Clinical Differential Diagnosis of Multifocal Motor Neuropathy

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Abstract

Multifocal motor neuropathy (MMN) is a rare, clinically well-defined condition within the spectrum of chronic, immune-mediated neuropathies. A typical patient history involves slowly or stepwise progressive, predominantly distal, asymmetrical limb weakness and muscle wasting, most frequently in the arm, that may have developed over a period of years. As a rare condition, MMN may present a diagnostic challenge for non-specialists and some patients may wait years for a correct diagnosis. Timely and accurate diagnosis is essential for patients with MMN. Unlike some motor neuropathies, MMN is treatable with intravenous immunoglobulin and untreated patients are likely to experience progressive muscle weakness that may result in serious functional impairment and impaired quality of life. The aim of this article is therefore to provide a guide for non-specialist neurologists to the clinical recognition and differential diagnosis of MMN.

Keywords

Multifocal motor neuropathy, diagnosis, symptoms, signs

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The term multifocal motor neuropathy (MMN) was first introduced over 20 years ago[1] and it is now recognised as a clinically well-defined condition within the spectrum of chronic, immune-mediated neuropathies.[2–4] MMN is a rare disease, with an estimated prevalence of no more than one or two per 100,000.[5] However, results from French and Dutch studies suggest that MMN is under-diagnosed and that it can take several years for patients to achieve an accurate diagnosis after they first present.[6]

Accurate and timely recognition of MMN is important because it is a treatable disorder. In randomised studies, immunomodulatory treatment with intravenous immunoglobulin (IVIg) results in a significant improvement in patient functioning and muscle strength[7–10] and the drug is now recognised as the gold-standard treatment of MMN.[11] If left untreated, MMN results in progressive muscle weakness that for some patients ultimately results in serious functional impairment.[12] Delayed diagnosis may also have implications for patients' response to IVIg, since early initiation of treatment may help to postpone axonal degeneration and permanent deficits.[6,13]

MMN is under-recognised because it is a rare disease and non-specialists report difficulty in its clinical and electrophysiological diagnosis.[14] As a result, the disorder may be confused with other presentations, some of which are life threatening and do not respond to immunomodulatory treatment. Since physicians report that increased dissemination of diagnostic criteria would raise awareness of the possibility of MMN,[14] the aim of this article is to provide a guide for non-specialist neurologists to the recognition and differential diagnosis of MMN.

Clinical Signs and Symptoms

MMN is a purely motor deficit that affects individual nerves. It predominantly occurs in younger people, with a median age of onset of 40 years.[6] The disorder is more frequently seen in men than in women in a ratio of 2.7:1, and age of onset is usually younger in men.[6]

A typical patient history involves slowly or stepwise progressive, predominantly distal, asymmetrical limb weakness and muscle wasting that may have developed over a period of years. In a study of 88 Dutch patients with confirmed MMN, onset of muscle weakness occurred most frequently in the distal arm – most often in the dominant hand – or rarely the distal leg.[6] Symptoms follow a relapsing course and worsen with exposure to cold. Muscle atrophy is mild in early MMN[15] but may develop with longer duration of disease.[16,17] Patients may describe loss of strength in the affected limb, within an anatomical distribution of individual motor nerves, so that they have difficulty in gripping objects and experience muscle cramps, involuntary muscle contractions and fatigue. The degree of disability generally correlates with the duration of the disease.[6]

Consensus clinical criteria for the diagnosis of MMN are shown in *Table 1*. The lack of objective sensory abnormalities is a core criterion

Case History

A man, 35 years old, first complained in 1998 of distal weakness in the upper right limb, together with cramps and fasciculations, leading to difficulty in writing, using his computer keyboard and turning a key in a door lock. Electrophysiological studies showed a reduction of distal compound muscle action potential (CMAP) in the interossei in the right arm and conduction block in the ulnar nerve between wrist and elbow.

