Multifocal motor neuropathy

In 1982 Lewis et al reported five patients with a chronic, asymmetric, motor and sensory neuropathy more pronounced in the upper than the lower limbs. This was electrodiagnostically characterised by the presence of persistent multifocal partial conduction blocks in motor but not sensory nerves. The neuropathy improved in two patients after treatment with steroids and was considered by the authors to be a “multifocal” variant of chronic inflammatory demyelinating polyneuropathy (CIDP). Between 1985 and 1986 Parry and Clark, Roth et al, and Chad et al almost simultaneously first reported four patients in whom the presence of persistent multifocal partial motor conduction blocks was associated with a chronic, asymmetric, pure motor neuropathy without (or with minimal) sensory impairment. Since then at least 120 patients have been reported with this form of motor neuropathy, which has been variably related to CIDP or motor neuron disease and is presently known as multifocal motor neuropathy.

Clinical features
Multifocal motor neuropathy is clinically characterised by a progressive, asymmetric limb weakness without or with minimal sensory impairment. Weakness is generally proximal and the arms are usually affected earlier and more severely than the legs. In less than 10% of patients, weakness is predominantly proximal or affects the legs more than the arms. Weakness can often be related to the distribution of individual nerves, particularly the radial (wrist drop), ulnar, and median nerves. Although muscle atrophy is often present in affected territories, it may not be evident in the early stage of the disease, or even later in its course, probably because muscles are not completely denervated. Fasciculations and cramps are present in about two thirds of the patients and myokymia has been reported occasionally. In about 50% of reported patients, reflexes were reduced in a patchy way, often, but not invariably, corresponding to weak and wasted muscles. In 25% a diffuse hyporeflexia was found, whereas the others had normal or even, although rarely, brisk reflexes. The latter finding, in association with the presence of weak, wasted, and fasciculating muscles, explains why it can be sometimes difficult to distinguish multifocal motor neuropathy from motor neuron disease on clinical grounds only. Cranial nerve involvement and respiratory failure have been reported occasionally. Although sensory symptoms, including numbness and paresthesiae, are sometimes reported, sensory loss is often not substantiated on clinical examination, except for a minor sensory loss in less than 20% of the patients.

The prevalence of multifocal motor neuropathy is not known but, even though a considerable number of papers have been recently devoted to this disease, it seems to be an extremely rare condition in clinical practice, much less frequent than motor neuron disease or CIDP. Almost 80% of the reported patients with multifocal motor neuropathy were men and the age of onset of symptoms in 80% of the patients was between 20 and 50 (mean 41-4, range 15-70) years with a duration, at the time of the reports, of three months to 30 (mean 7-5) years. Weakness is often steadily progressive although it may have a stepwise course. If stepwise, the interval between the onset of one symptom and the other may be years. Occasionally the disease may have a spontaneous remission. Only two patients have so far been reported to have died, both after more than 20 years of progressive weakness.

Electrophysiological features
The electrophysiological hallmark of multifocal motor neuropathy is the presence of persistent, multifocal, partial motor conduction blocks (PMCBs) outside the usual sites of nerve compression. Partial motor conduction block has been defined as a disproportionate reduction in the amplitude of the compound muscle action potential (CMAP) obtained by proximal versus distal stimulation of motor nerves. There is, however, some disagreement on the percentage that this reduction has to achieve to suggest a possible PMCB. In some reports PMCB has been defined as a reduction in the ratio of proximal to distal CMAP amplitude, or area, or both to less than 0.80 (a > 20% reduction), in the absence of abnormal temporal dispersion. The absence of abnormal temporal dispersion—defined as an increase in the ratio of proximal to distal negative peak duration above 1.15—is important in order to differentiate reduction of CMAP amplitude due to focal PMCB from that caused by diffuse demyelination. In the second condition, the increased range of conduction velocities may lead to an increased duration of the proximally stimulated CMAP (abnormal temporal dispersion) that may result itself in a reduced CMAP amplitude. Other authors use more stringent criteria to better distinguish true PMCB from the reduction of CMAP amplitude sometimes seen in chronic demyelination and
in chronic axonal loss, and consider a reduction of the proximal to distal CMAP amplitude or area of more than 40% or 50% to be significant. This is because when there is a large increase in range of conduction velocities (as in chronic demyelination), or an increased polyphasia and reduced number of motor unit potentials as in chronic axonal loss (for example, in motor neuron disease), there is an increased likelihood of overlap and cancellation of the positive and negative components of different motor unit action potentials (a phenomenon called "interphase cancellation"). This may lead to a reduction of CMAP amplitude out of proportion to the increased negative peak duration, mimicking a true PMCB. By means of a computer simulation of PMCB in rats it was shown, for instance, that the reduction in CMAP area due to "interphase cancellation" may reach 50%. Although the use of stringent diagnostic criteria may lead to underestimation of the presence of PMCB and possibly delay the diagnosis of a potentially treatable disease (see later), it is also true that PMCB is often misdiagnosed in clinical practice because of the conditions mentioned above that may mimic PMCB, and the difficulties sometimes encountered in achieving supramaximal nerve stimulation at proximal sites. These problems may be partly overcome, at least in some segments, by the use of "short segment stimulation" or the "waxing technique" — the repeated stimulation of nerve at several sites as close as 2-0 to 2-5 cm apart. This shows whether CMAP amplitude decreases abruptly at a single level, as in the case of PMCB, or progressively along the nerve as in the case of chronic demyelination or chronic axonal loss, therefore avoiding some of the difficulties in the diagnosis of PMCB.

