

Multifocal motor neuropathy

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INTRODUCTION

During the 1980s, patients were reported with a slowly evolving asymmetrical motor syndrome, often initially affecting the distal upper limbs. These patients were viewed as distinct from either spinal muscular atrophy or more typical chronic inflammatory neuropathies by the presence on clinical electrophysiological testing of very focal areas of conduction block in the motor fibres of peripheral nerves, with sparing of sensory fibres in the same nerve segments. It was subsequently demonstrated, first of all in case reports and then in larger series of patients, that a proportion of these cases had serum IgM antibodies to GM1 ganglioside. Thus the syndrome of multifocal motor neuropathy with conduction block (MMN) was born. Since then, the literature on this uncommon disease has grown considerably, particular highlights being its frequent and dramatic response to infusions with intravenous immunoglobulin (IVIg), its pathophysiological basis, and its nosological relationship with similar clinical syndromes (Nobile-Orazio 2001).

CLINICAL FEATURES

There are no accurate data on the prevalence of MMN, roughly estimated from large clinical practices at 1 : 100 000. In view of the very chronic course, possibly extending over 30 years or more, the incidence is much lower than this and new cases rarely appear. Analysis of the clinical data from published cases (approximately 300) has established that men are more

frequently affected than women in a ratio of 3 : 1, and the age of onset ranges from the second to the fifth decade in most patients although later onset is seen in around 20% of cases. The clinical course is most typically a slowly progressive pattern, although it may be step-wise progressive, arrested, or rarely spontaneously remitting.

The stage in the course of the illness at which a patient is seen will influence the clinical features that you see. The typical early clinical presentation is of gradually evolving weakness affecting a single peripheral nerve territory in an upper limb, often a radial nerve wrist drop or weakness of the median or ulnar intrinsic hand muscles. As the illness progresses other sites are involved, both in upper limbs (e.g. musculocutaneous nerve producing weakness in biceps) and lower limbs (e.g. common peroneal nerve producing foot drop). When patients are seen late in the course of the disease the pattern of clinical involvement may have evolved to appear confluent in all four limbs, despite asymmetry at onset.

At first, there is usually little or no muscle atrophy, even in profoundly weak muscles. However, denervation atrophy is a very frequent late feature in advanced disease (Fig. 1). Sensory nerves are classically spared although in practice one occasionally finds mild sensory symptoms or signs in nerves in which motor fibres are also affected. Loss of tendon reflexes is a very variable finding and indeed they may be normal, or on rare occasions, brisk. Other clinical features of note are the frequent occurrence of muscle cramp, fatigue, and twitching. These features

may occur spontaneously but more commonly follow prolonged or vigorous use of the limb. Clinical features outside the limbs are unusual but both lower cranial involvement and respiratory symptoms, due to phrenic nerve palsy have been described.

ELECTROPHYSIOLOGICAL FEATURES

The electrophysiological hallmark of MMN is conduction block in motor nerves. The block does not occur at the usual entrapment sites but commonly in the mid-forearm or motor roots. To make a confident diagnosis, conduction blocks in two or more nerves, or at two sites in the same nerve, in the presence of normal sensory conduction in the segments showing block is required. There are sometimes clues to the possibility of MMN. The electrophysiological correlate of weakness without wasting seen in early cases is a normal amplitude compound

motor action potential (CMAP) in a clinically-weak muscle. Proximal block should be suspected if F-waves are absent in an otherwise normal nerve conduction study.

The definition of conduction block is still controversial. Most workers agree that, when comparing CMAPs from adjacent stimulation sites (wrist, elbow, axilla and Erb's point), a reduction in amplitude of 50% or more with an increase in duration of the CMAP of less than 20% is indicative of definite block. This definition is probably too rigorous and whilst few cases of MMN would be misdiagnosed, some would fail to meet the criteria. More convincing can be the demonstration of a 10% reduction in CMAP amplitude when stimuli are applied at short, say 2 cm, intervals along the nerve. Electrical stimulation of motor roots may be required to demonstrate block in some patients (Fig. 2). Conduction velocity in motor nerves is usually normal.

Early in MMN, EMG during voluntary activity of clinically affected muscles shows only the signs associated with block, i.e. normal motor unit potentials in a reduced recruitment pattern. Later, secondary axonal loss leads to the acute and chronic neurogenic changes of fibrillation and large, long duration motor unit potentials. Spontaneous activity in muscle innervated by nerves showing block is frequently encountered. Most often this is fasciculation (and hence the importance of motor neurone disease in the differential diagnosis), but doublet discharges or even frank neuromyotonia with bursts of high frequency motor unit discharge are also seen. On clinical examination, fasciculation is common and occasional patients report true muscle hypertrophy, even in weak muscles, which has been attributed to continuous motor unit activity arising in relation to axonal hyperexcitability in demyelinated nerve segments.

