Multifocal Motor Neuropathy

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Authors/faculty have nothing to disclose.

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CME Information
Product: JR03 - Multifocal Motor Neuropathy

Course Description
Multifocal motor neuropathy (MMN) is now a well-defined purely motor multineuropathy characterized by the presence of multifocal partial motor conduction blocks (CB), frequent association with anti-GM1 IgM antibodies, and usually a good response to high-dose intravenous immunoglobulin (IVIg) therapy. However, several issues remain to be clarified in the diagnosis, pathogenesis, and therapy of this condition including its nosological position and its relation to other chronic dysimmune neuropathies; the degree of CB necessary for the diagnosis of MMN; the existence of an axonal form of MMN; the pathophysiological basis of CB; the pathogenetic role of antiganglioside antibodies; the mechanism of action of IVIg treatments in MMN and the most effective regimen; and the treatment to be used in unresponsive patients. These issues are addressed in this review of the main clinical, electrophysiological, immunological, and therapeutic features of this neuropathy.

Intended Audience
This course is intended for Neurologists, Physiatrists, and others who practice neuromuscular, musculoskeletal, and electrodiagnostic medicine with the intent to improve the quality of medical care to patients with muscle and nerve disorders.

Learning Objectives
Upon conclusion of this program, participants should be able to:
1. identify the clinical and electrodiagnostic features of multifocal motor neuropathy with conduction block.
2. differentiate between multifocal motor neuropathy and other disorders with conduction block, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy and ischemic (vasculitic) neuropathy.
3. recognize serological and imaging findings that support or refute the diagnosis of multifocal motor neuropathy.
4. design an appropriate diagnostic and therapeutic strategy for patients with multifocal motor neuropathy.

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Duration/Completion Time: 2 hours

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ABSTRACT: Multifocal motor neuropathy (MMN) is now a well-defined purely motor multineuropathy characterized by the presence of multifocal partial motor conduction blocks (CB), frequent association with anti-GM1 IgM antibodies, and usually a good response to high-dose intravenous immunoglobulin (IVIg) therapy. However, several issues remain to be clarified in the diagnosis, pathogenesis, and therapy of this condition including its nosological position and its relation to other chronic dysimmune neuropathies; the degree of CB necessary for the diagnosis of MMN; the existence of an axonal form of MMN; the pathophysiological basis of CB; the pathogenetic role of antiganglioside antibodies; the mechanism of action of IVIg treatments in MMN and the most effective regimen; and the treatment to be used in unresponsive patients. These issues are addressed in this review of the main clinical, electrophysiological, immunological, and therapeutic features of this neuropathy.

MULTIFOCAL MOTOR NEUROPATHY: CURRENT CONCEPTS AND CONTROVERSIES

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The term multifocal motor neuropathy (MMN) was first introduced in the literature in 1988 by Pestronk et al.,126 who reported two patients with a progressive purely motor, predominantly distal, asymmetric neuropathy with multifocal persistent conduction blocks (CB) on motor but not sensory nerves. A few similar patients had been reported some years before by several other investigators,37,122,123,137 but Pestronk et al.126 first highlighted two of the main features of this neuropathy: its frequent association with anti-GM1 IgM antibodies and response to immune therapies. Between 1992 and 1993, a number of investigators started independently to report the effectiveness in these patients of high-dose intravenous immunoglobulin (IVIg) therapy, which is now considered the “gold standard” for treatment of MMN.156 More recently, diagnostic criteria for this neuropathy have been proposed by various groups or associations such as the American Association of Electrodagnostic Medicine (AAEM).7,117 Although several points, including the identification of MMN as a separate nosological entity, have now been clarified and extensively reviewed,20,83,104 there are still unsettled and controversial issues in the diagnosis, pathogenesis, and treatment of this neuropathy.

CLINICAL FEATURES

Clinical Presentation. MMN is a rare disorder probably affecting no more than 1 or 2 individuals per 100,000. It is more frequent in men than women, with an approximate ratio of 2.6:1.104 It usually affects young adults with a mean age of onset around 40 years, and almost 80% of reported patients present their first symptoms at between 20 and 50 years of age.104

MMN almost invariably presents with asymmetric weakness often related to the distribution of individ-
ual nerves. Arms are usually affected earlier and more severely than legs, with more than 80% of patients initially affected in forearm or hand muscles. Occasional patients may present with more proximal or even girdle weakness (approximately 5%) or with symptoms in their legs (10%).

Early in the disease it is not infrequent for patients to have a typical crossed distribution (one arm and contralateral leg). Cranial nerve involvement has been reported occasionally in the course of the disease, often limited to the XIIth cranial nerve, although in one patient ophthalmoplegia was the presenting symptom. A few patients have been reported with unilateral or bilateral phrenic nerve palsy leading to respiratory failure that, in at least one of them, was the presenting symptom. More than 50% of MMN patients report fasciculations and cramps outside the territory of the affected nerves, whereas myokymia is seldom reported. In most patients, tendon reflexes are reduced in a patchy way or diffusely, but may be normal or even brisk in 20–30% of instances, highlighting the similarity of MMN with motor neuron disease (MND). Localized muscle atrophy is usually mild or irrelevant in the early stage of the disease, but we have seen occasional patients with severe focal atrophy a few months after onset of symptoms. Atrophy often correlates with the electrophysiological finding of a marked reduction of distal compound muscle action potential (CMAP) amplitude or of inexcitable nerves and often predicts a poor response to therapy.

One of the main clinical features of MMN is the purely motor impairment. Sensory symptoms are, however, reported by some patients in the course of the disease, and minor sensory loss has been documented in 20% of patients. It is not clear what degree of sensory impairment is acceptable for the diagnosis of MMN as opposed to multifocal demyelinating (sensory and motor) neuropathy, which was reported by Lewis et al. and is also known as Lewis–Sumner syndrome.

Clinical Course and Natural History. After onset, the majority of patients have a slowly progressive course. Some patients, however, have a stepwise progression with rapid deteriorations followed by prolonged stabilization, or even spontaneous remission on occasion. Asymmetry and predominance of arm involvement may become less evident during the course of the disease but usually remain present even after several years. Although some patients have a spontaneously favorable functional long-term prognosis in the absence of effective therapy, most eventually become impaired in their daily life, usually by a reduced dexterity in manual activities or by fatigue. In our series, for instance, the proportion of patients with a disability score above 2 on the Rankin scale before starting effective therapy was 12% at 5 years, 25% at 10 years, and 60% at 15 years, although most could still walk independently. Only a few patients have been reported to have a fatal outcome after several years of disease, whereas in others death was related to concomitant diseases among them MND.

