
CHAPTER 21

Multifocal motor neuropathy

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Objectives

The aim is to update the EFNS/PNS guideline for the definition, diagnosis, and treatment of multifocal motor neuropathy (MMN) based on available evidence and, where adequate evidence was not available, consensus.

Background

Patients with a pure motor, asymmetric neuropathy with multifocal conduction blocks (CB) have been reported from 1986 onwards [1–3]. Pestronk and colleagues first introduced the term multifocal motor neuropathy and highlighted the association with IgM anti-ganglioside GM1 antibodies and the response to immune-modulating therapies [4]. The diagnosis of MMN is based on clinical, laboratory, and electrophysiological characteristics [5–8]. Several diagnostic criteria for this neuropathy have been proposed [9–11]. These criteria share the following clinical features: slowly progressive, asymmetric, predominantly distal weakness without objective loss of sensation in the distribution of two or more individual peripheral nerves, and absence of upper motor neuron signs. The hallmark of the disease is the presence of mul-

tifocal conduction block on electrophysiological testing outside the usual sites of nerve compression [5, 12–15]. Conduction block is a reduction in the amplitude and area of the compound muscle action potential (CMAP) obtained by proximal versus distal stimulation of motor nerves in the absence of abnormal temporal dispersion [7, 12, 16]. The extent of reduction of the CMAP amplitude and/or area necessary to classify a reduction as a true conduction block is still a matter of debate. For this guideline, we present clinical and electrophysiological diagnostic criteria based on published criteria and consensus agreed upon by the task force.

MMN is a treatable disorder. A beneficial effect of various immunomodulatory drugs has been suggested in several uncontrolled studies [4, 17–25], and reviewed in a Cochrane systematic review [26]. Four trials have shown intravenous immunoglobulin (IVIg) therapy to be effective in MMN in the short term, and this treatment currently is considered the standard treatment for MMN [27–30]. These trials have also been reviewed in a Cochrane systematic review [31]. This small body of evidence has allowed evidence-based statements about treatment.

Search strategy

We searched MEDLINE from August 2004 to July 2009 for articles on ‘multifocal motor neuropathy’ and ‘diagnosis’ or ‘treatment’ or ‘guideline’. We also searched the Cochrane Library in July 2009.

Methods for reaching consensus

Task force members prepared draft statements about definition, diagnosis, and treatment. Evidence and recommendations were classified according to the scheme agreed for EFNS guidelines [32]. When only Class IV evidence was available but consensus could be reached, the task force offered advice as Good Practice Points (GPP). The statements were revised and collated into a single document that was then revised iteratively until consensus was reached.

Results

Diagnostic criteria for MMN

The task force developed its own diagnostic criteria based on the published criteria [5–11]. The clinical criteria are listed in table 21.1. The main clinical features are weakness without objective sensory loss, slowly progressive or stepwise progressive course, asymmetric involvement of two or more nerves, and absence of upper motor neuron signs. Recently, the extent of sensory signs and symptoms in MMN has been reconsidered and development of elec-

trophysiological sensory changes with or without sensory signs and symptoms over the course of MMN has been described [33, 34].

The presence of conduction block (CB) in motor nerve fibres is the hallmark of the disease. However, some patients with otherwise typical MMN have no detectable CB, probably because these blocks are activity dependent [35] or are located in nerve segments that cannot be assessed by routine electrophysiological examination [36, 37]. More recently, other techniques with restricted availability, such as transcranial magnetic stimulation, triple-stimulation technique, and transcutaneous cervical root stimulation, have been used to identify conduction blocks with greater sensitivity. These techniques may be useful, especially where CBs are proximally situated. The value of these techniques in routine clinical use has yet to be determined. 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. Computer modelling 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 [38]. Similar studies in man have shown that distal CMAP duration and proximal CMAP duration

Table 21.1 Clinical criteria for MMN.