Ten months later, he noted a slight muscle atrophy in the distal right upper limb and additional weakness in arm flexion. Clinical examination found a motor deficit in the following right arm muscles: flexor carpi radialis (Medical Research Council [MRC] score: 3), interossei (MRC score: 2) and abductor pollicis brevis (MRC score: 2) accompanied by atrophy. No motor deficit was noted in lower limbs. Deep tendon reflexes in the right upper limb were absent. There was no sensory deficit and no cranial nerves involvement. He scored three out of 12 points on the Overall Neuropathy Limitations Scale (ONLS).

Further electrophysiological study showed conduction blocks in both median and ulnar nerves on the right side between wrist and elbow. Additionally, there was reduced CMAP in interossi in the left side without obvious conduction block (CB) in the left ulnar nerve. There were no fibrillation potentials recorded at rest. Giant motor units potentials were recorded in the right and left interossei at full voluntary muscle contraction.

A full routine biochemistry was performed, including full blood counts, thyroid function tests, blood glucose, serum vitamin B12 and folate, and immunofixation looking for a monoclonal peak. Serum antibody reactivity against anti-myelin-associated (MAG) activity and ganglosides GM1, GM2, GM3, GD1a, GD1b, GT1b, GQ1b, GD3, was tested by ELISA assay and the titres compared to those of controls. Anti-GM1 antibodies were 1:200, limit of normal: 1:100, while other results were normal. The diagnosis of multifocal motor neuropathy (MMN) was then assessed.

for the diagnosis, but sensory symptoms such as paraesthesia or numbness may occasionally develop over the course of the disease. It is therefore advisable not to rule out a diagnosis of MMN in patients with sensory symptoms, if objective sensory abnormalities are absent. Tendon reflexes are usually diminished or absent in the territory of the affected nerve. Normal or slightly increased or brisk tendon reflexes have, however, been reported[6] and do not exclude a diagnosis of MMN if there are no upper motor neurone signs. Cranial nerve involvement is uncommon.

Investigations

Nerve Conduction Studies

Although it is theoretically possible to diagnose MMN in some patients on the basis of their clinical presentation alone, the hallmark of MMN is the presence of conduction block (CB) in motor, but not sensory, nerve fibres that do not involve common compression sites.[18] CB is defined as the failure of action potential propagation at a given site of a single axon. Some relatively simple electrophysiological techniques that can be used to diagnose CB in MMN by neurologists trained in nerve conduction studies are outlined elsewhere in this supplement.

Table 1: Clinical Criteria for Multifocal Motor Neuropathy[18]

Core Criteria (Both Must be Present)
1 Slowly progressive or stepwise progressive, focal, asymmetrical limb weakness; that is, motor involvement in the motor nerve distribution of at least two nerves, for more than one month and usually more than six months. If symptoms and signs are present only in the distribution of one nerve only a possible diagnosis can be made
2 No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs
Supportive Clinical Criteria
3 Predominant upper limb involvement
4 Decreased or absent tendon reflexes in the affected limb
5 Absence of cranial nerve involvement
6 Cramps and fasciculations in the affected limb
7 Response in terms of disability or muscle strength to immunomodulatory treatment
Exclusion Criteria
8 Upper motor signs
9 Marked bulbar involvement
10 Sensory impairment more marked than minor vibration loss in the lower limbs
11 Diffuse symmetrical weakness during the initial weeks

Table 2: Consensus Electrophysiological Criteria for Conduction Block[18]

1 Definite Motor Conduction Block
• Negative CMAP area reduction on proximal versus distal stimulation of at least 50 % whatever the nerve segment length (median, ulnar, peroneal)
• Negative CMAP amplitude on stimulation of the distal part of the segment with motor conduction block must be >20 % of the lower limit of normal and >1 mV
• Increase of proximal to distal negative peak CMAP must be duration ≤30 %
2 Probable Motor Conduction Block*
• Negative peak CMAP area reduction of at least 30 % over a long segment (e.g. wrist to elbow or elbow to axial) of an upper limb nerve with an increase of proximal to distal negative peak CMAP duration ≤30 % or:
• Negative CMAP area reduction of at least 50 % (same as definite) with an increase of proximal negative CMAP duration of >30 %
3 Normal Sensory Nerve Conduction in Upper Limb Segments with Conduction Block