A few patients have been reported with an acute and monophasic presentation of weakness involving the four limbs, which was distinguished from Guillain–Barré syndrome (GBS) by the unusually protracted progression of weakness, purely motor multifasciculating, and normal stretch reflexes, and presence of persistent conduction block with normal motor and sensory conduction velocities (CV). In some patients the disease was preceded by Campylobacter jejuni infections or therapeutic injection of a mixture of bovine gangliosides. Even if the investigators originally considered this form an acute variant of MMN, it probably corresponds to the acute motor conduction block neuropathy that was recently proposed as a variant of GBS.

Clinical Diagnostic Criteria and Differential Diagnosis.

Diagnostic criteria for this neuropathy have been proposed by several groups. These criteria all share similar clinical features, which are well represented by the AAEM (Table 1): (1) Weakness without objective sensory loss in the distribution of two or more named nerves (and not simply asymmetric weakness). During the early stages of symmetric weakness, a history or physical finding of diffuse, symmetric weakness excludes multifocal motor neuropathy. (2) The absence of each of the following upper motor neuron signs: spastic tone, clonus, extensor plantar responses, and pseudobulbar palsy. Additional clinical criteria (no more than seven of eight affected limb regions, predominance of weakness in the upper limbs, decreased or absent tendon reflexes, and age of onset between 20 and 65 years) have also been proposed. These features were associated with a more frequent response to immunoglobulin therapy, but it was unclear how they influenced diagnostic accuracy, and the absence of some of these features is not uncommon in patients with otherwise typical MMN.

From the clinical point of view, MMN should be differentiated mainly from MND, particularly in patients with predominant or exclusive lower motor neuron impairment. MMN is usu-
Table 1. Criteria for the diagnosis of multifocal motor neuropathy.

<table>
<thead>
<tr>
<th>Criteria for definite multifocal motor neuropathy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weakness without objective sensory loss in the distribution of two or more named nerves. During the early stages of symptomatic weakness, the presence of diffuse, symmetric weakness excludes multifocal motor neuropathy.</td>
</tr>
<tr>
<td>2. Definite conduction block (see Table 3) is present in two or more nerves outside of common entrapment sites.*</td>
</tr>
<tr>
<td>3. Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block.</td>
</tr>
<tr>
<td>4. Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested. The absence of each of the following upper motor neuron signs: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria for probable multifocal motor neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weakness without objective sensory loss in the distribution of two or more named nerves. During the initial weeks of symptomatic weakness, the presence of diffuse, symmetric weakness excludes multifocal motor neuropathy.</td>
</tr>
<tr>
<td>2. The presence of either:</td>
</tr>
<tr>
<td>(a) Probable conduction block in two or more motor nerve segments that are not common entrapment sites, or</td>
</tr>
<tr>
<td>(b) Definite conduction block in one motor nerve segment and probable conduction block in a different motor nerve segment, neither of which segments are common entrapment sites.</td>
</tr>
<tr>
<td>3. Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block, when this segment is technically feasible for study (i.e., this is not required for segments proximal to axilla or popliteal fossa).</td>
</tr>
<tr>
<td>4. Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested. The absence of each of the following upper motor neuron signs: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.</td>
</tr>
</tbody>
</table>

*Median nerve at wrist; ulnar nerve at elbow or wrist; peroneal nerve at fibular head. |
Reproduced from Olney et al.117

Electrophysiological Features

Definition and Diagnosis of Partial Conduction Block in MMN. The essential electrodiagnostic finding of MMN is persistent, multifocal, partial CB (Fig. 1) of motor axons outside the usual sites of nerve compression.40,84,124 It is, however, important to underline that even if CB is the hallmark for diagnosis of MMN (and Lewis–Sumner syndrome), it is not specific for these diseases as it can also be found in several other pathological conditions involving the peripheral nervous system including: (1) other acquired demyelinating neuropathies such as CIDP2 and GBS,24 wherein, unlike MMN, CB is associated with other prominent electrophysiological abnormalities suggestive of demyelination; (2) acute compressive neuropathy or nerve entrapment, in which the CB is found at the usual sites of nerve compression or entrapment; and (3) nerve ischemia, in which it is usually transient and reversible.63,65 Hence, the presence of a CB should be always interpreted in the context of the clinical presentation and of other neurophysiological abnormalities.

CB has been defined as a reduction in the amplitude or area of the CMAP on proximal compared to distal stimulation, accompanied by no significant or only focal abnormal temporal dispersion (TD).24,78,150 Unfortunately, no uniformly accepted criteria exist for CB identification, as the reduction of CMAP amplitude or area required to be significant for CB has varied considerably among different studies (Table 2). A greater than 20% decline in peak-to-peak amplitude with a less than 15% change in negative-peak duration of the CMAP has been used as evidence of CB in GBS24 and CIDP.2 In these diseases, however, the diagnosis of a demyelinating neuropathy does not rely only on the presence of CB but also on other abnormalities suggestive of demy-
attrition, including reduced conduction velocities and increased minimal F-wave latencies and distal latencies. This is not the case for MMN in which the electrophysiological diagnosis relies only on CB, justifying the need for more specific criteria. Most studies on MMN have used a CMAP amplitude reduction of >50% with a duration increase <15% as indicative of proximal CB. The use of these criteria has likely been influenced by the study of Rhee et al. on computer analysis of the effect of “interphase cancellation” on motor unit action potentials (MUAPs). This phenomenon is caused by the overlap and cancellation of the positive and negative components of different MUAPs that may occur in chronic axonal loss as a consequence of the increased polyphasia and reduced number of MUAPs, or in chronic demyelination due to the markedly increased range of conduction velocities. It may result in a disproportionate proximal CMAP amplitude reduction mimicking a true CB. Through a simulation of phase interactions of individual MUAPs, these investigators showed that the reduction of the CMAP area caused by interphase cancellation may reach 50% and that greater CMAP reduction may therefore be caused by some degree of CB. It remains unclear whether this model also applies in vivo to human diseases. In addition, substantial differences in the degree of CMAP amplitude reduction and duration increase on proximal stimulation have been reported among various nerves in normal controls, so that different criteria may be required for the diagnosis of CB in arm and leg nerves.

