Multifocal motor neuropathy

Raquel Guimarães-Costa, Francesco Bombelli, Jean-Marc Léger

Hôpital de la Salpêtrière, Referral Center for Rare Neuromuscular Diseases, Bâtiment Babinski, Paris, France

Correspondence:
Jean-Marc Léger, Hôpital de la Salpêtrière, Referral Center for Rare Neuromuscular Diseases, Bâtiment Babinski, Paris, France.
jean-marc.leger@psl.aphp.fr

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Summary

Multifocal motor neuropathy (MMN) is a chronic immune-mediated neuropathy that is particular for its asymmetric, multifocal, purely motor clinical presentation, often related to the distribution of individual nerves. Upper limbs are usually primarily and more severely affected, but lower limbs may be involved during the course of the disease. The hallmark of the disease is the presence, in electrophysiological studies, of persistent conduction blocks in the affected motor nerves, located outside the usual sites of nerve compression, contrasting with normal sensory nerve conduction velocities. The most typical laboratory finding is the presence of high levels of serum IgM antibodies to the ganglioside GM1, and less frequently to asialo-GM1, GD1α or GM2. These striking features may help distinguishing this neuropathy from both motor neuron disease and other chronic immune-mediated neuropathies. Several randomized controlled trials (RCT) have established the efficacy of high-dose intravenous immunoglobulin (IVig), as well as subcutaneous immunoglobulin (SCig). However, this therapy has a short-lasting effect, and need to be maintained with periodic infusions. This disappointing status has led to the search of other immune therapies whose efficacy has not been so far confirmed in RCT. This review intends to summarize current contents in the diagnosis and the treatment of MMN.

Multifocal motor neuropathy (MMN) was firstly reported in 1986 in original reports coming from two groups of authors [1,2], but was formally named by the group of Pestronk [3,4], who also highlighted its association with IgM GM1 anti-ganglioside serum autoantibodies and its response to immunomodulators. Although it may share some characteristics with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and its variant, multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy (also called Lewis-Sumner syndrome), it has progressively been recognized as a distinct entity among the group of the so-called chronic
immune-mediated neuropathies. However, many questions persist, mainly concerning the pathophysiology, the natural course, and the long-term treatment of the disease.

Epidemiology

MMN is a rare disorder affecting no more than 1 person per 100,000, with predominance in men (sex ratio: 2.6:1) and a median age around 40 years old (80% of cases range between 20 and 50 years old) [5]. In a retrospective study of 88 patients with MMN recently reported [6], the male to female ratio was 2.7:1, with a significantly younger age of onset in men (38 years) than in women (45 years). In another series reported by Slee et al. [7], the mean symptom duration prior to diagnosis was 6 years.

Interestingly, the prevalence of this disease was unknown for 37–46% of physicians (mainly neurologists, rheumatologists and internal medicine specialists), who completed a questionnaire survey in metropolitan France [8]. This study also showed that the patients with MMN were more frequently diagnosed and treated by physicians who worked in a hospital, than by the ones who had prevalent private practice. This last point is however usual for most orphan diseases.

Little is known about incidence and prevalence of MMN in children. Though, a single case of a 6-year-old-boy was reported by Moroni et al. [9]. This child presented with asymmetric wasting and weakness of hands and definite conduction blocks (CB) (see below) in the upper limbs, outside the usual entrapment sites. He had dramatic improvement of his motor deficit, and subsequent resolution of CB, with intravenous immunoglobulin (IVIg) at 2 g/kg. This case report raises questions about MMN in childhood, and suggests that clinical and electrophysiological features and response to IVIg may be similar to those observed in adults.

Diagnosis

Clinical aspects and electrophysiological abnormalities mainly support the diagnosis of MMN, both of them having been recently reviewed by a Task Force of both European Federation of Neurological Societies (EFNS) and Peripheral Nerve Society (PNS), which edited Guidelines on management of multifocal motor neuropathy, firstly revised in 2010 [10]. In addition, the diagnosis may be supported by laboratory and imaging data.

