Pathophysiology of multifocal motor neuropathy[1]

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Summary

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Multifocal motor neuropathy is a unique disease that not only challenges the electromyographer to make differential diagnosis from a fatal disease but also provides an opportunity to reconsider the mechanism of conduction block in demyelinating neuropathies. Conduction block or slowing is not always a consequence of demyelination, but can be due to membrane hyperpolarisation or depolarisation, as well as sodium channel blockage. Recent pieces of evidence suggest that clinical features of multifocal motor neuropathy, such as fasciculations, muscle fatigue, cold paralysis, sensory sparing and secondary axonal degeneration, can be explained by depolarisation and hyperpolarisation block in addition to focal demyelination.

Keywords: conduction block; demyelination; multifocal motor neuropathy; chronic inflammatory demyelinating polyneuropathy; threshold tracking; excitability; axoglial interaction

Introduction

Multifocal motor neuropathy (MMN) is a disease of lower motor neurons or motor nerves that produces asymmetric muscle weakness, often in association with fasciculations and cramping. Despite being a treatable disease, this condition may be misdiagnosed as amyotrophic lateral sclerosis (ALS), because of these fasciculations and lack of sensory symptoms. Multifocal motor neuropathy, however, is distinct from amyotrophic lateral sclerosis because its weakness is characteristically caused by persistent conduction block (CB) and often associated with anti-GM1 ganglioside antibodies.

Multifocal motor neuropathy was initially recognised from two different clinical presentations. Cases of weakness caused by persistent conduction block were first recognised among patients with chronic demyelinating polyneuropathy [1]. Many later cases were identified among patients who were initially thought to have motor neuron disease [2, 3]. It soon became widely known as a muscle wasting disease that can be treated successfully with intravenous immunoglobulins (IVIg).

Lewis and colleagues [1] first described a syndrome of chronic asymmetric weakness due to persistent motor conduction block in 5 patients, who also had sensory symptoms. Roth and colleagues [2] first reported two similar cases with prominent fasciculations or myokymia, which closely mimicked amyotrophic lateral sclerosis. Parry and Clarke [3] described patients with chronic asymmetric weakness due to persistent motor conduction block who did not have objective sensory abnormalities. In the meantime, Chad and colleagues [4] reported a case with multifocal weakness which showed spontaneous remission. Freddo and colleagues [5] recognised IgM antibody with activity directed against GM1 ganglioside in a patient with lower motor neuron weakness and a monoclonal gammopathy.

Motor conduction block, the characteristic feature of this disease, is suspected when the amplitude of compound muscle action potentials (CMAPs) suddenly drops at a proximal stimulation site across a nerve segment (fig. 1). This signifies a focal demyelinating lesion, but is not necessarily

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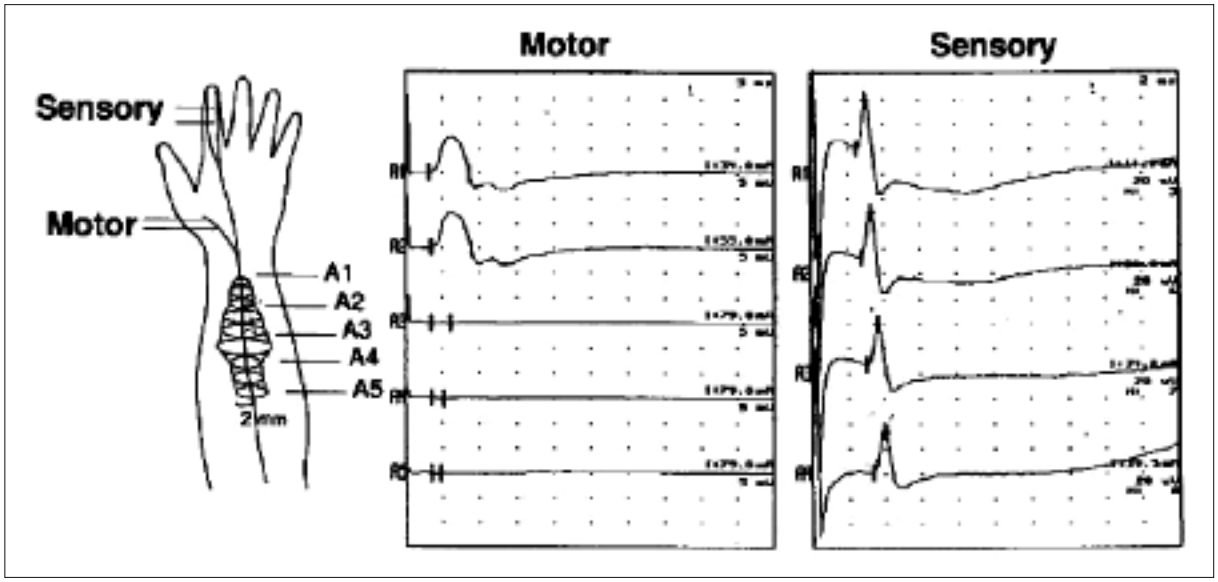
Figure 1 Left median motor and sensory (antidromic) conduction studies in a patient with multifocal motor neuropathy. Sites of stimulation (A1–A5) are shown on the left. Approximate diameters of the median nerve at each site obtained from serial MR images are shown in the inset. Motor nerves showed complete conduction block at the maximum nerve enlargement (A3), whereas sensory conduction was entirely normal. Reproduced from Kaji et al. (1993).



