Multifocal motor neuropathy: a review of pathogenesis, diagnosis, and treatment

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Abstract: Multifocal motor neuropathy (MMN) is an uncommon, purely motor neuropathy associated with asymmetric deficits with predilection for upper limb involvement. Even in the early descriptions of MMN, the associations of anti-GM1 antibodies and robust response to immunomodulatory treatment were recognized. These features highlight the likelihood of an underlying autoimmune etiology of MMN. The clinical presentation of MMN can closely mimic several neurological conditions including those with more malignant prognoses such as motor neuron disease. Therefore early and rapid recognition of MMN is critical. Serological evidence of anti GM-1 antibodies and electrodiagnostic findings of conduction block are helpful diagnostic clues for MMN. Importantly, these diagnostic features are not universally present, and patients lacking these characteristic findings can demonstrate similar robust response to immunomodulatory treatment. In the current review, recent research in the areas of diagnosis, pathogenesis, and treatment of MMN and needs for the future are discussed. The characteristic findings of MMN and treatment implications are reviewed and contrasted with other mimicking disorders.

Keywords: autoimmune, conduction block, electrodiagnosis, motor neuron, nerve, inflammatory

Background and prevalence
There are few disorders that are confined to nerves and produce a purely motor phenotype. It is important to differentiate the most recognized and fatal form, motor neuron disease, from other treatable or less malignant forms of motor neuropathy. Multifocal motor neuropathy (MMN) is much rarer but can closely mimic motor neuron disease. The accurate differentiation of MMN has very important clinical implications for the patient because of the obvious differences in prognosis and treatment. Prevalence estimates for MMN range from 0.3 to 3 cases in 100,000 depending on the case series examined and how estimates were derived;1–4 but MMN is clearly underrecognized.

In a longitudinal study of patients with MMN, the correct diagnosis was made by the referring neurologist in only 6 of 46 patients (13%) referred to a tertiary neuromuscular center, attesting to the importance of a good understanding of this disorder.5

Clinical features
MMN is a purely motor neuropathy characterized by motor deficits in the distribution of single nerves without associated sensory loss. Motor neuron disease is also characterized by motor deficits without sensory loss, but an important distinction from MMN is that it occurs in the distribution of spinal segments rather than single nerves. MMN predominantly affects males, almost three times as often as females (2.7:1). Onset is generally before the age of 50 years (80% of cases, with a mean age of onset of 40 years, range
Clinical criteria for the diagnosis of MMN

1. Slowly progressive or stepwise progressive, focal, asymmetric 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.

2. No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs.

Supportive

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 therapy.

Exclusion criteria

8. Upper motor neuron signs.


10. Sensory impairment more marked than minor vibration loss in the lower limbs.

11. Diffuse symmetric weakness during the initial weeks.


Abbreviation: MMN, multifocal motor neuropathy.

Electrophysiological features

Motor conduction block is defined as a reduction of compound muscle action potential amplitude recorded from a muscle or group of muscles following proximal nerve stimulation (across the site of conduction failure) as compared with distal nerve
stimulation (distal to the site of conduction failure). This drop of amplitude indicates a localized failure of action potential conduction along a structurally intact axon and is consistent with a myelinopathy. This can also occur with focal compression of nerves at compressible sites such as the elbow, wrist, fibular head, etc. In MMN, conduction block (CB) occurs at noncompressible sites along the nerve axons and does not affect sensory fibers; this is the diagnostic hallmark. However, MMN without CB has also been described and CB is not specific for MMN as it can be seen with other types of inflammatory myelinopathies.\(^\text{16, 17}\) Various nonconventional electrophysiological techniques have been used to investigate the pathophysiology of CB by indirectly assessing axonal excitability. Mixed findings have suggested either hyperpolarization or depolarization may occur at the site of CB in MMN.\(^\text{18, 19}\)

Importantly, patients with a clinical appearance consistent with MMN but without CB respond to intravenous immunoglobulin (IVIg) treatment similarly to those with CB; they also have a similar long term prognosis. The absence of CB in some patients may represent limitations of electrodiagnostic testing for identification of conduction block along very proximal or very distal segments of nerve; it may also represent other technical considerations. The possibility that MMN exists in a purely axonal form that is responsive to immunomodulatory therapy was raised in a report of a series of patients with axonal electrophysiology in the clinical setting of MMN.\(^\text{20}\) The authors proposed this as a variant of classic MMN.