Clinical features

The main clinical feature (boxes 1–4) is a purely motor deficit in a multifocal, asymmetric distribution of individual nerves, without any sensory involvement and without obvious upper motor neuron signs. Motor deficit usually starts and remains prominent in the distal arms, but 34% of patients in a recent series of 88 patients with MMN, had onset in the distal legs [6]. Minor sensory symptoms may be reported, although they are not usually accompanied by objective loss of sensation [11], except for a slight diminution of vibration in the only distal lower limbs [6]. Recently, the extent of sensory signs and symptoms has been reconsidered, mainly the development of only electrophysiological sensory changes without sensory signs/symptoms over the course [12,13]. In addition, patients frequently report an exacerbation of weakness with cold, probably due to an ionic channel mechanism [14]. In the affected motor nerves, cramps and fasciculations are frequent, as well as motor deficit with no or slight amyotrophy, this last condition being considered typical of the disease and reflecting the clinical expression of CB. Tendon reflexes are usually diminished or abolished in the affected territories, but may be normal or even brisk in rare cases [6]. For some authors, differential motor deficit across

Box 1

Clinical criteria for multifocal motor neuropathy [10]

Core criteria (both must be present):

- slowly progressive or stepwise progressive, focal, asymmetric 1 limb weakness, that is, motor involvement in the motor nerve distribution of at least two nerves, for more than 1 month. If symptoms and signs are present only in the distribution of one nerve only a possible diagnosis can be made (box 4);
- no objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs 2.

Supportive clinical criteria:

- 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;
- response in terms of disability or muscle strength to immunomodulatory treatment.

Exclusion criteria:

- upper motor neuron signs;
- marked bulbar involvement;
- sensory impairment more marked than minor vibration loss in the lower limbs;
- diffuse symmetric weakness during the initial weeks.

1Asymmetric = a difference of 1 MRC grade if strength is MRC > 3 and 2 MRC grades if strength is MRC ≤ 3.

2Usually more than 6 months.

3Sensory signs and symptoms may develop over the course of MMN.

4At onset, predominantly lower limb involvement account for nearly 10% of the cases.

5Slightly increased tendon reflexes, in particular in the affected arm, have been reported and do not exclude the diagnosis of MMN provided criterion 8 is met.

6Twelfth nerve palsy has been reported.
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**Box 2**

**Electrophysiological criteria for conduction block** [10]

<table>
<thead>
<tr>
<th>Definite motor CB:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• negative peak CMAP area reduction on proximal vs. distal stimulation of at least 50% whatever the nerve segment length (median, ulnar, and peroneal). Negative peak CMAP amplitude on stimulation of the distal part of the segment with motor CB must be &gt; 20% of the lower limit of normal and &gt; 1 mV and increase of proximal to distal negative peak CMAP duration must be ≤ 30%</td>
</tr>
<tr>
<td>Probable motor CB:</td>
</tr>
<tr>
<td>• negative peak CMAP area reduction of at least 30% over a long segment (e.g., wrist to elbow or elbow to axilla) of an upper limb nerve with increase of proximal to distal negative peak CMAP duration ≤ 30% or;</td>
</tr>
<tr>
<td>• negative peak CMAP area reduction of at least 50% (same as definite) with an increase of proximal to distal negative peak CMAP duration &gt; 30%.</td>
</tr>
</tbody>
</table>

Normal sensory nerve conduction in upper limb segments with CB (see exclusion criteria).

CB: conduction block; CMAP: compound muscle action potential.

1Evidence for CB must be found at sites distinct from common entrapment or compression syndromes.

**Box 3**

**Supportive criteria** [10]

- Elevated IgM anti-ganglioside GM1 antibodies.
  - Laboratory: increased CSF protein (< 1 g/L).
  - Magnetic resonance imaging showing increased signal intensity on T2-weighted imaging associated with a diffuse nerve swelling of the brachial plexus.
  - Objective clinical improvement following intravenous immunoglobulin treatment.