associated with marked slowing of conduction, which is commonly found in chronic inflammatory demyelinating polyneuropathy (CIDP). Multifocal motor neuropathy is distinguished from CIDP by the asymmetry of symptoms and involvement of a few to several named nerves or roots, frequently beginning in the upper extremity.

As for the treatment, Parry and colleagues [6] described a patient with a syndrome resembling motor neuron disease associated with monoclonal IgM protein that appeared to be responsive to immunosuppression. Pestronk and colleagues [7] reported two patients with a reversible syndrome of motor neuron disease in which both patients presented with asymmetric hand weakness due to persistent motor conduction block that was associated with high titres of IgM anti-GM1 ganglioside antibody without a monoclonal gammopathy. These two patients did not respond to treatment with prednisone and plasmapheresis, but did improve with cyclophosphamide. They coined the term "multifocal motor neuropathy" in this article describing the association between multifocal motor neuropathy and anti-GM1 ganglioside antibodies.

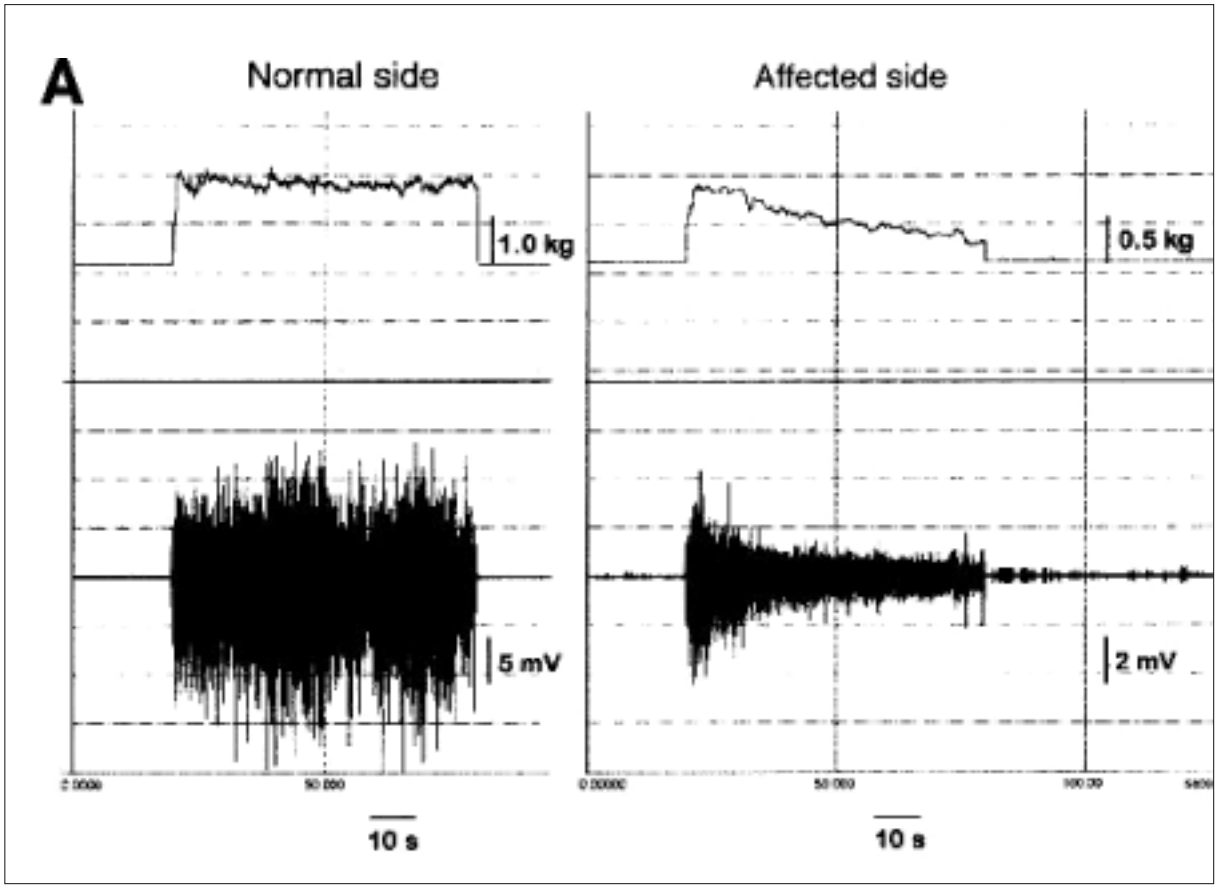
Mezaki, Kaji and colleagues [8] and Kaji and colleagues [9] were the first to demonstrate the effectiveness of intravenous immunoglobulin infusion (IVIg) in treating multifocal motor neuropathy. Similar case reports followed [10–12], and double-blind controlled studies confirmed its significant efficacy in treatment [13–16]. Although IVIg has become the treatment of choice for multifocal motor neuropathy [17], its long-term effect is variable [18, 19], and its optimum dose has been explored in only one study [20], which showed significantly better outcome in patients who received 400 mg/kg/day for 5 days than those who had 200 or 50 mg/kg/day for 5 days.