**Evidence for conduction block must be found at sites distinct from common entrapment and compression sites. CMAP = compound muscle action potential.*

Electrophysiological investigation may show a combination of motor CB and slowing of motor conduction consistent with demyelination, but with normal sensory conduction. Apart from decreased distal compound muscle action potentials (CMAP), other signs of motor axon loss include fibrillations at rest and a neurogenic pattern at full muscle contraction on needle electromyography (EMG).[18,19] There has been some debate on the degree of CMAP necessary to define definite, probable or possible CB. The evidence remains limited, but recently revised European guidelines include consensus good practice points that provide electrophysiological diagnostic criteria for CB (see *Table 2*).

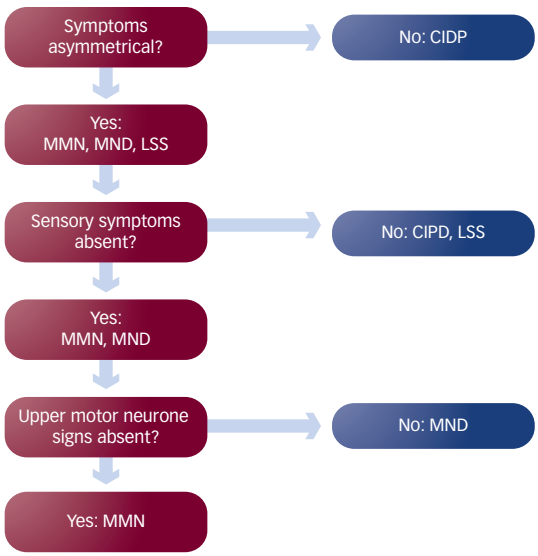
Nerve conduction studies in the nerves with motor abnormalities play an essential role in distinguishing MMN from other disorders with a similar clinical presentation. However, some patients present with

Table 3: Differential Diagnosis in Multifocal Motor Neuropathy

	MMN	MND	CIDP	LSS
Clinical Presentation				
• Pattern of symptoms	Asymmetrical, usually distal, following distinct peripheral nerves	Asymmetrical usually at onset	Symmetrical, distal and proximal	Asymmetrical
• Sensory symptoms	None*	None	Yes	Yes, sometimes associated with pain
• Upper motor neurone signs	Absent	Present	Absent	Absent
Tendon reflexes	Decreased	Increased	Decreased or absent	Decreased or absent
Disease course	Slowly progressive	Rapidly progressive	Progressive/relapsing	Progressive/relapsing
Investigations				
• Electrophysiology	Normal SNAP, focal demyelinating lesions usual	Normal SNAP, focal demyelinating lesions absent	Low to absent SNAP or normal, focal demyelinating lesions frequent	Low SNAP, focal demyelinating lesions usual
• IgM anti-GM1 antibodies	30–80 % patients	Absent at significant titres	Absent at significant titres	Absent
• CSF protein	Normal or slightly elevated (<1 g/l)	Normal or slightly elevated	Elevated (may be normal)	Normal or slightly elevated
Response to Immunomodulatory Treatment				
• IVIg	Response	None	Response	Response
• Corticosteroids	None and possibly worsening	None	Response	Response

**Paraesthesia or numbness may develop occasionally in long-term disease. CIDP = chronic inflammatory demyelinating polyneuropathy; CSF = cerebral spinal fluid; IVIg = intravenous immunoglobulin; LSS = Lewis-Sumner syndrome; MMN = multifocal motor neuropathy; MND = motor neurone disease; SNAP = sensory nerve action potential.*

Figure 1: Avoiding Common Pitfalls in the Clinical Differential Diagnosis of Multifocal Motor Neuropathy