**Box 4**

**Diagnostic categories** [10]

Definite multifocal motor neuropathy:

- clinical criteria 1, 2, and 8–11 (box 1) and electrophysiological criteria 1 and 3 in one nerve (box 2).

Probable multifocal motor neuropathy:

- clinical criteria 1, 2, and 8–11 and electrophysiological criteria 2 and 3 in two nerves;
- clinical criteria 1, 2, and 8–11 and electrophysiological criteria 2 and 3 in one nerve AND at least two supportive criteria 1–4 (box 3).

Possible multifocal motor neuropathy:

- clinical criteria 1, 2, and 8–11 and normal sensory nerve conduction studies and supportive criteria 4;
- clinical criteria 1 with clinical signs present in only one nerve, clinical criteria 2, and 8–11 and electrophysiological criteria 1 or 2 and 3 in one nerve.

**Electrophysiological features**

The presence of CB in motor nerve fibers outside the usual sites of nerve compression is the hallmark of the disease. However, some patients with otherwise typical MMN have no detectable CB, probably because these blocks are activity-dependant or are located in segments which cannot be assessed by routine electrophysiological examination [16]. More recently, other techniques with restricted availability, such as triple-stimulation technique, and transcutaneous cervical root stimulation, have been used to identify CB with greater sensitivity. These techniques may be useful, especially where CB are located in the proximal segments of motor nerves [10,17,18]. CB have been defined as a significant reduction in the amplitude of area of the compound muscle action potential (CMAP) obtained by proximal compared to distal stimulation. The first papers defined CB as a 20–30% amplitude or area reduction if the distal CMAP duration did not exceed 15% greater than normal. However, computer modeling of CB and temporal dispersion in an animal model has demonstrated that up to 50% area reduction of the proximal to distal CMAP can be due entirely to interphase cancellation [19]. Similar studies in man have shown that distal CMAP duration and proximal CMAP duration prolongation are important factors for the definition of CB in the median nerve segment over the forearm: the shorter the distal duration and proximal duration prolongation, the less CMAP amplitude reduction, is needed to diagnose a CB.
Electromyography (EMG) may disclose fasciculations and myokymies. In clinically weak muscles with preserved bulk, EMG at full contraction may objective reduced motor unit action potential recruitment. Fibrillations are usually detected in territories with marked amyotrophy and are consistent with an active axonal degeneration [5,11]. The amplitude of sensory potentials is usually normal. It may be significantly reduced in a number of patients over the course, without related obvious sensory deficit [12,13].

**Immunological features**

The most typical immunological feature in MMN is the presence of significant titers of serum IgM auto antibodies binding to the ganglioside GM1 in 40–50% of cases, and less frequently to other glycolipids including asialo-GM1, GD1A or GM2. In the series of 88 patients with MMN [25] 43% had anti-GM1 IgM antibodies, 3.4% had anti-GM1 IgM and IgA antibodies, 1% had isolated anti-GM1 IgA antibodies, 1% had anti-GM1 IgM, IgA and IgG antibodies. Association of anti-GD1b antibodies and anti-GM1 IgM antibodies was observed in 9% of patients. It is known that IgM antibodies to GM1 have cross-reactivity with asialo-GM1 and GD1b, which may explain the presence of antibodies binding to these two gangliosides in MMN patients [26]. Anti-ganglioside complexes can enhance or attenuate the detection of anti-GM1 binding, suggesting that interaction of different gangliosides may alter antibody reactivity, by either new antibody formation or by hiding reactive antigens [27,28].

Correlations between clinical features and serum IgM anti-ganglioside antibodies has been widely discussed, although it remains controversial. In their retrospective study, Cats et al. [25] found as a significant result, that anti-GM1 IgM antibodies were associated with more marked disability and axonal loss, when compared with patients who were negative for these antibodies.