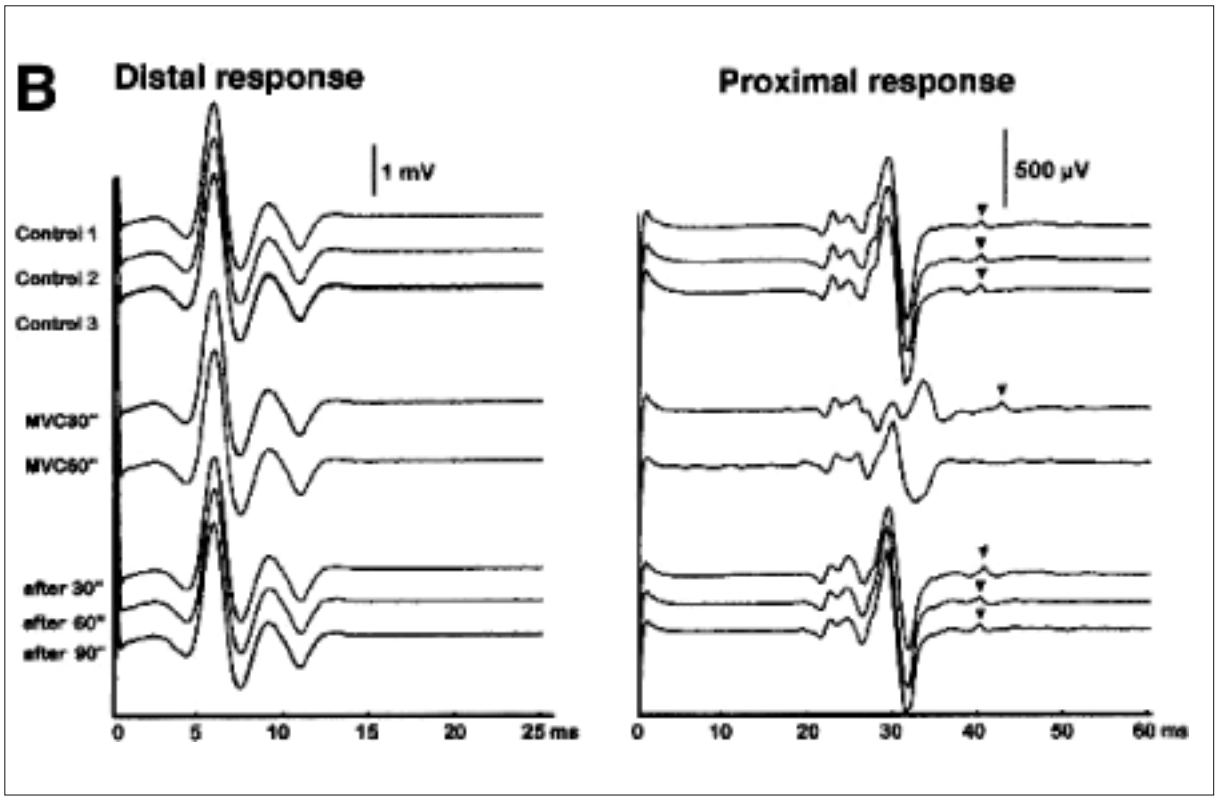
Clinical features of multifocal motor neuropathy

In a large series of patients with multifocal motor neuropathy [21] its clinical and laboratory features were analysed in detail; two-thirds of patients were men, and two-thirds were less than the age of 45. The report described that weakness usually begins in one hand and may remain restricted to that one hand for years or may gradually spread to all four limbs. The patients usually show slower progression of weakness than those with amyotrophic lateral sclerosis, but some may have a rapid course [22, 23]. A few could show spontaneous remission [4]. Tendon reflexes may be brisk, especially early in the course of the disease; however, spasticity, clonus, extensor plantar responses and pseudobulbar palsy do not occur. Cranial nerve signs are rare early in the course [9, 24]. Respiratory involvement is also rare, but if this happens, it may eventually become life threatening [2].