### Etiology

Early in its description, MMN was associated with elevated serum levels of IgM antibodies against ganglioside GM1. These findings, along with the response of MMN to immunomodulatory therapy, implicate an autoimmune etiology in its pathogenesis.\(^\text{21–23}\) There appears to be a link between the GM1 antibody and a motor predominant phenotype. The association with GM1 antibodies is seen not only in MMN but...
Table 3 Electrophysiological criteria for conduction block

<table>
<thead>
<tr>
<th>Definite*</th>
<th>Probable</th>
<th>or</th>
<th>Probable</th>
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<tr>
<td>Negative peak CMAP area reduction on proximal versus distal stimulation of at least 50% regardless of nerve segment length (median, ulnar, and peroneal).</td>
<td>Negative peak CMAP area reduction of at least 30% over a long segment (eg, wrist to elbow or elbow to axilla) of an upper limb nerve with an increase of proximal to distal negative peak CMAP duration of &gt;30%.</td>
<td>All core criteria (1,2)</td>
<td>All exclusion criteria (8–11)</td>
</tr>
<tr>
<td>Increase of proximal to distal negative peak CMAP duration of ≥30%.</td>
<td>Increase of proximal to distal negative peak CMAP duration of &gt;30%.</td>
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Abbreviations: CB, conduction block; CMAP, compound muscle action potential; MMN, multifocal motor neuropathy.

Table 4 Diagnostic criteria for definite or probable MMN

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<thead>
<tr>
<th>Definite (or Probable)</th>
<th>Probable (or Definite)</th>
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<tbody>
<tr>
<td>Clinical</td>
<td>Electrophysiologic</td>
</tr>
<tr>
<td>All core criteria (1,2)</td>
<td>Definite CB criteria, one nerve</td>
</tr>
<tr>
<td>All exclusion criteria (8–11)</td>
<td>Normal SNAP conduction in motor nerve(s) with CB</td>
</tr>
<tr>
<td>Probable CB criteria, two nerves</td>
<td>Probable CB criteria, one nerve</td>
</tr>
<tr>
<td>Normal SNAP conduction in motor nerve(s) with CB</td>
<td>Normal SNAP conduction in motor nerve(s) with CB</td>
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Abbreviations: CB, conduction block; CSF, cerebrospinal fluid; IgM, immunoglobulin M; IVIg, intravenous immunoglobulin; MMN, multifocal motor neuropathy; MRI, magnetic resonance imaging; SNAP, sensory nerve action potential.


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Also in other immune-mediated neuropathies; in particular, the pure motor variant of Guillain-Barré syndrome (GBS), acute motor axonal neuropathy (AMAN), and most patients were treated with IVIg, implicating an immune mechanism triggered by toxic exposure.

**Natural history**

MMN presents with weakness in the distribution of single peripheral nerves accounting for its asymmetry; because weakness derives from CB rather than axonal loss, muscle atrophy does not occur despite fairly pronounced symptoms. There is slow progression with time to a more confluent and segmental pattern that may be more difficult to distinguish from motor neuron disease. Chronicity is associated with axonal loss and, frequency of a human leukocyte antigen haplotype in MMN patients that is seen in patients with multiple sclerosis. First degree relatives of patients with MMN have a significantly increased incidence of other autoimmune disorders including Hashimoto’s thyroiditis, celiac disease, and type 1 diabetes. Taken together, these lines of evidence provide supporting evidence for an autoimmune etiology for MMN.