In summary, specificity of anti-ganglioside antibodies in sera from MMN patients has limitations, as their absence does not exclude the diagnosis. Thus, results of serum anti-ganglioside antibodies must be interpreted in line with clinical and electrophysiological data.

**Other laboratory findings**

Most parameters are normal, but creatine kinase might be elevated in about two thirds of patients. Serum electrophoresis can detect polyclonal antibody formation, but monoclonal peaks are rare. Cerebrospinal fluid analysis is usually normal or detects a slight elevation of protein count (< 1 g/L) [10,11,24].

**Imaging findings**

Imaging studies of the peripheral nerves may show non-specific features that may be helpful in the diagnosis. In 40–50% of

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**Box 5**

**Recommendations and Good Practice Points [10]**

Good Practice Points for diagnostic criteria:
- clinical: the two core criteria and all exclusion criteria should be met (box 1);
- electrodiagnostic: definite or probable CB in at least one nerve (box 2);
- supportive: anti-GM1 antibodies, MRI, CSF, and treatment response (box 3);
- categories: definite and probable MMN (box 4).

Good Practice Points for diagnostic tests:
- clinical examination and electrodiagnostic tests should be done in all patients;
- anti-ganglioside GM1 antibody testing, MRI of the brachial plexus, and CSF examination should be considered in selected patients;
- investigations to discover concomitant disease or exclude other possible causes should be considered, but the choice of tests will depend on the individual circumstances.

Good Practice Points for treatment:
- IVIg (2 g/kg given over 2–5 days) should be the first-line treatment (level A) when disability is sufficiently severe to warrant treatment;
- corticosteroids are not recommended;
- if an initial treatment with IVIg is effective, repeated IVIg treatment should be considered in selected patients (level C). The frequency of IVIg maintenance therapy should be guided by the response. Typical treatment regimens are 1 g/kg every 2–4 weeks or 2 g/kg every 1–2 months;
- if IVIg is not sufficiently effective then immunosuppressive treatment may be considered. However, no agent has shown to be beneficial in a clinical trial and data from case series are conflicting;
- toxicity makes cyclophosphamide a less desirable option.

CB: conduction block; MRI: magnetic resonance imaging; CSF: cerebrospinal fluid; MMN: multifocal motor neuropathy; IVIg: intravenous immunoglobulin.

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[20]. Several articles and expert’s opinion reports aimed to define the diagnostic criteria of MMN, grading it as definite or probable, as well as definite, probable, and possible [10,21–23]. There is only class IV evidence concerning all these matters. Nevertheless, the Task Force agreed on Good Practice Points to define clinical and electrophysiological diagnostic criteria for MMN (box 5) [10]. Other electrophysiological alterations may be found such as prolonged distal motor latencies, prolonged or absent F-waves, slight diminution of motor nerve conduction velocities and temporal dispersion [5,11,24].
patients, it may show hyperintense signals on T2-weighted magnetic resonance imaging (MRI) or contrasted-enhanced T1 sequences in the brachial plexus. These abnormalities usually correlate with the distribution of muscle weakness and eventually with CB [24,29].

In MMN, abnormal MRI signals are frequently asymmetric, contrasting with symmetrical similar abnormalities observed in patients with CIDP, and with normal imaging data in motor neuron diseases [10].

Neuropathological features

Since sensory nerves are by definition normal, nerve biopsies performed have been rarely performed, mainly in sensory nerves in atypical cases. Some studies have reported aspects of demyelination/remyelination and onion bulbs in the topography of suspected CB, with scarce cell infiltrates [11,24].

Differential diagnosis and associated conditions

In most cases, MMN is easily recognizable but some conditions can mimic MMN. Thus, differential diagnostic may be considered to allow the right diagnosis and treatment [30].