The patients show fasciculations and cramping in weakened muscles, and this is the reason why they are frequently misdiagnosed as having lower motor neuron forms of amyotrophic lateral scle-

Figure 2 **A:** Muscle fatigue in abductor digiti minimi muscle (ADM) from a patient with multifocal motor neuropathy. Left: force recording (above) and surface EMG recording (below) from the normal side (left). Right: Those from the affected side (right). Prominent fatigue is seen during maximal voluntary contraction of 60 seconds.
B: Serial changes in conduction block recorded from the right ulnar nerve in the same patient. Distal response was elicited after electrically stimulating the ulnar nerve at the wrist. Proximal response was obtained by stimulating the T1 root with a magnetic coil. After 3 runs of control recording, the subject made maximal voluntary contraction of ADM of 30 or 60 seconds. Three runs follow to pick up the return of the response. Note the serial changes of the late component (arrow heads) in the proximal response. Adapted from Kaji et al. (2000).





rosis (ALS). They often have frequent runs of fasciculations or myokymia. These may be distinguished from those in amyotrophic lateral sclerosis, which occur at longer intervals. The distribution of weakness typically conforms to the territory of a few peripheral nerves or roots, and this finding often gives the first clue to the diagnosis. As discussed later, patients with multifocal motor neuropathy often show fatigue of affected muscles, which develops after sustained voluntary contractions of 30 to 60 seconds [25]. Fasciculations or myokymia tend to be more frequent after voluntary muscle activation. The weakness is usually increased by exposure to cold (cold paralysis).

Electrophysiological testing showed conduction blocks at multiple nerve segments in motor fibres. The clinical course is monophasic, in contrast with that of CIDP, which characteristically is relapsing. Serum testings by thin-layer chromatography and enzyme-linked immunosorbent assay reveal high titres of antibody directed against GM1 and other gangliosides. Therapeutic trials of steroids are unsuccessful or even aggravate the symptoms [9, 26].

Sensory function is usually normal at clinical and electrodiagnostic examination, but there are cases with mild sensory loss that becomes evident after detailed examination [27]. Although weakness in multifocal motor neuropathy is mainly caused by partial conduction block of motor fibres, degeneration of motor axons may contribute to the weakness later in the course. This secondary axonal degeneration is explained by membrane depolarisation at the lesion site as discussed later. This results in axonal multifocal motor neuropathy without overt conduction block or chronic motor axonal neuropathy (CMAN), showing even closer resemblance to motor neuron disease [28–31]. These patients respond to IVIg less optimally than those with conduction block, but some showed modest improvement after repeated infusions.

For diagnosing axonal multifocal motor neuropathy, clinical signs, such as the distribution of the weakness corresponding to named peripheral nerves, or the lack of upper motor neuron signs are important. Laboratory findings such as T_2-high signal abnormalities of the corticospinal tract in magnetic resonance imaging (MRI) or prolonged central motor conduction time as revealed by transcranial magnetic stimulation favour the diagnosis of amyotrophic lateral sclerosis. High titres of anti-GM1 IgM antibodies point to multifocal motor neuropathy, but axonal multifocal motor neuropathy is frequently associated with elevation of IgG class.

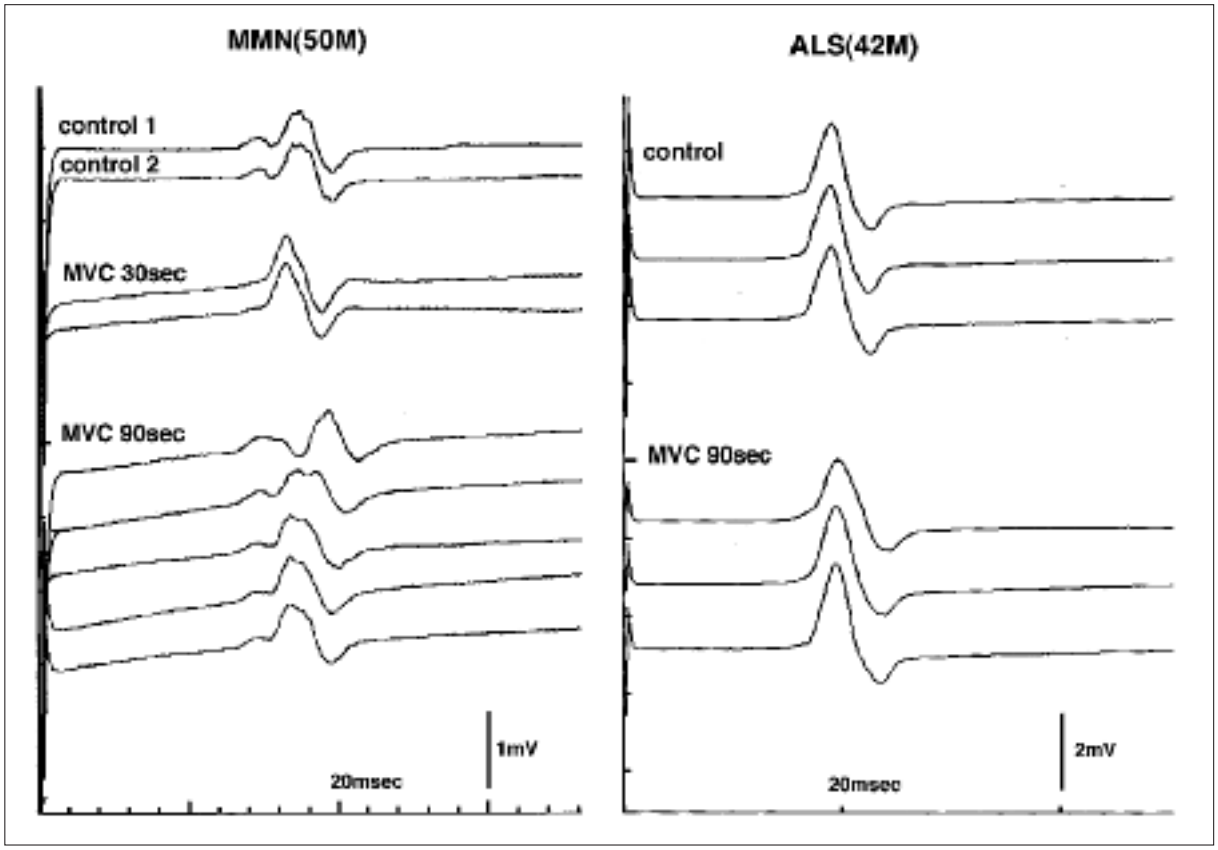
Because the minor sensory symptoms may be detected by careful examination in patients with multifocal motor neuropathy, distinction between this neuropathy and those originally reported by Lewis, Sumner and others (multifocal motor-sensory neuropathy with persistent conduction block or Lewis-Sumner syndrome) seems arbitrary. In general, multifocal motor neuropathy is a more appropriate term than Lewis-Sumner syndrome when the patient has no subjective sensory symptoms.