Core criteria (both must be present)

- 1 Slowly progressive or stepwise progressive, focal, asymmetric^a limb weakness, i.e. motor involvement in the motor nerve distribution of at least two nerves, for more than one month^b. If symptoms and signs are present only in the distribution of one nerve only a possible diagnosis can be made (see table 21.4).
- 2 No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs^c

Supportive clinical criteria

- 3 Predominant upper limb involvement^d
- 4 Decreased or absent tendon reflexes in the affected limb^e
- 5 Absence of cranial nerve involvement^f
- 6 Cramps and fasciculations in the affected limb
- 7 Response in terms of disability or muscle strength to immunomodulatory treatment

Exclusion criteria

- 8 Upper motor neuron signs
- 9 Marked bulbar involvement
- 10 Sensory impairment more marked than minor vibration loss in the lower limbs
- 11 Diffuse symmetric weakness during the initial weeks

^aasymmetric = a difference of 1 MRC grade if strength is MRC >3 and 2 MRC grades if strength is MRC ≤3;

^busually more than 6 months;

^csensory signs and symptoms may develop over the course of MMN;

^dat onset, predominantly lower limb involvement account for nearly 10% of the cases;

^eslightly 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;

^f12th nerve palsy has been reported.

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 conduction block [39]. In one of the main papers concerning the diagnostic criteria of MMN, grading of CB was defined as definite or probable, and in the other as definite, probable, and possible [9–11]. 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 (tables 20.1 and 20.2).

Investigation of MMN

Based on consensus expert opinion, consideration of MMN should enter the differential diagnosis of any patient with a slowly or stepwise progressive asymmetrical limb weakness without objective sensory abnormalities, upper motor neuron, or bulbar signs or symptoms. MMN should be differentiated from motor neuron disease, entrapment neuropathies, hereditary neuropathy with liability to pressure palsies, Lewis–Sumner syndrome, and chronic inflammatory demyelinating polyradiculoneuropathy, in particular its purely motor variant [1, 3, 9, 40–51].

Clinical examination and electrodiagnostic tests are mandatory and the features suggesting a diagnosis of MMN are listed under diagnostic criteria. A family history should be obtained. The association between MMN and IgM anti-ganglioside GM1 (anti-GM1) antibodies was already suggested in the first report recognizing MMN as a distinct disease entity [4]. However, the

diagnostic accuracy of anti-GM1 testing in diagnosing MMN is unclear. The literature reports the presence of anti-GM1 IgM antibodies in between 30 and 80% of MMN patients [52, 53]. Furthermore, anti-GM1 antibodies don't seem to be specific for MMN. Anti-GM1 antibodies have been reported to occur in other dysimmune neuropathies and in patients with motor neuron disease, which may mimic MMN, albeit infrequently and in lower titres. Other tests that can support the diagnosis of MMN are CSF protein <1 g/l [54], and increased signal intensity on T2-weighted MRI scans of the brachial plexus associated with a diffuse nerve swelling [6, 9, 22].

Cerebrospinal fluid (CSF), anti-ganglioside GM1 antibodies, and magnetic resonance imaging (MRI) scans of the brachial plexus are not normally needed for patients fulfilling the clinical and electrodiagnostic criteria of MMN. Nerve biopsies are not routinely performed in MMN but can be useful in detecting an alternative cause [55, 56]. Needle EMG, serum and urine paraprotein detection by immunofixation [57], thyroid function [58], creatine kinase [6, 20], CSF cells, and protein [6, 59] are investigations that can be helpful to discover concomitant disease or exclude other possible causes. This list is not complete and additional investigations should be guided by the clinical findings.

Treatment of MMN

The treatment options for people with MMN are limited. In contrast to the response in CIDP, MMN does not usually respond to steroids or plasma exchange (PE), and patients may worsen when they receive these treatments [7, 51, 60–63].

Table 21.2 Electrophysiological criteria for conduction block.^a

1	Definite motor CB ^a Negative peak CMAP area reduction on proximal versus 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 >20% of the lower limit of normal and >1 mV and increase of proximal to distal negative peak CMAP duration must be ≤30%.
2	Probable motor CB ^a 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 Negative peak CMAP area reduction of at least 50% (same as definite) with an increase of proximal to distal negative peak CMAP duration >30%;
3	Normal sensory nerve conduction in upper limb segments with CB (see exclusion criteria).

^aEvidence for CB must be found at sites distinct from common entrapment or compression syndromes.