Interestingly, there are cases of toxic motor neuropathy with CB that are indistinguishable from MMN following treatment with infliximab; a human/murine immunoglobulin G1 antitumor necrosis factor-a (TNF) antibody. The mechanism by which the infliximab triggers the characteristic immune attack that occurs in MMN patients is unknown, but it differs from idiopathic MMN in that it is more rapidly progressive; some of the cases evolve rapidly into axonal loss.

In the cases described, there was inconsistent presence of GM1 antibodies and most patients were treated with IVIg to resolve the weakness. Although there are also reports of patients improving spontaneously after withdrawal of the TNF-inhibitor, most of the patients reported required IVIg, implicating an immune mechanism triggered by toxic exposure.
at that point, patients may develop muscle wasting, mimicking motor neuron disease. Longitudinal assessments of treated MMN patients were performed using a validated instrument, the Neuropathy Impairment Score (NIS, in a study of 46 patients with MMN-CB). Using the NIS (W) (referring to the portion of the scale measuring weakness), muscle power is assessed as normal (0) or complete paralysis (4) with intermediate grades; 1 representing a muscle that is deemed 25% weak by clinical strength testing, 2 as 50% weak, 3 as 75% weak, 3.25 as movement against gravity, 3.50 as movement with gravity eliminated, and 3.75 as muscle flicker. The NIS is a clinically based tool that has been used in epidemiologic and controlled clinical trials in diabetes and other neuropathies; the NIS (W) is comprised of a composite strength score that sums the weakness of head, trunk, and limb muscles. Using this metric, authors of the study of 46 MMN patients identified worsening of the median NIS (W) strength score over a period of 88 months. This was also demonstrated by a composite electrophysiological score in which median summed compound muscle action potential amplitudes unequivocally diminished over time. The 46 patients with MMN demonstrated progression of their disease at a rate of 1.3 points on the NIS (W) per year after initiating therapy as compared to 4.2 points per year prior to IVIg. These findings suggest a beneficial effect of therapy on the natural history of MMN. Despite the progressive nature of the weakness, none of the studied patients lost their job or their ability to comply with their professional duties as a result of the disease, attesting to a relatively modest effect of the disease on function as compared to some other inflammatory neuropathies. The number of years without IVIg therapy and the degree of axonal loss are identified as important determinants of disability and permanent weakness in MMN patients. Life expectancy in MMN is normal but conversely spontaneous remission has not been reported. Life-threatening respiratory weakness associated with hypventilation and respiratory insufficiency due to phrenic nerve involvement with diaphragmatic paresis has been described but is thought to be a rare manifestation of MMN.

As noted above, MMN with CB does not differ clinically from MMN without CB. In a comparative study of these two groups conducted over a 7-year period, the distribution of peripheral nerves involved, weakness as measured by a composite Medical Research Council (MRC) sum score, and ancillary symptoms of cramps and fasciculations were similar at initial assessment and at follow-up examinations. Subtle differences were described but these were not significant, and both groups responded equally well to IVIg. It is not clear if patients seropositive for anti-GM1 antibodies have a different clinical course than seronegative patients. Independent determinants for more severe weakness included axon loss and chronicity of disease; a greater proportion of patients with anti-GM1 antibodies had axon loss than those without antibodies. There have been reports of seropositive patients responding more robustly to IVIg than seronegative patients; however, other studies do not corroborate this finding. It is generally well accepted, however, that early recognition of MMN and initiation of therapy delays progression to axonal loss and more severe disability.

### Pathophysiology

One of the compelling immunologic features of MMN is the presence of serum IgM antibodies against the ganglioside GM1 in up to half of MMN patients. GM1 localizes to both the axolemma and myelin of peripheral nerves, being found in greatest abundance at the nodes of Ranvier and adjacent paranodes. Although ubiquitous, GM1 is found most abundantly in peripheral motor rather than sensory nerves, and it concentrates in cholesterol-enriched domains of the plasma membrane. These domains have a number of functions, the most relevant of which is paranodal stabilization and ion channel clustering. GM1 is thought to facilitate the maintenance of tight junctions through this paranodal stabilization as it also provides an anchor for potassium channels and concentrates sodium channels. These functions are important for action potential propagation and maintenance of conduction velocity in the peripheral nerves. Disruption of these functions would be expected to induce failure of conduction across paranodal regions; thus, the mechanism of CB may be a primary dysfunction of the axon at the paranodes.