Consensus criteria for the diagnosis of CB have been proposed recently by the AAEM (Table 3). In this consensus, the proponents emphasized the need to ensure supramaximal stimulation of nerves, particularly in obese individuals or in the presence of limb edema. They also advised not to apply these criteria in the context of severe axonal loss, quantified as a distal CMAP amplitude of less than 20% of the lower normal limit. The criteria proposed for both definite CB and probable partial CB were intentionally restrictive to avoid confusion between real CB and CMAP amplitude reduction due to interphase cancellation, and varied with different nerves, being more restrictive for the radial, peroneal, and tibial nerves than for the ulnar and median nerves. The use of these stringent criteria may, however, lead to the underdiagnosis of MMN, a potentially treatable neuropathy. Although CB is considered to be persistent, it is a dynamic entity that changes over time, and a CMAP reduction of >50% may be preceded by a smaller decrease. This was exemplified by one of our patients who initially presented with a 24% reduction of proximal vs. distal CMAP amplitude without temporal dispersion (TD) in the right ulnar and median nerves innervating weak muscles, which, 2 years later, as the patient became more severely affected, increased to 70% and 88%, respectively. However, minor degrees of CB may be found in nerves to muscles with normal strength and should be therefore interpreted cautiously. In some nerves, CB can be diagnosed, even if it does not attain the aforementioned level, by stimulation at several sites as close...
as 2–2.5 cm apart ("inching" technique). Using this technique, the localization of an abrupt, focal reduction of CMAP amplitude to a relatively small region of nerve (Fig. 1) may allow the distinction between focal CB and the pseudo-CB sometimes observed in chronic axonal loss and characterized by a gradual reduction in CMAP amplitude with increasing separation of stimulation sites.

CB may be present in several different nerves and in several segments (Fig. 1) along the course of the same nerve. Motor nerve stimulation up to the axilla fails to detect CB occurring in the most proximal segments. The absence of an F-wave, although suggestive, cannot be relied upon as secure evidence of proximal CB. Recently, magnetic or transcutaneous cervical stimulation was found useful in the localization of proximal CB in patients suspected of having MMN. Even if this technique is useful when no CB can be identified by more distal stimulation, it should be interpreted with caution due to the difficulty in producing supramaximal stimulation of demyelinated nerve roots, especially by magnetic stimulation. CB distal to the most distal site of stimulation is suggested by a low-amplitude CMAP recorded by a weak, but not wasted, muscle. Weakness of a muscle supplied by a nerve with no evident motor CB raises the possibility of anomalous innervation of the affected muscle by a contiguous nerve with CB.

### Table 2. Reported diagnostic criteria for partial conduction block (CB) in patients with multifocal motor neuropathy.

<table>
<thead>
<tr>
<th>Reference no.</th>
<th>No. of patients</th>
<th>Reduction of proximal to distal CMAP</th>
<th>Increase of proximal to distal CMAP duration (maximal TD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>138</td>
<td>1</td>
<td>&gt;20%</td>
<td>15%</td>
</tr>
<tr>
<td>165</td>
<td>1</td>
<td>&gt;20%</td>
<td>15%</td>
</tr>
<tr>
<td>57</td>
<td>13</td>
<td>&gt;30%</td>
<td>15%</td>
</tr>
<tr>
<td>87</td>
<td>10</td>
<td>&gt;50%</td>
<td>30% (&gt;30% CB + TD)</td>
</tr>
<tr>
<td>68, 69</td>
<td>3</td>
<td>&gt;40%</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>106</td>
<td>5</td>
<td>&gt;15% median, &gt;20% ulnar</td>
<td>15%</td>
</tr>
<tr>
<td>9</td>
<td>5</td>
<td>&gt;50%</td>
<td>15%</td>
</tr>
<tr>
<td>51</td>
<td>4</td>
<td>&gt;40%</td>
<td>15%</td>
</tr>
<tr>
<td>21, 90</td>
<td>24</td>
<td>&gt;50% proximal to axilla</td>
<td>&gt;50% proximal to axilla 30%</td>
</tr>
<tr>
<td>136</td>
<td>8</td>
<td>&gt;50%</td>
<td>&gt;30% distal to axilla 30%</td>
</tr>
<tr>
<td>162</td>
<td>6</td>
<td>&gt;50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>66</td>
<td>8</td>
<td>&gt;50%</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>74</td>
<td>16 (5 no CB)</td>
<td>&gt;50%</td>
<td>&gt;50% 30% (&gt;30% possible CB)</td>
</tr>
<tr>
<td>171</td>
<td>9</td>
<td>Definite: &gt;50%; possible: &gt;30% arm, 40% leg</td>
<td>15%</td>
</tr>
<tr>
<td>118</td>
<td>5 (no CB)</td>
<td>&gt;50%</td>
<td>15%</td>
</tr>
<tr>
<td>164</td>
<td>7 (5)</td>
<td>&gt;50%</td>
<td>15%</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>&gt;40%</td>
<td>15%</td>
</tr>
<tr>
<td>16</td>
<td>9</td>
<td>&gt;50%</td>
<td>15%</td>
</tr>
<tr>
<td>101</td>
<td>12</td>
<td>&gt;50%</td>
<td>15%</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>See Table 3</td>
<td></td>
</tr>
<tr>
<td>148</td>
<td>46</td>
<td>Definite: &gt;20% within 10 cm or &gt;80% over 10 cm (except tibial); probable: 50–79% within 10 cm (except tibial) or &gt;75% for tibial; possible: 30–49% within 10 cm (except tibial) or 50–74% for tibial</td>
<td>15%</td>
</tr>
<tr>
<td>56</td>
<td>16</td>
<td>&gt;30%</td>
<td>&gt;30%</td>
</tr>
<tr>
<td>166</td>
<td>37</td>
<td>Definite: 50% area in long segment or 30% amplitude over 2.5 cm; probable: 30% amplitude in an arm nerve (distal CMAP must be &gt;1 mV)</td>
<td>15%</td>
</tr>
<tr>
<td>75</td>
<td>9 (no CB)</td>
<td>30% in amplitude or area across any standard segment</td>
<td>30%</td>
</tr>
<tr>
<td>107*</td>
<td>23 (3 no CB)</td>
<td>30% arm, 40% leg or 40% arm and 50% leg or 50% arm and 60% leg</td>
<td>30%</td>
</tr>
</tbody>
</table>