The efficacy of IVIg has been suggested by many open, uncontrolled studies. Four randomized controlled, double-blind trials of IVIg for treating MMN have been done [27–30]. These four RCTs included a total of 45 patients with MMN and have been summarized in a Cochrane systematic review [31]. IVIg treatment was superior to placebo in inducing an improvement in muscle strength in patients with MMN (NNT 1.4, 95% CI 1.1–1.8). As weakness is the only determinant of disability in patients with MMN, it is to be expected that in patients whose muscle strength improves after IVIg treatment, disability will improve as well. Elevated anti-ganglioside GM1 antibodies and definite CB were significantly correlated with a favourable response to IVIg in one large retrospective study [6], but in a more recent retrospective study no factors associated with treatment response were found [25]. In this series, approximately 20% of patients achieved prolonged remission (>12 months) after IVIg alone; approximately 70% of patients needed repeated long term IVIg infusions and, of them, half needed additional immunosuppressive treatment [25]. Maintenance IVIg therapy should be tailored to the need of individual patients [64]. During long-term IVIg

treatment effectiveness declines as muscle strength decreases, even when dosage is increased [65–69]. This process is due to ongoing axonal degeneration [66, 67, 69]. In one retrospective study, treatment with higher than normal maintenance doses of IVIg (1.6–2.0 g/kg given over 4–5 days) promoted reinnervation, decreased the number of CBs, and prevented axonal degeneration in 10 MMN patients for up to 12 years [68]. However, further long-term studies are needed to determine whether disease progression can be prevented by high-dose IVIg.

One randomized, single-blinded trial and one open pilot study suggest that short-term subcutaneous administered Ig is feasible, safe, and as effective as IVIg [70, 71]. Mycophenolate mofetil added to IVIg has no additional beneficial effect and no IVIg-sparing effect [72]. Uncontrolled studies suggest a beneficial effect in some patients of cyclophosphamide [4, 17, 18, 20–22, 73], interferon beta1a [23, 24], cyclosporine [74], methotrexate [75], and azathioprine [19]. There is conflicting evidence for rituximab [76–80]. Cyclophosphamide was not recommended by one group of experts because concern exists about its short- and long-term toxicity and lack of evidence of efficacy in MMN [10].

Recommendations

Diagnostic criteria

- 1 Clinical: the two core criteria and all exclusion criteria should be met (see in front of table 21.1) (GPP).
- 2 Electrodiagnostic: definite or probable conduction block in at least one nerve (table 21.2) (GPP).
- 3 Supportive: anti-GM1 antibodies, MRI, CSF, and treatment response (table 21.3) (GPP).
- 4 Categories: definite and probable MMN (table 21.4) (GPP).

Diagnostic tests

- 1 Clinical examination and electrodiagnostic tests should be done in all patients (GPP).
- 2 Anti-ganglioside GM1 antibody testing, MRI of the brachial plexus, and CSF examination should be considered in selected patients (GPP).
- 3 Investigations to discover concomitant disease or exclude other possible causes should be considered but the choice of tests will depend on the individual circumstances (GPP).

Treatment

- 1 IVIg (2 g/kg (total cumulative dose) given over 2–5 days) should be the first-line treatment (Level A) when disability is sufficiently severe to warrant treatment.
- 2 Corticosteroids are not recommended (GPP).
- 3 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 (GPP). Typical treatment regimens are 1 g/kg every 2–4 weeks, or 2 g/kg every 1–2 months (GPP).
- 4 If IVIg is not or 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 (GPP).
- 5 Toxicity makes cyclophosphamide a less desirable option (GPP).

Table 21.3 Supportive criteria.

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

Table 21.4 Diagnostic categories.*Definite MMN*

- Clinical criteria 1, 2 and 8–11 (table 21.1) AND electrophysiological criteria 1 and 3 in one nerve (table 21.2)

Probable MMN

- 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 (table 21.3)

Possible MMN

- 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, 2 and 8–11 AND electrophysiological criteria 1 or 2 and 3 in one nerve

Conflicts of interest

The following authors have reported conflicts of interest.

I. N. van Schaik: personal none, unrestricted departmental research grant from Sanquin blood supply foundation.

D. Cornblath: personal honoraria from Merck, Pfizer, Mitsubishi Pharma, Sangamo, Sanofi-Aventis, Bristol-Myers Squibb, Eisai, Octapharma, Sun Pharma, Acorda, DP Clinical, Exelixis, Geron, Johnson & Johnson, Genzyme, Cebix, Abbott, CSL Behring, Bionevia, Schwarz Biosciences, Avigen, FoldRx, GlaxoSmithKline.

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E. Nobile-Orazio: personal from Kedrion, Baxter, LFB (and he has been commissioned by Kedrion and Baxter to give expert opinions to the Italian Ministry of Health on the use of IVIg in dysimmune neuropathies).

J. Pollard: departmental research grants from Biogen-Idec and Schering.

P. van Doorn: personal none, departmental research grants or honoraria from Baxter, Bayer, and Talecris.

The other authors have nothing to declare.

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