Pathophysiology

Demonstration of conduction block is essential for diagnosing multifocal motor neuropathy. Sensory conduction studies, however, usually show normal findings through the segment with motor conduction block (fig. 1). The sparing of sensory fibres and fasciculations frequently seen in this neuropathy not only make differential diagnosis difficult, but raise a number of questions on their pathophysiological basis. Why are sensory fibres spared despite the focal lesion at mixed nerves? Some patients show increase in muscle power immediately after the IVIg infusion, and it is unknown why they respond so quickly. Magnetic resonance images demonstrated a focal nerve enlargement with disruption of blood-nerve barrier at the site of conduction block. Pathological findings have comprised scattered demyelination, but not the prominent remyelination or Schwann cell proliferation usually seen in chronic inflammatory demyelinating polyneuropathy (CIDP) [32]. Nor was there clear morphological evidence that sensory fibres were spared. Approximately half of multifocal motor neuropathy patients show elevated titres of anti-GM1 IgM antibodies, but the role of these antibodies in pathogenesis remains elusive.

Muscle fatigue has been documented in diseases of neuromuscular junction or anterior horn cell as well as in CNS diseases. We first demonstrated muscle fatigue caused by peripheral demyelination [25]: we found a patient with multifocal motor neuropathy who complained of prominent muscle fatigue, which was evident only after a sustained voluntary contraction of 30–60 seconds (fig. 2). The degree of conduction block was assessed before, during and after the maximal voluntary contraction. The amplitude of the CMAP evoked proximal to the lesion decreased significantly in parallel with muscle fatigue and gradually recovered to the baseline after the contraction, whereas the distal response remained the same. It was concluded that conduction block transiently developed after

Figure 3 Motor-evoked potentials after magnetic stimulation of T1 root before (control), after 30 sec of maximal voluntary contraction (MVC 30 sec) or 90 sec (MVC 90 sec). *Left:* Recording from a patient with multifocal motor neuropathy without over conduction block, who responded to IVIg infusion. Note change in the waveform associated with latency changes which gradually returned to the baseline after MVC. *Right:* Similar recording from a patient with ALS. Note no significant changes by MVC.



voluntary contraction. The axonal membrane potential was monitored by the double-stimulation technique using the threshold tracking technique. The development of conduction block was concurrent with membrane hyperpolarisation as evidenced by increased supernormality. This was most consistent with the activity-dependent or hyperpolarisation conduction block due to electrogenic sodium-potassium pump activation. This phenomenon is useful for differential diagnosis of multifocal motor neuropathy from amyotrophic lateral sclerosis, which showed no exercise-induced fatigue (fig. 3) [33].