*Criteria for possible CB.
MMN without Partial CB: An Unsettled Issue. Some investigators have questioned whether the presence of CB should be considered a mandatory criterion for the diagnosis of MMN for patients with an otherwise typical clinical presentation. In some of these patients without CB, a lesser degree of amplitude reduction than required by the current diagnostic criteria was present, whereas in others no evidence of CB could be found, although some other minor features of demyelination were often present. More recently, Katz et al. introduced the term “axonal MMN” to describe nine patients with a clinically typical presentation of MMN who had neither CB nor other features of demyelination. Some of these patients also had anti-GM1 antibodies and improved with IVIg therapy. However, it was unclear whether these patients ever or no longer had CB. We and others have observed, for instance, patients in whom typical CB may decrease or even disappear in some nerves after several years of the disease because of a progressive reduction in distal CMAP amplitude. This could reflect either secondary axonal degeneration or the appearance of unrecognized, very distal CB. This may occur early in the disease, as was probably the case in one of our patients presenting with a 1-year history of weakness in the territory of the left ulnar nerve, resulting in severe muscle atrophy, followed by more recent involvement of muscles innervated by the left median nerve. At our first evaluation, motor nerve conduction studies disclosed a markedly reduced distal and proximal CMAP amplitude (0.5 mV) in the initially affected left ulnar nerve, and a 45% CB with minimal TD in the more recently affected left median nerve (Fig. 2). This example clarifies how the same pathological process may express itself in different nerves with electrodiagnostic features consistent with either CB or axonal degeneration. In any case, we prefer to consider CB an essential electrodiagnostic marker of MMN, although for this diagnosis we accept the less restrictive criteria of possible CB (Table 2), defined as a 10% lesser degree of CMAP reduction than required by the AAEM for probable CB. This approach is appropriate because patients with the typical clinical features of MMN and a possible CB had the same clinical and immunological

Table 3. Proposed criteria for partial conduction block.

<table>
<thead>
<tr>
<th>Nerve segment (proximal/distal stimulation sites)</th>
<th>Definite partial conduction block</th>
<th>Probable partial conduction block</th>
<th>Probable partial conduction block</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amplitude reduction (%)</td>
<td>Area reduction (%)</td>
<td>Amplitude reduction (%)</td>
</tr>
<tr>
<td>Median</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm (elbow/wrist)</td>
<td>&gt;50</td>
<td>&gt;40</td>
<td>40–49</td>
</tr>
<tr>
<td>Arm (axilla/ELbow)</td>
<td>&gt;50</td>
<td>&gt;40</td>
<td>40–49</td>
</tr>
<tr>
<td>Proximal (EP/axilla)</td>
<td>Not accepted*</td>
<td>Not accepted*</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Ulnar</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm (below elbow/wrist)</td>
<td>&gt;50</td>
<td>&gt;40</td>
<td>40–49</td>
</tr>
<tr>
<td>Across elbow (above/below)</td>
<td>&gt;50</td>
<td>&gt;40</td>
<td>40–49</td>
</tr>
<tr>
<td>Arm (axilla/above elbow)</td>
<td>&gt;50</td>
<td>&gt;40</td>
<td>40–49</td>
</tr>
<tr>
<td>Proximal (EP/axilla)</td>
<td>Not accepted*</td>
<td>Not accepted*</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Radial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forearm (elbow/distal forearm)</td>
<td>Not accepted*</td>
<td>Not accepted*</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Arm (axilla/above elbow)</td>
<td>Not accepted*</td>
<td>Not accepted*</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Proximal (EP/axilla)</td>
<td>Not accepted*</td>
<td>Not accepted*</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Peroneal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg (below fibular/ankle)</td>
<td>&gt;60</td>
<td>&gt;50</td>
<td>50–59</td>
</tr>
<tr>
<td>Across fibular head (above/below)</td>
<td>&gt;50</td>
<td>&gt;40</td>
<td>40–49</td>
</tr>
<tr>
<td>Thigh (SN/above fibular)</td>
<td>Not accepted*</td>
<td>Not accepted*</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Tibial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg (knee/ankle)</td>
<td>&gt;60</td>
<td>&gt;50</td>
<td>50–59</td>
</tr>
<tr>
<td>Thigh (SN/knee)</td>
<td>Not accepted*</td>
<td>Not accepted*</td>
<td>&gt;50</td>
</tr>
</tbody>
</table>

Reproduced from the American Association of Electrodiagnostic Medicine. * Reprinted with the permission from reference 1, which can also be consulted for the reason that definite partial conduction block is not accepted for these segments.
features and response to therapy as those with probable or definite CB according to AAEM criteria.106

Other Electrodiagnostic Findings in MMN. Nerve conduction velocity across the small regions with CB is usually markedly reduced, suggesting demyelination, although it may be normal or reduced only slightly.6 Motor nerve conduction studies may also display other, usually mild, features of demyelination, such as prolonged distal CMAP latencies and prolonged or absent F waves.40,74,84,106 All these markers help in confirming the demyelinating process in MMN and support the hypothesis that CB in MMN is probably only the most striking feature of a concomitant, although less intense, diffuse involvement of motor fibers.

Sensory nerve conduction studies are usually normal or only minimally affected in MMN, even in the region of mixed peripheral nerves where motor CB has been detected.106 A possible concomitant proximal sensory impairment has been revealed in some patients with MMN by somatosensory evoked potentials,160 although this finding has not yet been confirmed.