LABORATORY INVESTIGATIONS

Routine biochemical and haematological indices are normal. Cerebrospinal fluid (CSF) examination may show a mildly elevated protein in one third of cases but the cell count is normal. Total serum IgM levels may be mildly elevated and occasional patients have a detectable IgM paraprotein, classified as a monoclonal gammopathy of undetermined significance (MGUS). Creatine kinase may be mildly elevated, consistent with neurogenic muscle weakness. Anti-GM1 ganglioside IgM antibodies, which can be measured in specialised neuroimmunological



Figure 1 Left upper limb of a man with multifocal motor neuropathy, which shows widespread denervation atrophy in the forearm and hand. His symptoms started at the age of 29 and evolved over 15 years, when this picture was taken.

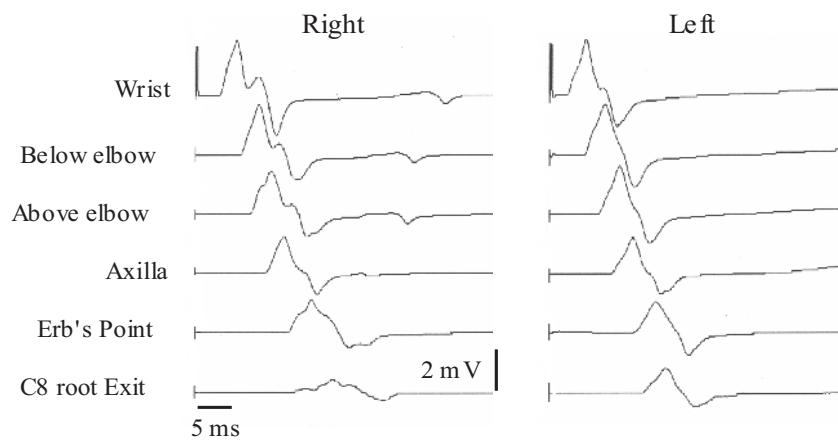


Figure 2 Compound muscle action potentials recorded from the right and left abductor digiti minimi muscles evoked by supramaximal stimulation of ulnar motor fibres at sites from the C8 root exit distally. The left side is normal. The right side shows motor conduction block between the motor root and Erb's point.

laboratories, are detectable in approximately 50% of cases. There is considerable variation in assay methodology between laboratories and this may account for the wide range in reported prevalence of anti-GM1 antibodies in different series of patients. Anti-GM1 antibodies invariably cross-react with asialo-GM1 and GD1b that share a common sugar epitope with GM1. More rarely patients are seen with anti-GM1 antibodies that cross-react with GM2. Thus the presence of anti-GM1 antibodies is diagnostically useful but their absence is unhelpful.

Magnetic resonance imaging (MRI) is not usually conducted for diagnostic purposes but in approximately 50% of cases can detect an increased signal intensity on T2-weighted images in parts of the brachial plexus, either in the axilla or in the ventral rami of the roots, corresponding with the distribution of symptoms. MRI lesions in MMN may be more focal and asymmetrical than the diffuse bilateral abnormalities seen in chronic inflammatory demyelinating polyneuropathy (CIDP) and also may help to distinguish MMN from spinal muscular atrophies where such lesions are not seen, and from other disease processes affecting the brachial plexus such as tumour or compression.

Nerve biopsy is rarely performed for diagnostic purposes in typical cases. It is inappropriate to biopsy a sensory nerve, such as the sural nerve, in a motor syndrome. Motor, or mixed nerve biopsy may show demyelination, onion bulb formation and axonal atrophy. This is a highly specialised procedure and not routinely recommended. Only if there is significant doubt about the diagnosis, such as differentiating nerve tumour or vasculitis, is an appropriate nerve biopsy indicated.

DIFFERENTIAL DIAGNOSIS

In cases of MMN with both a typical clinical

In cases of MMN with both a typical clinical presentation and characteristic electrophysiological features, the diagnosis is straightforward

presentation and characteristic electrophysiological features, the diagnosis is straightforward. However, occasional difficulty arises in distinguishing MMN from CIDP, motor neurone disease and spinal muscular atrophies, or variant syndromes including the eponymous Lewis Sumner syndrome, now also referred to as multifocal acquired demyelinating sensory and motor neuropathy (MADSAM). This latter syndrome was described several years before MMN and comprises a multifocal demyelinating sensory and motor neuropathy that is responsive to steroids; its nosological relationship to MMN remains a matter of debate. Purists may prefer to classify MMN cases with clear sensory features as MADSAM, whereas others allow for more latitude in their definition.