Motor neuron diseases, mainly amyotrophic lateral sclerosis (ALS) in its initial course, may have common features with MMN: asymmetric motor deficit, cramps, fasciculations, amyotrophy. However the following may help distinguishing the two diseases: MMN is not a diffuse motor disease but affects individual motor nerves in a multifocal pattern, and is never associated with upper motor neuron signs. Moreover, in electromyographic studies, CB are only present in MMN, and fibrillations are more frequent in MND. However, lower motor neuron diseases may constitute a challenge, especially when CB are difficult to objective. The distinction of both entities can eventually be made by detection of anti-GM1 IgM antibodies and response to IVIg.

On the other hand, MADSAM neuropathy, a multifocal variant of CIDP, is a very similar condition, with obvious CB in electrophysiological studies. Nevertheless, the presence of sensory symptoms and signs in affected territories, together with abnormalities of sensory nerve conduction velocities, and absence of serum anti-GM1 antibodies, are classical ways to distinguish the two diseases (Table 1, Figure 1).

Associated autoimmune conditions with MMN, such as celiac disease and Hashimoto’s thyroid disease have been recently reported. Moreover, first-degree family members also apparently have a higher incidence of diabetes type 1, celiac disease and Hashimoto’s thyroid disease [31]. These associations may suggest a similar pathogenic mechanism and outline the need for search for associated conditions that may contribute to impair patient’s quality of life. In the same way, a higher expression of HLA-DRB1*15 was detected in patients with multifocal motor neuropathy which may suggest a similar pathogenic pathway with other diseases, such as multiple sclerosis and CIDP, which share a higher frequency of this specific HLA than in controls. Unfortunately, until the present, no correlation with this HLA and age of onset, clinical course or disease severity had been found [32].

<table>
<thead>
<tr>
<th>Features</th>
<th>MMN</th>
<th>MDSAM</th>
</tr>
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<tbody>
<tr>
<td>Sensory symptoms</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Pain</td>
<td>No</td>
<td>Yes/no</td>
</tr>
<tr>
<td>Multifocal motor involvement</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Presence of CB</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Anti-GM1 antibodies</td>
<td>Yes/no</td>
<td>No</td>
</tr>
<tr>
<td>Cerebrospinal fluid protein</td>
<td>&lt; 1 g/L</td>
<td>Can be &gt; 1 g/L</td>
</tr>
</tbody>
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CB: conduction blocks.

Avoiding common pitfalls in the clinical differential diagnosis of multifocal motor neuropathy

CIDP: chronic inflammatory demyelinating polyneuropathy; MDSAM: multifocal acquired demyelinating sensory and motor neuropathy with persistent conduction block; MND: motor neuron disease [30].
Treatment

Intravenous immunoglobulins

The vast majority of patients with MMN fail to respond to steroids, even given IV, and to plasma exchanges (PE), which may be followed by clinical worsening [11,33–36]. That highlights the importance of the distinction between MMN and CIDP or its variant, MADSAM neuropathy, in which steroids and PE are effective [37].

Nowadays, IVIg is the first-line treatment, as its efficacy has been demonstrated by several double-blind, placebo-controlled trials [38–41]. Despite that, the mechanism of acting has not clearly been established for IVIg. Some studies suggest an alteration of classical complement pathways particularly in anti-GM1 positive patients [42,43] while reduction of anti-GM1 circulating antibodies and induction of inhibitory of B cells receptors have also been proposed to support IVIg effectiveness [44].

IVIg are initially effective in 70–86% of patients with firstly improvement of muscle strength, sometimes accompanied by disappearance of partial CB. On the other hand, anti-GM1 antibodies titers do not change under IVIg treatment. Randomized controlled trials (RCT) used an initial dose of 2 g/kg body weight given on 2–5 consecutive days. Since it is observed a decline in the beneficial effect after some weeks, it is necessary to maintain a periodic regime (0.4 g/kg IVIg once a week or 1–2 g/kg in monthly intervals) [45].