Needle electromyography (EMG) shows reduced MUAP recruitment in clinically weak muscles with preserved bulk; fasciculation potentials may be detected. Fibrillation potentials and positive sharp waves may occur in the presence of secondary axonal loss, when muscle wasting may also be clinically evident.6 Needle EMG abnormalities may therefore help to determine whether a reduction of distal CMAP amplitude is caused by axonal loss or distal conduction block.27

LABORATORY FINDINGS

Routine Laboratory Studies. Routine hematological and biochemical laboratory findings are usually normal in MMN apart from slightly to moderately increased serum creatine kinase activity, observed in up to 67% of patients.39,166 Because a similar increase is not infrequent in patients with MND, this does not help in distinguishing MMN from MND. Similarly unhelpful in this distinction is cerebrospinal fluid (CSF) examination, which has shown slightly increased protein levels (usually up to 80 mg/dl) in 33% of MMN patients, with normal CSF findings in the others, including absence of oligoclonal bands.104,148,166 This finding may help, however, in distinguishing MMN from CIDP, in which CSF proteins are often markedly increased. Serum protein electrophoresis may occasionally reveal the presence of a monoclonal or polyclonal gammopathy, mostly of the IgM isotype (2 of 23 in our series)107 that is only occasionally related to lymphoma.108

Antiganglioside Antibodies. The most typical laboratory findings in MMN is the presence of increased levels of serum IgM antibodies to the ganglioside GM1,126 and, to a lesser extent, other glycolipids, including asialo-GM1, GD1a, or GM2.36,84,128,148,179 There are, however, considerable differences in the prevalence of these antibodies, particularly anti-GM1
IgM, in MMN, with figures ranging in different series from 30% to 80%, although usually between 40% and 50%. These discrepancies have been variably attributed to technical differences in the procedures adopted by different laboratories or in the often unclear diagnostic criteria adopted for MMN or in the controls used to establish normal reference values. Still, the reasons for such a wide variation in the percentage of abnormal findings remains to be elucidated.

The issue of the diagnostic relevance of these antibodies is further complicated by the fact that these antibodies are not specific for MMN as they have also been reported, although less frequently, in other dysimmune neuropathies, in approximately 10% of patients with MND with exclusive signs of lower motor neuron impairment and no CB, and in 5% of those with amyotrophic lateral sclerosis (ALS). Several attempts have been made, with conflicting results, to standardize the anti-GM1 assay used among different laboratories, or to improve the sensitivity and specificity for MMN of these antibodies using more sophisticated enzyme-linked immunosassay (ELISA) techniques or agglutination immunossays. However, there remains no consensus on the most effective and reproducible ELISA procedure and, even more importantly, on the diagnostic relevance of this assay in the diagnosis of MMN. In the aforementioned diagnostic criteria of the AAEM, for instance, the presence of these antibodies is not even included as possibly supportive laboratory criteria for this diagnosis, and in those proposed by others it was less relevant than normal or slightly increased levels of CSF protein. However, two large studies, including a meta-analysis on the diagnostic value of anti-GM1 IgM antibodies, indicated that their presence can help to distinguish MMN from MND. This assay therefore may be helpful for patients in whom a definitive diagnosis cannot be established after clinical and electrophysiological evaluation, even though the absence of these antibodies does not exclude the diagnosis of MMN.

### PATHOLOGICAL FEATURES

Nerve biopsy is seldom if ever useful in the diagnosis of MMN because it is routinely performed on the sural or other sensory nerves, which are typically clinically and electrophysiologically normal in MMN. This may explain why pathological studies have either shown normal findings or mild axonal degeneration or demyelination, or both. Even ultrastructural studies on these nerves may reveal only mild pathological abnormalities consistent with a demyelinating process. Sural nerve biopsy is therefore not indicated in the diagnosis of MMN unless other diagnoses, such as CIDP, Lewis–Sumner syndrome, or nerve vasculitis, are also suspected. Motor nerve biopsy has been proposed to differentiate motor neuropathy, including MMN, from motor neuron disease, as it showed in the former a significantly higher density of regenerative small myelinated fibers associated in some patients with evidence of demyelination with thinly myelinated axons and small onion-bulb formations. This procedure is available in only a few centers and is definitely more invasive than sensory nerve biopsy. In two patients in whom a motor or mixed nerve biopsy was performed adjacent to the site of CB, pathological studies showed demyelination with onion bulbs without inflammatory infiltrates. The presence of demyelination at the level of the motor CB in the brachial plexus was also observed at autopsy in a patient in whom MMN was associated with an otherwise clinically typical and ultimately fatal MND unresponsive to immune therapies, and with the pathological features of MND in the spinal cord. These pathological findings at the site of CB were not confirmed in a systematic study of seven patients with typical MMN in whom fascicular nerve biopsy at the site of the CB disclosed only multifocal fiber degeneration and loss and clusters of regenerating fibers without obvious sign of demyelination. In two patients with predominantly motor neuropathy with multifocal CB, the pathological features of CIDP were reported with widespread segmental demyelination, and generally prominent inflammatory cell infiltrates in the motor cranial nerves and motor roots or in the brachial plexus, where large onion bulbs were also observed. However, the markedly reduced motor conduction velocities observed in both patients, together with the diffuse although asymmetric motor impairment in one and the remarkable vibratory impairment with prominent sensory conduction abnormalities in the other, were more reminiscent of CIDP or Lewis–Sumner syndrome than of MMN.

### MAGNETIC RESONANCE IMAGING

Magnetic resonance (MR) imaging studies of the forearm or brachial plexus reportedly show, in some patients with MMN, an asymmetrically increased signal intensity in T2-weighted images or in T1-weighted images after gadolinium enhancement, often colocalizing with CB, and thus confirming the focality of the pathological process in MMN. Even if
these findings do not clarify the nature of the underlying pathological process except for demonstrating the presence of an impaired blood–nerve barrier, they indicate that this noninvasive technique may have potential for diagnostic usefulness in MMN, particularly with regard to exploration of proximal nerve segments.

**PATHOPHYSIOLOGY OF MMN**

**Axonal Excitability Studies.** Although the pathological basis of persistent partial CB is believed to be focal demyelination, with a consequent lack of conduction of the nervous impulse through a “nude” axon, this hypothesis has been confirmed only rarely in MMN by morphological studies, so that the pathophysiological mechanisms underlying MMN remain largely unclear.

In recent years, special neurophysiological techniques for assessing axonal excitability noninvasively in humans have expanded understanding of peripheral nervous system pathophysiology. Although an exhaustive description is beyond the scope of this review and can be found elsewhere, these approaches indirectly estimate the ionic mechanisms involved in impulse conduction along human axons. They have also prompted interesting hypotheses concerning the differential functional involvement of specific regions in the axo-myelinic complex and morphological–functional correlations of nervous impulse conduction along peripheral myelinated fibers. Although relatively simple, the currently available techniques for studying axonal excitability are still essentially limited to research applications and their results should be interpreted with caution because they derive from an indirect approach. During axonal excitability testing, human nerve fibers are stimulated through the skin, subcutaneous tissues, and endoneurial space, and motor axon properties are estimated indirectly from changes in the muscle evoked responses. Hence, there is the need to take into account the resistive-capacitative properties of non-nerve tissue and the possible bias introduced by the complex dynamics of the motor endplate.