Figure 4 shows threshold electrotonus recordings, which reflect membrane potential, from the left median nerve in the same multifocal motor neuropathy patient as depicted in figure 2 [34]. If the tracking curves' extending upward and downward is greater than in the normal nerve segment (fanning-out), it signifies membrane hyperpolarisation. In case of smaller deflections (fanning-in), the membrane is depolarised [35]. Left traces are from the site distal to the lesion (A1 in fig. 2; normal segment). A focal lesion was found near the recording site of the middle traces (A2 in fig. 2). Clear 'fanning-out' was found near the lesion site (A2), suggesting membrane hyperpolarisation. Concurrent with clinical improvement, the degree of fanning recorded from the same site was decreased after intravenous immunoglobulin therapy, as shown on the right of figure 5. A recent study in multifocal motor neuropathy confirmed 'fanning-out' in threshold electrotonus [36] and demonstrated increased supernormality near the lesion site, both representing membrane hyperpolarisation caused by pump activation. Surprisingly, the hyperpolarisation was stable near the lesion site, and there must be a constant supply of sodium ions inside the axon to activate the electrogenic pump. The longitudinal diffusion of sodium ions is the most likely source for the supply, and a constant inflow of sodium ions and the reduced activity of the sodium-potassium pump must be present nearby (fig. 6).

To investigate whether the membrane hyperpolarisation is compensating focal depolarisation, we dosed this subject with intravenous digoxin infusion [34]. Digitalis is a specific inhibitor of the pump and causes membrane depolarisation in normal nerves, although it does not penetrate the blood-nerve barrier efficiently. If it acts directly on the segment with hyperpolarisation, threshold

electrotonus would show fanning-in. After digitalis, however, we observed fanning-out rather than fanning-in (fig. 5). The only possible explanation was that digitalis gained access to the lesion site through the disrupted blood-nerve barrier and inhibited the pump, thus increasing the depolarisation. Pumps at perilesional nerve segments with intact blood-nerve barrier were further activated to manage the increased sodium load from the lesion site, producing greater hyperpolarisation than before. Constant sodium inflow must therefore be through spontaneous firing of motor

Figure 4 Threshold electrotonus recording in the same patient as in figure 2. Applied conditioning current is shown below, and induced changes in threshold, representing the membrane potential, are shown above. *Left:* Recording from a normal segment (A1 in fig. 2) of the median nerve. Depolarising or hyperpolarising currents of 40 or 20% of the threshold intensity (d40, d20, h20, h40) and 100 msec duration were used. Thick traces represent the mean of those from normal subjects. Thin traces represent those from the patient. *Middle:* Recording from a site adjacent to the lesion (A2 in fig. 5). Prominent fanning-out was seen (large arrows). *Right:* Recording from the same site (A2) after IVIg. The degree of fanning-out became smaller than before (small arrows). Modified from Kaji and Kojima (1997).

