motor neuropathy (MMN) is a rare disorder of the peripheral nervous system characterised by the presence of focal motor conduction blocks. Although the pathological basis of conduction block is believed to be focal demyelination, in multifocal motor neuropathy this mechanism lacks definitive proof from morphological studies. In recent years special neurophysiological techniques for assessing axonal excitability non-invasively in humans have expanded knowledge on the pathophysiology of multifocal motor neuropathy. Nonetheless, several findings support the hypothesis that conduction blocks probably arise from more than one pathogenetic mechanism (hyperpolarisation or depolarisation) which can change during the course of the disease and probably represent the “tip of the iceberg” of axo-myelinic abnormalities.

*Keywords: multifocal motor neuropathy; depolarisation; hyperpolarisation; conduction block*

Multifocal motor neuropathy (MMN) is a rare disorder of the peripheral nervous system characterised by the presence of focal motor conduction blocks. Electrophysiological examination in patients with multifocal motor neuropathy discloses several features of demyelination including conduction block, increased temporal dispersion and

usually focal conduction slowing [1]. Although the pathological basis of conduction block is believed to be focal demyelination, in multifocal motor neuropathy this mechanism lacks definitive proof from morphological studies [2]. The neurophysiological assessment of conduction block is also made difficult by the elevated threshold/rheobase ratio at the site of block that makes the nerve motor fibres almost unexcitable. In recent years special neurophysiological techniques for assessing axonal excitability non-invasively in humans have expanded knowledge on the pathophysiology of peripheral nervous system diseases.

Several indirect observations, often made in only a few nerves, have been used to argue that the axonal membrane is depolarised at the site of conduction block [3] and that focal depolarisation leads to conduction block (i.e. a depolarising block). When hyperpolarisation involves the rest of the membrane above and below the conduction block [4, 5], hyperpolarisation outside the block presumably compensates for depolarisation at the site of conduction block. Even if this is a key mechanism in the pathophysiology of multifocal motor neuropathy, definitive evidence of axonal depolarisation at the site of conduction block is still lacking because the markedly increased threshold [6] and rheobasic current at the site of conduction block make local membrane properties impossible to assess. An important issue arguing against focal depolarisation arises from the observation that instead of improving conduction block – as it should do if the membrane at the site of block is depolarised – activity-dependent hyperpolarisation worsens conduction block in multifocal motor neuropathy [7]. Indeed, when we delivered polarising pulses over conduction blocks in 6 patients with multifocal motor neuropathy [8], we obtained somewhat contrasting results. By reversing membrane depolarisation at the site of a depolarising block, anodal direct currents (DCs) should in theory improve motor conduction in multifocal motor neuropathy. In the patients with multifocal motor neuropathy we studied, polarising DC pulses delivered over conduction blocks

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induced heterogeneous changes in motor conduction. In some nerves hyperpolarisation improved whereas depolarisation worsened motor conduction across the block. Our experiments using segmental nerve polarisation show that opposite types of pathophysiological abnormalities exist at the site of conduction block in multifocal motor neuropathy, possibly reflecting disease evolution. These findings support Kaji's hypothesis that depolarisation leads to a depolarising block in multifocal motor neuropathy [3], but only in some cases. Surprisingly, other MMN nerves responded to polarising currents in an opposite manner: hyperpolarisation worsened whereas depolarisation improved motor conduction across the block. Hence conduction blocks in multifocal motor neuropathy probably arise from more than one pathogenetic mechanism (hyperpolarisation or depolarisation) and these mechanisms can change during the course of the disease.

Few data are available on axonal excitability outside the block in multifocal motor neuropathy. Two patients with multifocal motor neuropathy had increased motor threshold also outside the conduction block and it was interpreted as impaired remyelination or a block of sodium channels [9]. Other investigators observed a prolonged chronaxie and normal supernormality in 3 patients with multifocal motor neuropathy [10]. In 6 patients with multifocal motor neuropathy, Kiernan et al. [4] studying the median nerve distal to the conduction block reported a significantly abnormal rheobase, threshold, stimulus-response slope and superexcitability but a normal strength-duration curve time-constant. They suggested a distal hyperpolarisation compensatory to an intraaxonal sodium flux away from the block. We also assessed the strength-duration curve and its descriptors in 22 ulnar nerves from patients with multifocal motor neuropathy and found that the strength-duration curve time-constant was abnormally short [5]. Collectively, apart from some differences, both these latter two studies agree in observing that motor axonal hyperpolarisation outside the site of conduction block probably arises from impaired Na<sup>+</sup> conductances and also involves clinically unaffected nerves. How far these slight axonal abnormalities extend is important in distinguishing whether hyperpolarisation serves to merely compensate for an eventual focal depolarisation or is a primary membrane abnormality. Even though the mechanisms underlying hyperpolarisation remain unclear, the widespread axonal involvement tends to support the frequent observation of diffuse hyporeflexia/areflexia and cramps/fasciculations outside the territory innervated by nerves with con-

duction block in patients with multifocal motor neuropathy. Furthermore, compensatory hyperpolarisation extends for more than a few centimetres outside the conduction block.

Conduction block could simply reflect an abnormal focal axonal hyperpolarisation outside the block whereas the increased rheobase and threshold at the site of the conduction block could arise from a complete inactivation of resting Na<sup>+</sup> conductances. Focal hyperpolarisation could therefore explain why further activity-dependent polarisation worsens rather than improves conduction block. A further focal increase in axonal hyperpolarisation, and possibly in the other subtle physiological abnormalities observed outside the conduction block, might help to explain the conduction block in multifocal motor neuropathy. Electrodiagnostic findings leave the possibly multiple pathophysiological mechanisms underlying conduction block and several abnormalities of axonal excitability outside the conduction block. The block is probably no more than a tip of the iceberg of axonal-myelinic abnormalities in multifocal motor neuropathy.

A final unanswered question is whether the observed changes in motor axonal excitability are specific to multifocal motor neuropathy or also common to other disorders involving motor axons. A study comparing axonal excitability in patients with multifocal motor neuropathy and lower motor neuron disease (LMND) shows that patients with LMND have distinctive axonal abnormalities [5]. In contrast, patients with chronic inflammatory demyelinating polyneuropathy (CIDP) have a typical pattern of rheobasic and strength-duration abnormalities [11], resembling those in patients with multifocal motor neuropathy. These abnormal axonal patterns in CIDP and in LMND suggest that abnormal ionic conductance in multifocal motor neuropathy results from an abnormal axonal myelinic interaction.

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