Partial motor conduction block may occur at any level of motor nerves. It has been most often reported in the ulnar and median nerves, usually in the forearm but also in the arm and axilla; less often it is reported in the peripheral and posterior tibial nerves in the leg. As already mentioned, the finding of PMCB across the common sites of entrapment is not considered helpful in establishing a diagnosis of multifocal motor neuropathy. Motor conduction velocities in multifocal motor neuropathy are usually normal or slightly reduced outside and, sometimes, even at the level of, segments with PMCB. In our series of patients, greatly reduced conduction velocities were found in five of the 34 nerves tested (in which 16 PMCBs were detected) and usually, although not invariably, corresponded to segments with pronounced PMCB, confirming the prominently focal nature of the demyelinating process. In these patients, however, other, usually mild, features of demyelination are often present in motor nerves, including mildly prolonged distal and F wave latencies, slightly reduced conduction velocities, and abnormal temporal dispersion, indicating a concomitant, although less intense, diffuse involvement of motor fibres.

Another typical feature of multifocal motor neuropathy is the presence of normal sensory conduction studies, even in nerves affected by motor PMCB. The reasons for the selective impairment of motor nerves are not known although it may reflect a different antigenic composition or expression in motor compared with sensory nerves or a different susceptibility to nerve injury or repair capability between motor and sensory fibres. Whatever the pathogenetic mechanism of this discrepancy, the clinically and electrophysiologically selective motor impairment may explain why the initial diagnosis in some originally reported patients with multifocal motor neuropathy was motor neuron disease.

Needle EMG in multifocal motor neuropathy often shows fibrillations and fasciculations and motor unit action potentials of increased amplitude and duration, usually confined to muscle innervated by nerve with PMCB, a feature distinguishing this disease from motor neuron disease, in which these abnormalities are usually widespread and can be found in clinically normal muscles.

**Laboratory findings**

Routine haematological and biochemical findings are usually normal in multifocal motor neuropathy, apart from serum creatine kinase activity, which is often increased. Occasional patients have a detectable IgM M-protein on serum protein electrophoresis.

Examination of CSF produced normal results in almost 90% of patients, whereas the others had slightly increased CSF protein concentrations (up to 84 mg/dl) and a finding that may help to distinguish multifocal motor neuropathy from CIDP, a disease in which CSF proteins are often greatly increased. After the original report of Pestronk et al in 1988, serum antibodies—mostly IgM, to the ganglioside GM1 or, less often, to asialo-GM1, or both—have often been associated with multifocal motor neuropathy and CIDP, as well as in a consistent proportion of patients with Guillain-Barré syndrome, when they are often of the IgG isotype, but not in patients with other neurological or immunological disease. These findings suggest that these antibodies may be a useful marker of an immune response involving the nerve, but cannot be used as a specific test for any of the disorders mentioned above.

**Morphological findings**

Although the pathological basis of focal PMCB is deemed to be focal demyelination, this has rarely been confirmed in patients with multifocal motor neuropathy by morphological studies on nerve biopsies. In most of these patients pathological studies have been performed on sensory nerves (mostly the sural nerve) and were either normal or inconsistent, showing mild axonal degeneration or demyelination, or both. A recent pathological study on sural nerves from eight patients with multifocal motor neuropathy showed, however, that, even if the total fibre density was preserved, there were mild pathological abnormalities consistent with a demyelinating process. Thinly myelinated axons, often surrounded by minor onion bulbs composed of redundant supernumerary Schwann cells, were nearly always present and were sometimes associated with occasional signs of Wallerian-like degeneration and axonal regeneration. In the only two patients on whom a motor nerve biopsy was performed adjacent to the site of PMCB, pathological studies showed demyelination with onion bulbs without inflammatory infiltrates. A recent necropsy study of a patient diagnosed as multifocal motor neuropathy showed the pathological features of inflammatory demyelinating polyradiculoneuropathy with widespread segmental demyelination and scattered inflammatory cells in the motor cranial nerves and motor roots. Several clinical and electrodiagnostic features in this patient, however, including a remarkable vibratory impairment, prominent sensory conduction abnormalities, and greatly reduced motor conduction velocities, were more consistent with a diagnosis of CIDP than of multifocal motor neuropathy.
Pathogenesis of multifocal motor neuropathy