Early in the clinical course of MMN, when only a single peripheral nerve is affected, other causes of solitary or multiple mononeuropathies should be considered. In circumstances of diagnostic difficulty, follow-up with repeat electrophysiological examination at appropriate intervals is indicated. In specific clinical circumstances it may also be appropriate to perform other specialised tests. Thus screening for serum lead levels, genetic tests for hereditary neuropathy with liability to pressure palsy or motor neurone syndromes, and other causes of multifocal neuropathies may be necessary.

PROGNOSIS AND TREATMENT

A proportion of patients have relatively little disability and, following discussion, may prefer to remain untreated. Because MMN is believed to have an autoimmune basis, therapeutic approaches have been immunologically based. However, the only intervention with a clearly demonstrable and clinically worthwhile benefit is intravenous immunoglobulin (IVIg) (Pritchard & Hughes 2001). Several randomised

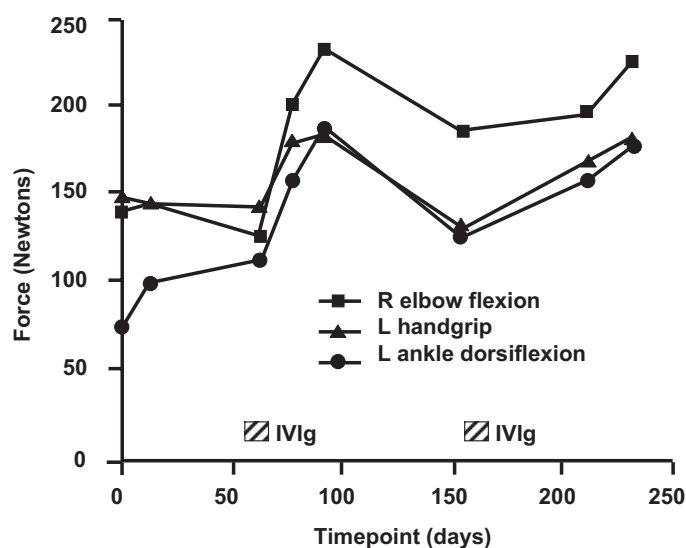


Figure 3 Myometry assessment of three affected muscle groups in a 46-year-old-man with an 18-year history. Serial measurements were recorded at a pretreatment baseline, and following two courses of IVIg. The treatment effect lasted 3 months.

double blind placebo controlled trials have all demonstrated benefit (reviewed in Nobile-Orazio 2001). Treatment with IVIg produces an improvement that can occur surprisingly quickly, usually peaks by 2 weeks and then gradually fades over subsequent months. Thus infusions need to be repeated at intervals.

Individual patients may favour particular dosing regimes in order to maximize clinically useful benefit. Some patients prefer to have periodic infusions of 2 g/kg spread over 3–5 days, separated by 2–3 months. Other patients prefer monthly infusions at 1 g/kg, and occasional patients require more frequent treatment, with an appropriate reduction in dose. Occasional patients respond well to the early infusions and then become refractory to treatment. Although changing the dosing regime can help, this is often an irretrievable situation. If the clinical benefit is modest, treatment should be withdrawn. The response pattern to IVIg of a typical patient is shown in Fig. 3.

Patients should be counselled about adverse effects of IVIg, including headache, flu-like symptoms, aseptic meningitis, skin rashes, anaphylaxis (especially in patients with congenital IgA deficiency), and thromboembolism. The cumulative risk of acquiring transmissible infection is particularly important as many patients will be repeatedly treated over long periods of time. The high cost of IVIg and its limited supply are also issues to consider.

A wide range of other immunomodulatory therapies have been tested in individual patients and in small studies, but without clear evidence of benefit (Umaphathi *et al.* 2002). Oral steroids are not effective in the vast majority of patients and can paradoxically produce a dramatic de-

terioration. Similarly plasma exchange, another mainstay of treatment for CIDP, is ineffective, and also occasionally results in clinical worsening. A number of reports have described clinical benefit with cyclophosphamide, either given as a pulse treatment intravenously or used orally. Cyclophosphamide is however, a very toxic drug with significant adverse effects and cannot be used long-term because of the cumulative life time toxicity. It is therefore usually inappropriate for a chronic disease, possibly requiring decades of treatment, and that has a relatively benign prognosis and affects patients at a young age. Other treatments that have been tried in small numbers of patients include azathioprine and interferon beta 1a.

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Hallmarks of multifocal motor neuropathy

- asymmetric onset in an upper limb
- selective motor involvement
- focal motor conduction block on electrophysiological testing
- presence of anti-GM1 antibodies in ~50% of cases
- therapeutic response to intravenous immunoglobulin