**Axonal Excitability Outside the Conduction Block.** Published data on axonal excitability in patients with MMN are rare, occasionally contradictory among the various groups, and often derive from small study samples, mainly due to the rarity of this condition. Yokota et al. examined two patients with MMN and found in both an increased motor axonal threshold also outside the CB. They hypothesized either impaired remyelination or a block of Na⁺ channels. Cappelen-Smith et al. measured axonal excitability after median nerve stimulation outside the site of the CB in three patients with MMN, and found that supernormality was comparable to healthy controls, but the strength–duration curve time-constant (chronaxie) was prolonged. In a later study, Kiernan et al. measured multiple axonal excitability variables in the median nerve of six patients with MMN. They stimulated the median nerve in the forearm just distal to a well-identified CB and recorded the CMAP from the abductor pollicis brevis muscle. Although the strength–duration curve time-constant almost matched control values, the rheobase, threshold, stimulus–response slope, and superexcitability were significantly abnormal. Because depolarizing current normalized these indices of axonal excitability, they suggested that motor axons distal to the CB are hyperpolarized in MMN, whereas motor axons at the site of the CB are depolarized. They also hypothesized that the distal hyperpolarization might compensate for proximal depolarization with an intraaxonal Na⁺ flux going away from the block. In addition, the abnormal increase in Na⁺ influx at the site of the block might eventually lead to axonal degeneration through an intraaxonal increase in Ca²⁺.

We also assessed the strength–duration curve and its descriptors in 22 ulnar nerves from patients with MMN and found that the strength–duration curve time-constant was abnormally short. In addition, the axonal threshold and rheobasic current were abnormally increased and abnormalities were at least partly reversed soon after IVIg treatment (Fig. 3). These findings suggest that axons are hyperpolarized and that nodal resting Na⁺ conductances are impaired in MMN, even outside the site of the CB. Yet, remarkably, several ulnar nerves had no documented conduction block up to the axilla.

In conclusion, despite some differences, these studies agree in reporting motor axonal hyperpolarization outside the site of the CB, probably arising from impaired Na⁺ conductances and involving clinically unaffected nerves as well. Determining how far these subtle axonal abnormalities extend is important because hyperpolarization could be either compensatory to a hypothetical focal depolarization at the site of the CB, or simply a primary membrane abnormality. Although the origin of hyperpolarization is still unclear, the frequent observation of diffuse hyporeflexia or areflexia and cramps or fasciculation outside the territory innervated by nerves with CB in patients with MMN argue in favor of widespread axonal involvement. Furthermore, it is unlikely that compensatory hyperpolarization ex-
tends for more than a few centimeters outside the CB.

Finally, one may wonder whether the observed changes in motor axonal excitability are specific to MMN or are also common to other disorders involving the motor axons. When we compared axonal excitability in patients with MMN and MND, we found that the latter group showed a distinctive profile of abnormalities. Conversely, patients with CIDP have a pattern of rheobasic and strength–duration abnormalities, qualitatively resembling that of patients with MMN. The similar pattern of abnormalities in CIDP and the different pattern in MND suggest that, in MMN, abnormal ionic conductances arise from an abnormal axomyelinic interaction, far more complex than a specific conductance abnormality linked primarily to a pure axonal dysfunction.

**Axonal Excitability at the Site of the Conduction Block.**

Assessing motor nerve abnormalities at the site of the CB is difficult for two reasons: first, the CB site is almost inexcitable by an electrical shock (i.e., the threshold is very high); and second, the effects of CB are indirectly estimated from changes in the CMAP elicited in a muscle several centimeters distal to the site of the CB. These findings imply that the conduction abnormalities in MMN might arise also from other pathogenetic factors involving the axonal membrane outside the block. Despite these limitations, studies involving stimulation outside the CB have been used for indirectly studying the membrane properties at the site of the block.

In five patients with MMN, Kaji et al. studied the effects of voluntary muscle activation on the degree of CB and on the force developed by muscle twitch. Because motor activity worsened the CB, they concluded that CB accounts for the pronounced muscle fatigue seen in patients with MMN and that voluntary contraction could represent a reliable method (i.e., a sort of stress test) for improving the detection of CB in routine electrodiagnostic examinations.

A number of indirect observations, often made in only a few nerves, have been used to argue that the axonal membrane is depolarized at the site of the CB, and that focal depolarization leads to CB (i.e., a depolarizing block). When the rest of the membrane above and below the CB is hyperpolarized, the hyperpolarization outside the block presumably compensates for the supposed depolarization at the site of CB. Even if this issue is crucial for the pathophysiology of MMN, an ultimate proof for axonal depolarization at the site of the block is still lacking, because, as mentioned earlier, both the threshold and the rheobasic current (personal observation) are markedly increased at the site of the block, not allowing reliable local assessment of membrane properties. An important issue arguing against the hypothesis of focal depolarization arises from the observation that activity-dependent hyperpolarization worsens the CB in MMN, whereas it should improve it if the membrane at the site of the CB is depolarized. CB could simply reflect an enhancement of the axonal hyperpolarization present outside the block with a complete inactivation of resting Na+ conductances accounting for the increased rheobase and threshold at the site of the CB. Focal hyperpolarization would thus explain why a further activity-dependent polarization worsens, rather than improves, the CB.

In conclusion, in MMN motor axons are hyperpolarized, probably owing to a diffuse, but variable impairment of nodal resting Na+ conductances. The degree of CB in MMN is proportional to the recent history of impulse conduction along the motor axon: sustained voluntary activity can transiently worsen CB in MMN by eliciting hyperpolarization. A further focal increase of axonal hyperpolarization, and possibly of the other subtle physiological abnormalities observed outside the CB, might help to explain the CB in MMN. Although the pathophysiological mechanisms underlying CB are still largely unknown and probably multiple, even in the same patient, the block can be viewed as the “tip of the iceberg” of axo-myelinic abnormalities in MMN.