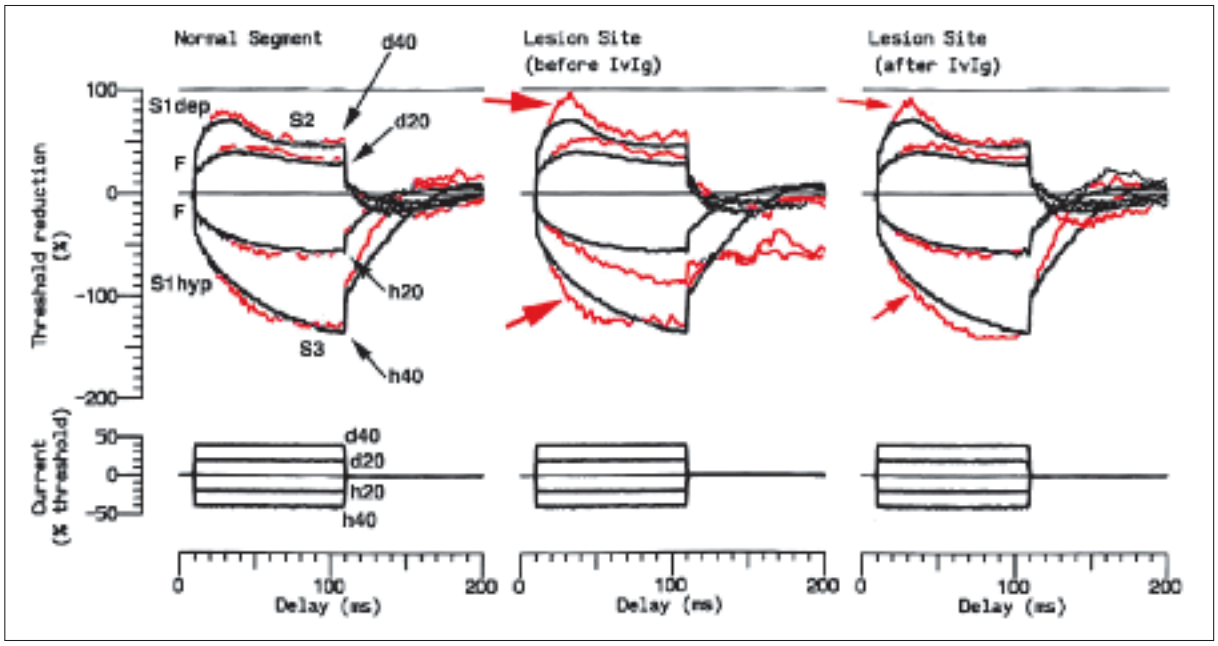


Figure 5 Paradoxical fanning-out after digitalis. Threshold electrotonus from the same subject as in figure 2. Recordings were made from A2. A long conditioning pulse duration of 300 msec was used. Adapted from Kaji and Kojima (1997). *Left:* Before digitalis infusion, the patient's recording (thick traces) showed less fanning than the control trace before IVIg (thin trace indicated as "Before Tx"). *Middle:* After digitalis, the traces showed fanning-out (arrows), suggesting membrane hyperpolarisation, despite the depolarising action of digitalis. *Right:* One day after the digitalis infusion when its action had disappeared, fanning-out returned back to pre-infusion (arrows).

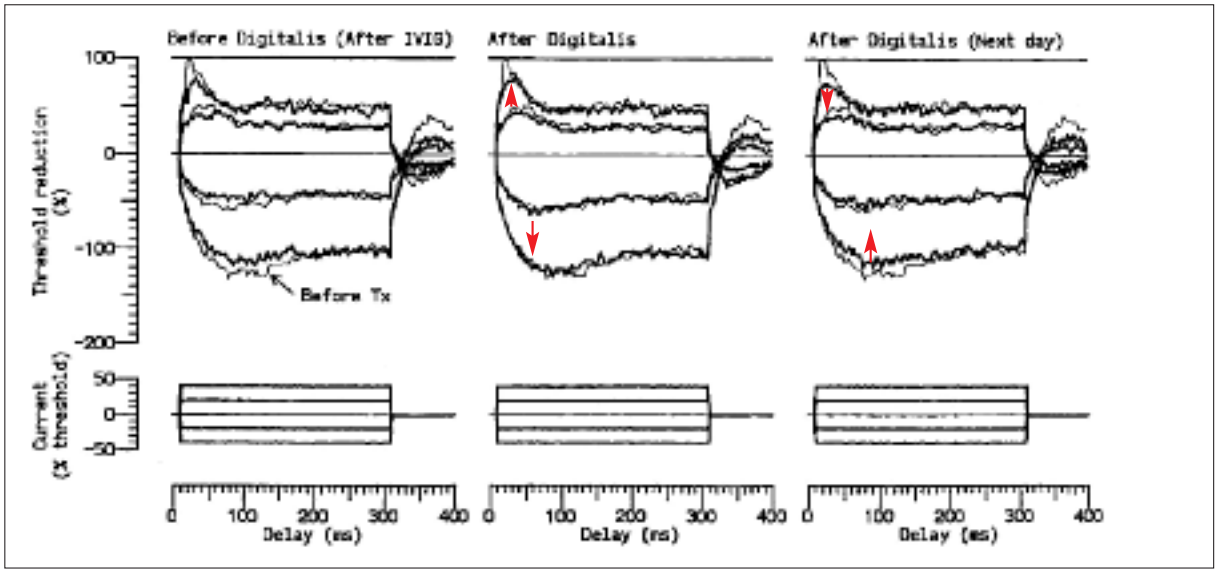
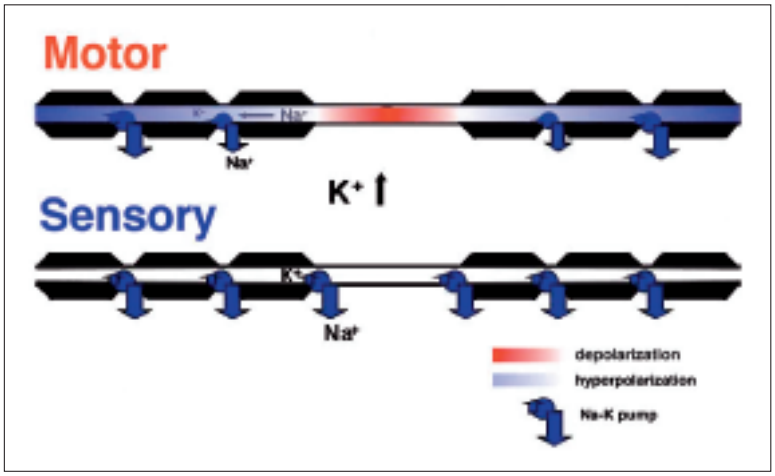


Figure 6 Hypothesis on the mechanism of fasciculations and selective motor conduction block in multifocal motor neuropathy. Because the blood-nerve barrier is impaired at the lesion site, the endoneurial potassium level is increased to the serum level. If sensory fibres had larger functional reserve of the pump than motor fibres, they could cope with high potassium concentration. Motor fibres would not be able to catch up with the potassium load outside and the sodium load inside because of the less efficient pump action, resulting in depolarisation block. Increased sodium must be excluded from the axon in the adjacent segments through longitudinal diffusion within the axon. Membrane hyperpolarisation would be present nearby.



axons or fasciculations generated by the depolarisation-hyperpolarisation, as discussed later [37]. The search for direct evidence for focal depolarisation has been unsuccessful because of the threshold increase [36]. In summary, a focal depolarised segment of the nerve is juxtaposed by segments of perifocal hyperpolarisation representing the compensatory pump action (fig. 6).