### Diagnostic criteria for possible MMN

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<tr>
<th>Clinical</th>
<th>Possible or Possible</th>
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<tr>
<td>All core criteria (1,2)</td>
<td>All core criteria (1,2), one nerve</td>
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<tr>
<td>All exclusion criteria (8–11)</td>
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<td>Normal SNAP conduction in motor nerve(s) with CB</td>
<td>Definite or probable CB, one nerve</td>
</tr>
<tr>
<td>Laboratory/supportive</td>
<td>Supportive only (not necessary)</td>
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Treatment

Intravenous immunoglobulin

The treatment of choice continues to be IVIg in MMN with good response seen in as many as 80% of patients. The proposed mechanisms of action are myriad but generally thought to be related to the inhibition or consumption of complement depositing at nodes of Ranvier. Improvement in weakness after the initial dose is seen rapidly, usually in the first week, and especially early when pathology is predominantly CB. The efficacy of IVIg on muscle strength has been demonstrated by randomized double-blind placebo-controlled trials, the largest of which being comprised of a total of 44 patients. Dosing is generally initiated at a total of 2 g/kg administered intravenously over 2–5 days; although response may be rapid, it is seldom sustained and maintenance dosing is often required. Maintenance dosing is subject to institutional variability as there have been no studies establishing the optimal dose or interval for maintenance therapy. However, it is generally initiated at a lower dose with intervals of 1–6 weeks depending on clinical response. Some authors advocate waiting until clinical improvement has reached a plateau or patients begin to experience weakness before inititating maintenance therapy while others institute a specific regimen every two weeks with adjustment according to clinical response over time. In general, however, maintenance is 0.4 g/kg every week – 1–2 g/kg every 2–6 weeks depending on response and tolerance. This requires close monitoring over the period immediately following initial infusion in order to gauge strength and tolerance of IVIg. Renal function should be monitored regularly, and patients should be offered symptomatic therapy for the common flu-like reaction that can occur variably related to the specific infusion-infusion mix of immunoglobulin. Serious side effects to IVIg include an increased incidence of thrombotic events including stroke and myocardial infarction, and aseptic meningitis.

Although many MMN patients respond to IVIg therapy, the response is not universal or complete; clinical improvement has been associated with reductions in conduction block but not in reductions in GM1 antibody titers. Most patients become less responsive to IVIg over time, requiring higher doses or more frequent dosing intervals to maintain their responsiveness. This loss of responsiveness correlates with progressively lower compound muscle action potential amplitudes, supporting the idea that loss of responsiveness to IVIg occurs because of the development of axonal loss with progression of the disease.

Subcutaneous immunoglobulin

The subcutaneous form of immunoglobulin provides the advantage of greater convenience and possibly fewer side effects in patients requiring frequent infusions. Its efficacy has been demonstrated in both open-label studies and a single randomized single-blinded trial. The greatest drawback to this...
therapy is short-term and potential long-term effects of large subcutaneous volumes required for maintenance therapy.

**Steroids and plasma exchange**

In acute inflammatory demyelinating neuropathy, or Guillain-Barré syndrome, it is now well accepted that corticosteroids do not have a beneficial effect, unlike CIDP. Plasma exchange, however, has been proven to be equivalent in its efficacy compared to IVIg in the treatment of GBS. In MMN there is similarly little evidence for the efficacy of steroids, attesting to its overlap with GBS and AMAN. In a proportion of patients with MMN, steroids worsened weakness, sometimes dramatically. Surprisingly, plasma exchange is also ineffective in MMN and may result in clinical and electrophysiological worsening. This puzzling finding underscores the unique pathophysiology of MMN as an entity distinct from motor predominant GBS, or other variants of inflammatory neuropathy, and remains one of the interesting aspects of MMN yet to be elucidated. In contrast, patients with the clinical phenotype of MMN but with axonal features on electrodiagnostic testing rather than CB, referred to as multifocal acquired motor axonopathy, respond not only to IVIg but also to steroids. This implies a pathogenesis more similar to CIDP than to MMN and establishes MMN as distinctive.