![FIGURE 3. Motor axonal excitability in MMN. The time-constant of the strength–duration curve \(t_{SD}\) (left panel) and the rheobasic current for eliciting a 50% CMAP \(rh_{50\%}\) (right panel). Columns are means, error bars are SD. Cross-hatched columns are control nerves \((n = 22)\), open columns are non–recently treated nerves \((n = 9)\), and solid columns are recently treated nerves \((n = 9)\). Whereas in recently treated nerves only the rheobasic current was significantly abnormal, in non–recently treated nerves both the \(t_{SD}\) and the \(rh_{50\%}\) differed significantly from control nerves. Hence, IVIg treatment seems to correct motor axonal hyperpolarization and nodal abnormalities in MMN (from Priori et al.134).](image-url)
IMMUNOPATHOGENESIS

The frequent association of MMN with antiglycolipid antibodies, and the improvement observed in most patients after IVIg or other immune therapies support the widespread opinion that the disease is immunologically mediated and possibly caused by binding of anti-GM1 antibodies to neural structures. Several pieces of data support this hypothesis but some argue against it. As already mentioned, anti-GM1 IgM antibodies are significantly associated with MMN and reportedly decrease during clinical improvement, particularly after therapy with cyclophosphamide. There is, however, a consistent proportion of patients in most series (50%) not bearing these antibodies, making it unclear what causes the disease in such patients. Most of these patients also respond to immune therapies in a way similar to GM1-positive patients. In addition, response to IVIg does not correlate with a consistent decrease in antibody titers. If this lack of correlation seems to exclude the possibility that IVIg interferes with antibody synthesis or binding to GM1 in the in vitro system used to test them, it cannot exclude an effect on their binding to the nerve in vivo.

The presence of high titers of anti-GM1 IgM in at least 5–10% of patients with MND or other dysimmune neuropathies, and the absence of a definite correlation between the fine specificity or reactivity with neural structures of anti-GM1 IgM and the different clinical syndromes, also make it unclear how similar antibodies cause different diseases. GM1 may be an ideal target for an immune response causing CB, being highly represented in the peripheral nervous system where it is localized at the level of the nodes of Ranvier, compact or outer myelin, and motor endplate at the neuromuscular junction. The higher concentration of GM1 (and GD1a) in motor than in sensory nerve myelin is also consistent with the selective motor impairment in MMN. IgM deposits have been detected at the level of the nodes of Ranvier in the sural nerve of a patient with MND, multifocal CB, and high titers of anti-GM1 IgM antibodies, although this finding has not been confirmed in other patients and, most importantly, in motor nerves. The concomitant presence of GM1 in sensory structures and spinal motor neuron and gray matter leaves it unclear why these structures are not also affected in MMN. Differences in the distribution or expression of gangliosides or in their ceramide composition in motor and sensory fibers, or in the different susceptibility to nerve injury or repair capability of motor and sensory fibers, may theoretically explain the selective motor impairment in MMN; however, the reason for this discrepancy remains unknown, as does the almost invariable predominant upper-limb involvement in these patients.

Similarly inconclusive are the results of experimental studies both in vitro and in vivo directed at testing the capacity of these antibodies to cause CB. Intraneural injection or exposure to sera from patients with high anti-GM1 antibodies and MMN, but not with MND, was able to induce focal CB in vivo and in vitro. The latter results were not confirmed, however, using purified anti-GM1 antibodies, even when binding of the antibody to the nodes of Ranvier and consequent complement activation was demonstrated. In another study, a similar blocking effect on mouse distal motor nerve conduction was experimentally induced in vitro by sera from MMN patients with and without high anti-GM1 antibodies, suggesting that sera from patients with MMN may indeed contain a soluble factor able to affect neural transmission in vitro, although the role of anti-GM1 antibody in this blocking effect remains to be proven. A different mechanism for anti-GM1 antibodies was suggested by the selective capacity of mouse anti-GM1 antibodies to affect in vitro the permeability of the blood–nerve barrier, possibly by interfering with the recognition or signaling modulation properties of glycosphingolipids. This possibility may be supported by the more pronounced disruption of the blood–nerve barrier observed in the sural nerve of patients with antibodies vs. those without. It is unclear whether this mechanism may be also postulated in MMN, because the degree of gadolinium enhancement observed by MR, which is a marker of blood–nerve barrier damage, did not seem to correlate with the presence of these antibodies.

If the possible role of anti-GM1 antibodies in the pathogenesis of MMN remains to be clarified, it is even less clear what causes the production of these antibodies in MMN. In GBS, high anti-GM1 IgG antibodies have been significantly associated with an antecedent infection by particular strains of the enteropathogenic bacteria Campylobacter jejuni, which has a lipopolysaccharide that is responsible for the induction of antiganglioside antibodies by a mechanism of molecular mimicry. A similar association has been raised in some patients who were believed to develop MMN and high titers of anti-GM1 antibodies after C. jejuni enteritis even if the acute, monophasic, and symmetrical presentation in most patients was more consistent with an
consistent improvement of MMN after IVIg, and by the induction in vivo of these antibodies by the lipopolysaccharide of *C. jejuni*. Only 1 of our 20 patients with MMN had high anti-*C. jejuni* antibodies, however, making it unlikely that *C. jejuni* is responsible for the disease in most patients.

In conclusion, even if all available data are consistent with the hypothesis that MMN is an immune-mediated neuropathy, the effector mechanisms and the antigenic targets of this immune response still remain to be fully elucidated.

**THERAPY OF MMN**

Since the original report by Pestronk et al. on the response to intravenous cyclophosphamide in two patients with MMN, a number of immune therapies have been used on the assumption that MMN is an immune-mediated disease.

**Steroids and Plasma Exchange.** The vast majority of patients with MMN fail to respond to steroids, even when given in high doses intravenously; indeed, almost 20% have been reported to worsen, even dramatically, when on this therapy. For instance, we had a patient with recurrent but consistent worsening during the spring, which disappeared after he stopped using steroid-containing nasal spray for allergic asthma.

Plasma exchange, immunoabsorption, and CSF filtration are similarly ineffective in most reported patients with MMN and marginally effective in a few of them. In occasional patients, plasma exchange was rapidly followed by severe clinical worsening and by the appearance of CB in previously clinically unaffected motor nerves. These findings highlight the fact that the distinction between MMN and CIDP or Lewis–Sumner syndrome is not purely of theoretical interest, because steroids and plasma exchange, which are usually effective in CIDP and Lewis–Sumner syndrome, are ineffective or even dangerous in MMN.