The pathogenesis of multifocal motor neuropathy is not known, but the disease may have an immunological basis, because of clinical improvement after immunological treatments (see below). The precise mechanism and the potential target antigens of this immune response are still unknown. As already mentioned, high concentrations of serum anti-GM1 or anti-iasialo-GM1 antibodies, mostly IgM, have often been found in patients with multifocal motor neuropathy. Some of these patients improved after therapeutic reduction of antibody titres, supporting a pathogenetic role for these antibodies. There is, however, a consistent proportion of patients with multifocal motor neuropathy, some of whom respond to immunological treatments, who do not have high antiganglioside antibodies. On the other hand, increased anti-GM1 has been also found in some patients with motor neuron disease, or Guillain-Barré syndrome. No definite correlation between the different clinical syndromes and the fine specificity of these antibodies has been so far convincingly demonstrated leaving it unclear how similar antibodies may cause different diseases. Deposits of IgM have been detected at the level of the nodes of Ranvier in the sural nerve of a patient with motor neuron disease who had multifocal PMCB and high anti-GM1 titres and focal PMCB has been experimentally induced in vivo and in vitro by intraneuronal injection or exposure to serum from patients with high anti-GM1 antibodies and multifocal PMCB but not with lower motor neuron disease. The latter results were not confirmed when purified anti-GM1 antibodies were used. More recently a similar blocking effect on mouse distal motor nerve conduction has been induced in vitro with serum from patients with multifocal motor neuropathy with and without high anti-GM1 antibodies, suggesting that either current tests for anti-GM1 antibodies are not sensitive enough or that serum components other than anti-GM1 antibodies might be responsible for PMCB in multifocal motor neuropathy. It is my opinion that these antibodies represent a reliable, although non-specific, marker of an ongoing immunological process. The pathogenetic target of which is not known but probably differs in the different diseases; although probably not primarily pathogenetic, they may help to identify patients for whom immunological treatment may be useful.

Treatment of multifocal motor neuropathy

The hypothesis that multifocal motor neuropathy is an immune mediated neuropathy has led to the trial of several immunological treatments in these patients. More than 40 patients with multifocal motor neuropathy have been treated with steroids alone or in combination with plasma exchange, immunosuppressants, or both, but only a few of them improved and some worsened, even dramatically. Plasma exchange alone was ineffective in the patients with multifocal motor neuropathy so far reported. Among the immunosuppressants, only cyclophosphamide given at high doses intravenously followed by maintenance oral cyclophosphamide treatment was reported to be consistently effective, whereas oral cyclophosphamide alone was rarely effective. This treatment may have side effects, especially when given at high doses, and may therefore be unsuitable for the less severely affected patients, especially if young. Furthermore, improvement with cyclophosphamide is not immediate and often requires two to five months of treatment.

More recently, high dose intravenous immunoglobulin (IVlg) treatment was found effective in up to 90% of patients with multifocal motor neuropathy. Improvement often occurred within a week of treatment although it usually lasted only a few weeks and had to be maintained with periodic IVlg infusions with an almost invariable stereotypical effect in each patient. Improvement was usually more evident in the recently affected limb territories with only minor or no effect on stabilised deficits, and was often, though not invariably, associated with reduction or resolution of motor nerve conduction block in some but not all nerves. The efficacy of IVlg treatment in multifocal motor neuropathy is, however, limited by its cost and by the recent finding that it might not ultimately affect the progression of the disease. Addition of low dose oral cyclophosphamide in our experience permitted progressive delay in the frequency of IVlg infusions and, in some cases, their cessation. We now use IVlg treatment to induce a rapid response before low, and in our experience well tolerated, doses of oral cyclophosphamide become effective.

Differentiating multiple motor neuropathy from CIDP and lower motor neuron disease

Even though multifocal motor neuropathy has often been related to CIDP, there are some features that may help to distinguish between the two (for a review on CIDP see Dyck et al). Clinically, weakness is usually symmetric in CIDP with an almost invariable proximal involvement whereas it is typically distal and asymmetric in multifocal motor neuropathy. Sensory impairment is also frequent in CIDP and absent or minimal in multifocal motor neuropathy. It is not infrequent, however, for CIDP to be purely motor and asymmetric. Electrophysiologically, CIDP is often characterised by a widespread reduction of motor and sensory conduction velocities with increased distal latencies, reflecting a diffuse rather than focal demyelinating process. Similarly, demyelination with only some inflammatory infiltrates are often found in sural nerve biopsies in patients with CIDP but not in patients with multifocal motor neuropathy. Protein is often increased in CSF in CIDP but not in multifocal motor neuropathy, whereas serum antganglioside antibodies, although originally associated with multifocal motor neuropathy, may occasionally be found also in CIDP (see above). Whether CIDP and multifocal motor neuropathy represent the two ends of a range of chronic demyelinating neuropathies, as possibly suggested by the presence of intermediate forms such as the multifocal sensorimotor neuropathy reported by Lewis et al and the purely motor form of CIDP, or are totally unrelated diseases is still debated. The distinction between CIDP and multifocal motor neuropathy is not purely of theoretical interest as steroids and plasma


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