CIDP = chronic inflammatory demyelinating polyneuropathy; LSS = Lewis-Sumner syndrome; MMN = multifocal motor neuropathy; MND = motor neurone disease.

typical clinical symptoms of MMN, but without detectable CB on nerve conduction studies. The probable reason is that these blocks are activity dependent, or are located in nerve segments that cannot be assessed on routine electrophysiological examination.[20,21]

Techniques such as transcranial magnetic stimulation, triple-stimulation technique or transcutaneous cervical root stimulation have been used to identify CBs with greater sensitivity. These may be useful, especially if CBs are proximally sited, but their value has yet to be determined in routine clinical use. In practice, it should be noted that in long–term follow-up, MMN patients with and without CB show a similar response to IVIg.[20] As a result, objective clinical improvement following IVIg treatment is included among supportive criteria for the diagnosis of MMN.[18]

Other Tests

Patients fulfilling clinical and electrophysiological diagnostic criteria for MMN do not usually require further tests. When there is doubt, supportive criteria for the diagnosis include raised IgM anti–ganglioside GM1 (anti-GM1) serum antibodies,[22,23] elevated cerebral spinal fluid (CSF) protein (<1 gl/l) but with normal cell counts[24] and increased signal intensity on T2-weighted magnetic resonance imaging (MRI) scans of the brachial plexus associated with diffuse nerve swelling.[24,25]

High titres of IgM anti-GM1 serum antibodies are the most common laboratory findings in MMN. These antibodies are not, however, a diagnostic marker for MMN, since they also occur – albeit infrequently and in lower titres – in some patients with other immune-mediated neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP) and in motor neurone disease (MND).[18] Consequently, while a positive test for anti-GM1 antibodies supports the diagnosis, a negative result does not rule out the possibility of MMN.

Investigations such as nerve biopsies, serum and urine paraprotein detection by human immunofixation, thyroid function, creatine kinase and CSF cells and protein are not routinely recommended in patients with MMN. These tests may, however, help to rule out other causes or discover concomitant disease.[18]

Differential Diagnosis

MMN should enter the differential diagnosis in any patient presenting with slowly or stepwise progressive, asymmetrical limb weakness without objective sensory abnormalities, upper motor neurone or bulbar signs or symptoms.[18] *Table 3* provides a guide to differentiating MMN from other disorders with a similar clinical presentation, including MND, CIDP and Lewis-Sumner syndrome (LSS)/multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy.

The algorithm shown in *Figure 1* is intended to help in avoiding some common pitfalls in differential diagnosis. These include confusion between MMN and MND. Both MMN and MND are characterised by asymmetrical muscle weakness, but in MMN this weakness follows individual peripheral nerves. In addition, there are no upper motor neurone signs in MMN and sensory symptoms are usually absent. CB on electrophysiological testing and serum IgM anti-GM1 antibodies also help to distinguish MMN from respectively MND and CIDP. The absence of sensory symptoms and symmetrical muscle weakness also help to differentiate MMN from classical CIDP.

It is important to differentiate between MMN and LSS. This is because, while some patients with LSS respond to corticosteroids, these drugs are ineffective or may exacerbate symptoms in MMN.[26] Like MMN, LSS is a multifocal neuropathy with CB, but patients experience sensory symptoms, often with neuropathic pain. If clinical symptoms are insufficient for differential diagnosis, the finding of clinical sensory abnormalities, together with altered sensory potentials and the absence of anti-GM1 antibodies indicates LSS.

Conclusion

MMN can represent a diagnostic challenge for non-specialists and patients may wait years for a correct diagnosis. There are several differential diagnoses, but confusion between MMN and MND is especially frequent. This has especially adverse implications for patients, given the lack of effective treatment for and greatly reduced lifespan associated with MND. In contrast, patients with MMN can generally expect a normal life expectancy and, if diagnosed at an early stage of the disease, a beneficial response to periodic infusions with IVIg. ■

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