Another interesting clinical feature in multifocal motor neuropathy is cold paralysis [34]; patients often complain that weakness worsens in cold weather or at exposure to a cold environment. It is well known that symptoms of multiple sclerosis are aggravated in hot conditions (Uhthoff's phenomenon); demyelinative conduction block increases because the duration of sodium channel opening shortens at high temperature, thus reducing the driving current. In cold weather, by contrast, the reversal of conduction block is expected. The cold sensitivity of multifocal motor neuropathy patients therefore cannot be explained by demyelination.

If the hyperpolarising activity of the pump compensates for the membrane depolarisation, decreased temperature would inhibit the pump action and intensify the depolarisation, resulting in further weakness. These circumstantial pieces of evidence point to depolarisation block as the main cause of static or resting conduction failure in multifocal motor neuropathy [36]. However, activity-dependent conduction failure is caused by membrane hyperpolarisation as discussed before. Therefore, depolarised and hyperpolarised segments may co-exist in a single nerve, resulting in different types of conduction block.

Fasciculation is a characteristic finding in multifocal motor neuropathy, and the model from above helps understand its origin. Bostock and colleagues [37] investigated the mechanism of post-ischaemic fasciculation in human nerve and found a bimodal distribution of thresholds among motor fibres after ischaemia; transition between two threshold states coincided with fasciculation. Based on these findings, they concluded that under extracellular high potassium concentration and increased electrogenic pump activity the membrane potential takes two stable values and this instability causes abrupt depolarisation leading to an extra-discharge.

In the above-presented model of multifocal motor neuropathy (fig. 6), the focal depolarised lesion site is surrounded by hyperpolarised segments of increased pump activity. Because of the disruption of the blood-nerve barrier, which raises the endoneurial potassium concentration to the high serum level [38] and because of the deficiency of Schwann cells scavenging the extracellular potassium [32], the potassium concentration at the lesion site is most likely increased. This would be even more pronounced if the pump is inhibited at the lesion site. Therefore, two conditions leading to the generation of extra-discharges are met near the lesion site in multifocal motor neuropathy.

The present hypothesis might also explain the immediate action of IVIg seen in some patients. IVIg was found to have restored the disrupted blood-nerve barrier and may decrease the potassium concentration at the lesion and reverse the depolarisation block, resulting in the increased muscle power and decreased fasciculations observed in this patient after therapy.

The physiological background of sensory sparing in multifocal motor neuropathy is less clear. Although it is possible that motor fibres are vulnerable because of an immunological difference from sensory fibres, rare pathological studies at the lesion lent no morphological support to the selective motor involvement [32]. Physiological differences between them have been suggested. Sensory fibres are protected against excessive membrane hyperpolarisation by greater inward rectification and persistent sodium conductance than motor fibres. A recent study [39] demonstrated that sodium-potassium pumps contribute more to the resting membrane potentials in sensory than motor axons. This efficient pump action in sensory

fibres may complete sodium excretion so quickly that hyperpolarisation becomes smaller than in motor fibres. As a result, sensory fibres are less likely to develop activity-dependent conduction block than motor fibres [40]. If the premise on the pump activity difference is correct, sensory fibres are resistant to depolarisation because the pump promptly restores the resting membrane potential from a depolarised state by its hyperpolarising activity. This would therefore explain why sensory fibres are unlikely to develop depolarisation block.

Cases of multifocal motor neuropathy without demonstrable conduction block have been reported as a lower motor neuron syndrome or chronic motor axonal neuropathy [21]. These are characterised by axonal degeneration in electrophysiological studies and by the presence of anti-ganglioside antibodies. Some include cases similar to juvenile monomelic amyotrophy of the upper extremity or Hirayama disease [41], and they share common clinical features such as cold paralysis and a peripheral nerve distribution of weakness. However, even typical cases of multifocal motor neuropathy show significant findings of axonal degeneration as well as conduction block. If the depolarisation block and sodium accumulation take place at the lesion site, axonal degeneration may follow, because the reverse operation of sodium-calcium exchanger allows calcium entry into the axon, leading to its degeneration [42]. Other cases of muscular atrophies with a similar pathophysiological basis, especially those with asymmetry and slow progression, may escape from recognition because of the lack of antibodies. Anti-GM1 antibodies have been advocated as a diagnostic marker of multifocal motor neuropathy [7], but so many cases lack their elevation that they are no longer regarded as a hallmark. It has yet to be determined whether antibodies are pathogenic on their own [43]. Immunological mechanisms are nonetheless important in multifocal motor neuropathy, because some patients respond to immunosuppressive agents as well as IVIg.

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