A frequently asked question is the long-term treatment of MMN. Van den Berg-Vos et al. [46] performed a long-term follow-up of 11 patients with MMN, who received maintenance treatment with IVIg during 4–8 years. The authors concluded that IVIg maintenance therapy has a beneficial long-term effect on muscle strength and upper limb disability, but may not prevent a slight decrease in muscle strength. They therefore concluded that IVIg treatment favorably influences the mechanisms of remyelination or reinnervation, but that axon loss cannot be prevented. Similarly, Terenghi et al. [47] showed that effectiveness of IVIg in MMN often declines after several years, possibly due to the development of axonal degeneration. Finally, Léger et al. [48] found, in a retrospective study in 40 patients with MMN, that more than two third of the studied patients were IVIg-dependent at the time of the study.

On the other hand, Vucic et al. [49] concluded that long-term IVIg therapy improves muscle strength and functional disability, decreases the number of CB and the extent of axonal degeneration, and promotes reinnervation. The difference from previous findings may be explained by the different regimen in giving IVIg, the patients in this last study being treated with significantly higher IVIg periodic infusions. Confirming this study, Cats et al. [6] found that years without treatment, instead of duration of IVIg treatment, are a determinant for more severe weakness and disability. The progression of weakness and axon loss were more pronounced in the years without than in the years with IVIg treatment, indicating that an early start of IVIg, followed by a maintenance treatment, is at present the only intervention that may prevent axonal loss and a more severe outcome [6].

Alternative treatment with subcutaneous immunoglobulin (SCIG) in MMN patients was firstly proposed by jakobsen et al. [50] in a 2-year-long protocol with six IVIg-responsive patients. Dosage varied between 13 and 51 g per week (80–320 mL) infused twice or three times weekly. There were no major side effects and impairment and disability scores remained stable. This approach may be considered, allowing patients to have a better autonomy.

Mycophenolate mofetil

Piepers et al. [51] conducted a randomized, single-centre, placebo-controlled, “add-on” study of mycophenolate mofetil 1 g twice a day for 1 year which failed to show any significant difference in MRC sumscore, IVIg dose or IgM anti-GM1 with mycophenolate mofetil, when compared to placebo.

Cyclophosphamide

Uncontrolled trials showed that cyclophosphamide, especially given intravenously at high-doses, may have a moderate effect. Despite these reports, the efficacy of cyclophosphamide has no longer been studied in RCT. This is due mainly to its relevant side effects, and to the fact that there is a persistent doubt concerning its suitability in a non-life threatening disease such as MMN.

Others immunosuppressors [52]

Small series or case reports indicate a possible clinical improvement, though without Improvement on Rankin scale on patients treated with beta-interferon 1a.

Similarly there are some single case reports indicating benefits of treatment with cyclosporin, azathioprine or rituximab [10].

On the other hand, use of tumor necrosis factor alpha blocking therapy, particularly infliximab seems to be associated to development of peripheral neuropathies, the majority with MMN features. This class-drug should not, in the present, be proposed in MMN treatment [10].

Finally, a study with eculizumab for 14 weeks in 13 patients, 10 of whom in association with IVIg, was recently published. Eculizumab is a monoclonal antibody which binds and neutralizes human factor C5 preventing terminal complement activation and membrane lysis via membrane attack complex [53].

A trend towards an improvement in patient-rated subjective scores and increased muscle strength as measured by myometry, were observed. In electrophysiological measurements, there was a small but significant decrease in the degree of CB across the nerves studied. This study gives a possibility for further
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research concerning the use of complement inhibitors in the treatment of MMN.

Conclusion

Although MMN does not diminish life span, it often compromises quality of life in affected patient. After its initial description, a number of set of criteria have been edited, which are certainly helpful in the diagnosis in clinical practice, and also for clinical trials.

Even though IV Ig is most of time efficacious in short-term periods, leading to an improvement in strength and global function, almost thirty years after the description of this disease it was still not defined a therapy, which could definitely prevent secondary axonal degeneration and thus slow progression of atrophy and motor deficit.

Increasing knowledge concerning pathophysiological mechanisms, such as the role of ionic channels in the nodes of Ranvier, and the auto immune system might unveil new possibilities of treatment to MMN patients.

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