**IVIg.** After initial reports on the frequent and consistent improvement of MMN after IVIg, this therapy has been used widely in MMN. Almost 80% of patients with MMN respond to IVIg, which has an efficacy that has been now confirmed in four randomized, double-blind, placebo-controlled trials on a total of 46 patients. Response to treatment was more frequent in patients with than in those without anti-GM1 antibodies, although this has not been confirmed by all investigators. IVIg induces a rapid improvement, which often occurs within 1 week of treatment, and is usually more evident in recently affected limb regions with minor or no effect on stabilized deficits. This correlates with the fact that, although responding patients more frequently have definite or probable CB, nonresponding patients, at least in our experience, usually have a longer disease duration before therapy, increased severity of the disease, and more frequent signs of axonal degeneration that may have caused the disappearance of the CB. Clinical improvement is variably associated with reduction or resolution of motor CB in some but not all of the nerves involved; yet does not consistently correlate with a reduction of antiganglioside antibody titers. Only a few patients have persistent improvement after a single or a few courses of therapy; in the vast majority, the effect of IVIg only lasts for a few weeks and has to be maintained by periodic IVIg infusions for long periods, if not indefinitely.

IVIg therapy in MMN patients is usually started at the standard dose of 2 g/kg on 2–5 consecutive days. This is followed by a variable regimen of maintenance infusions ranging from 0.4 g/kg once a week to 1–2 g/kg on 2–5 days monthly or at the time of or immediately before clinical worsening, which usually occurs after 3–8 weeks. Most patients become progressively less responsive to IVIg after a few years or even a few months of treatment, however, and require an increasing dosage (in case of insufficient response) or frequency (in case of reduced duration of the response) of IVIg to maintain improvement. Nevertheless, this response to increasing IVIg dose or frequency tends to decline after several years concurrently with the progressive reduction of distal CMAP amplitude, which reveals the development of secondary axonal degeneration. Still, it has been reported recently that early use of larger maintenance doses of IVIg might prevent the development of axonal degeneration and promote reinnervation.

IVIg is usually as safe and well tolerated in MMN as it is in other diseases; even if minor side effects, including headache, nausea, fever, chills, flushing, malaise, rash, and itching occur after IVIg infusions, they are usually transient and remit spontaneously. Major complications, such as acute renal failure,
congestive heart failure, aseptic meningitis, neutropenia, coagulopathy, anaphylaxis, and venous or arterial thromboembolism including stroke, are rare and are mostly associated with preexisting risk factors such as renal or heart disease, IgA deficiency, migraine, increased serum viscosity, stroke risk factors, or increased age. Transmission of hepatitis C virus does not seem to represent a problem since the introduction of new virucidal steps. In a review of the complications of IVIg in 88 neurological patients, major complications were observed in only 4 patients (4.5%), always occurring in patients with preexisting heart or renal disease and in a bedbound-state. Some patients may develop even severe allergic dermatitis after IVIg. This reaction is often caused not by the Ig but by residual products of sterilization and are usually prevented by changing the brand of Ig.

**Other Immune Therapies.** Less clear is how to proceed in MMN patients not responding or becoming resistant to IVIg. After the original report by Pestronk et al., cyclophosphamide given intravenously at high doses, followed by oral cyclophosphamide as maintenance therapy, was reported to be effective in approximately 50% of MMN patients assessed, whereas low-dose oral cyclophosphamide alone was seldom effective. This drug may have side effects, especially when given at high doses or for a long period of time, and may therefore be unsuitable for less severely affected patients, especially if young. Occasional patients improve or stabilize with azathioprine, whereas conflicting results were reported with mycophenolate mofetil. Two patients were recently reported to improve substantially with cyclosporine, but follow-up of these patients was relatively short. Interferon-β1a was also effective in a few patients with MMN, some of whom had failed to respond to other therapies, including IVIg. Some patients responded to this therapy better than to IVIg, whereas others deteriorated, probably because of interruption of previously effective IVIg therapy. More recently, a positive effect was reported with the anti-CD20 monoclonal antibody rituximab, directed against B-lymphocytes, even if the mean improvement in muscle strength was quite modest and delayed in time (1 year). These positive results were not confirmed in two other patients with purely motor chronic demyelinating neuropathy, including one patient with MMN and a declining response to IVIg, who had no response to treatment with rituximab during the following year. For all these therapies, the small numbers of reported patients and the lack of controlled studies do not allow any firm conclusion to be drawn on their possible efficacy in MMN, so they should be offered only to compromised MMN patients resistant or responding poorly to IVIg.

Similar consideration can be extended to the use of immunosuppressants as adjunctive therapy to reduce the frequency or even suspend costly infusions of IVIg in responsive MMN patients. Low-dose oral cyclophosphamide permitted the frequency of IVIg infusions to be delayed progressively, and sometimes their prolonged, although ultimately temporary, suspension. A similar sparing effect on IVIg was recently reported with mycophenolate mofetil. Both drugs were associated in some patients with side effects requiring their suspension. We believe that, until the cost–benefit ratio of the association of these immunosuppressive agents with IVIg in MMN is properly addressed in randomized trials, their use should be discouraged in patients responding to IVIg.

**CONCLUSION: OPEN ISSUES IN MMN**

MMN is one of the few recently described neurological disorders whose identification was followed soon after by the discovery of an effective, although probably not curative, treatment. However, several issues remain concerning this disease. As briefly mentioned, although typically characterized by the presence of a CB, the pathophysiological abnormalities in MMN probably extend far beyond it, suggesting that CB detected by standard electrodiagnostic techniques represents the “tip of the iceberg” of more widespread involvement of motor fibers. This might also explain why patients with otherwise clinically typical MMN but no detectable CB also improve with IVIg. It remains unclear whether the recently reported axonal MMN should be considered a variant of typical MMN with CB or may simply represent a possible evolution of the same disease. Similarly, because the presence of antiganglioside antibodies in MMN seems to represent a marker of an immune involvement in MMN that is of possible diagnostic relevance rather than the real effector of neural damage, this and the target of the immune response in MMN have yet to be clarified. It also remains unclear what causes this immune response and the role, if any, of cellular immunity in the disease. Finally, after more than 10 years of experience with IVIg in MMN, it is now evident that, although this therapy can improve the neuropathy for several years, it does not ultimately cure the condition, mak-
ing it necessary to search for more effective and possibly curative treatments for this disease.

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