**Other therapies**

Other agents such as cyclophosphamide, rituximab, mycophenolate mofetil, β-interferon, cyclosporine, azathioprine, and infliximab have been used for treatment of MMN; however, insufficient controlled trials support their use. Of these, there is most support for cyclophosphamide, even in patients unresponsive to IVIg. High dose intravenous cyclophosphamide has been shown to be effective in up to 50% of patients, but, interestingly, low dose cyclophosphamide does not demonstrate efficacy. The use of high-dose cyclophosphamide is limited by its toxicity in a non-life-threatening illness and the lack of randomized controlled trials demonstrating its effectiveness. Toxicities include bone marrow suppression, alopecia, hemorrhagic cystitis, delayed bladder cancer, teratogenicity, azoospermia, and infection risk.

Rituximab is a monoclonal antibody directed against CD20 surface antigen for peripheral B cell depletion. Treatment with rituximab has been shown to achieve clinical improvement even in patients with a declining or insufficient response to IVIg in five of seven reports and carries much less risk of toxicity compared with cyclophosphamide. The reports of its efficacy, however, are based on a small cumulative number of patients (total n=28) and are not consistent. The largest study (n=14) demonstrated a 13% improvement in strength (versus 3% in controls) over 1 year and a 23% strength improvement over 2 years. The next largest study (n=6), however, demonstrated no significant change in strength in IVIg responsive patients and did not allow for reduction in the IVIg dose. The dose is 375 mg/m² weekly for 2–4 weeks to achieve B cell depletion. Single booster doses at 375 mg/m² are administered as maintenance therapy if patients develop increased weakness.

Although single case reports exist regarding efficacy of other immunosuppressant agents, as noted above, these are small, and further randomized controlled trials are needed to gauge both efficacy and risk to patients with MMN.

**Patient focused perspectives**

MMN has major impacts on patient function, particularly in patients with generalized disease, but, interestingly, in one cohort, as many as 94% of patients remained employed. The focus of most studies to date has centered mainly on the motor effects of MMN. Not unexpectedly, the majority of impact on quality of life in patients with MMN is related to motor deficits. Impairment is mainly in the upper limb function but, with progression of the disease, there can be a more generalized impact. Cranial nerve impairment is rare. Somewhat surprisingly, sensory symptoms such as pain and dysesthesia are not uncommon. In some series, up to a quarter of patients present with neuropathic pain as a prominent feature, although, not surprisingly, pain was not an indicator of poor prognosis. Many patients will describe mild sensory disturbance, in agreement with studies that have shown sensory nerve pathology. Despite this, sensory nerve action potentials remain intact on electrodiagnostic assessments, attesting to the unique motor predominance of this disorder. Fatigue is a common but often overlooked feature of MMN. Interestingly, some patients are more disabled by the effects of fatigue than by the effects of the weakness. Electrophysiological assessment has demonstrated activity-dependent axonal failure, but whether symptoms of fatigue are directly related to motor deficits deserves further attention.

**Conclusion**

MMN is an important treatable cause of neuropathy. Early treatment is one of the most important factors in long term functional outcome. This makes recognition vital as MMN must be differentiated from other mimicking conditions for which immunomodulatory therapy is ineffective. Although good diagnostic criteria exist, an accurate diagnosis can be difficult to make due to significant overlap with other...
conditions and the rarity of MMN. Current treatment options, primarily IVIg, offer significant disease modulation in most patients, but these treatments have significant economic impact and, despite disease modification, patients typically develop gradual worsening with less robust response over time. Ongoing work is needed to enhance the current understanding of the underlying pathophysiological mechanism of MMN in order to develop more targeted and economical therapies that provide sustained treatment effect.

Disclosure

The authors report no conflicts of interest in this work.

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