Practical Electrophysiology for the Diagnosis of Multifocal Motor Neuropathy

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Abstract

Nerve conduction studies (NCS) are necessary to distinguish multifocal motor neuropathy (MMN) from other disorders with a similar clinical picture. In MMN, NCS may show a unique combination of conduction block (CB) or conduction slowing consistent with demyelination, whereas sensory conduction in the same nerve is normal. This contribution discusses a relatively simple and practical electrophysiological approach for the diagnosis of MMN that can be used by any neurologist who has had training in NCS. When diagnosing MMN, the most important practical points are: careful stimulation technique, investigation according to a standardised protocol that includes at least five nerves per arm with stimulation up to Erb's point, understanding of and adherence to criteria for conduction block and demyelinative slowing and exclusion of nerves with marked axon loss.

Keywords

Multifocal motor neuropathy, electrophysiology, nerve conduction studies, diagnosis, neuropathy

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Multifocal motor neuropathy (MMN) presents clinically as a disorder of lower motor neurones with asymmetrical distribution and predominance in distal upper limbs. Electrophysiological investigation is considerably more sensitive and specific for MMN than magnetic resonance imaging of the brachial plexus.[1,2] Nerve conduction studies (NCS) are therefore necessary to distinguish MMN from other disorders with a similar clinical picture, such as progressive spinal muscular atrophy, Hirayama disease, plexopathy and radiculopathy. NCS may show a combination of findings unique to MMN, comprising motor conduction block (CB), slowing of motor conduction consistent with demyelination and, in the nerves with motor abnormalities, normal sensory conduction. There may also be evidence of motor axon loss, such as decreased distally evoked compound muscle action potentials (CMAP) and marked signs of denervation and re-innervation on needle electromyography.[3] It has not been resolved whether motor CB and slowing represent paranodal demyelination, segmental demyelination, or ion channel dysfunction at the node of Ranvier.

As discussed below, there is some debate concerning precise electrophysiological diagnostic criteria for MMN, but it is nevertheless possible to outline relatively simple electrophysiological techniques that can be used to diagnose MMN by neurologists who have been trained in NCS. Advanced techniques, such as the single fibre electromyography test for detection of conduction block in single axons, inching and the triple-collision technique, fall outside the scope of this paper.

Stimulation

NCS performed in the diagnosis of MMN are usually extensive and may require strong stimuli. It is therefore essential to use a careful technique to stimulate each site of a nerve. This reduces patient discomfort and technical errors arising from unwanted co-stimulation.

The stimulator must have soft ends with felt pads and a large distance between cathode and anode. Stimulators with sharp metal ends will cause unnecessary pain, since it may be necessary to apply pressure on the skin with the stimulus electrodes in order to achieve supramaximal stimulation. A large distance between cathode and anode also makes it more likely that the stimulus reaches the nerve; this is particularly essential when stimulating at Erb's point. A large cathode-anode distance can be achieved by a fixed stimulator block with an inter-electrode distance of 4 cm. Alternatively, for stimulation at Erb's point, the cathode can be a monopolar bar and the anode a pad above the scapula.

Proper stimulation entails that the largest response is evoked by the least possible current. This avoids unnecessary pain and errors

Table 1: Recommended Stimulation Technique for Motor Nerve Conduction Studies

Recommended Stimulation Technique
• Place the stimulator on the site where the nerve is most likely located
• To check for unwanted artefacts, deliver a stimulus of zero mA
• Increase stimulus current in steps of about 5 mA until a small response appears
• Do not change stimulus current and stimulate the nerve either slightly medial or slightly lateral to the original stimulus site
• The optimal site is the one with the largest response. At this site, increase stimulus current in small steps until the response does not increase further. This is the current for maximal stimulation
• Increase the maximal current by 20 % (for Erb's point 30 %). This is the current for supramaximal stimulation at which the response should be judged

due to unintended co-stimulation of other nerves that lie nearby. The recommended technique is summarised in *Table 1* and *Figure 1*. The standard stimulus duration of 0.2 ms is often insufficient to achieve the required supramaximal stimulation. To avoid an unnecessary number of stimuli before supramaximal stimulation is achieved, it is wise to set the stimulus duration for stimulation at Erb's point at 1.0 ms.

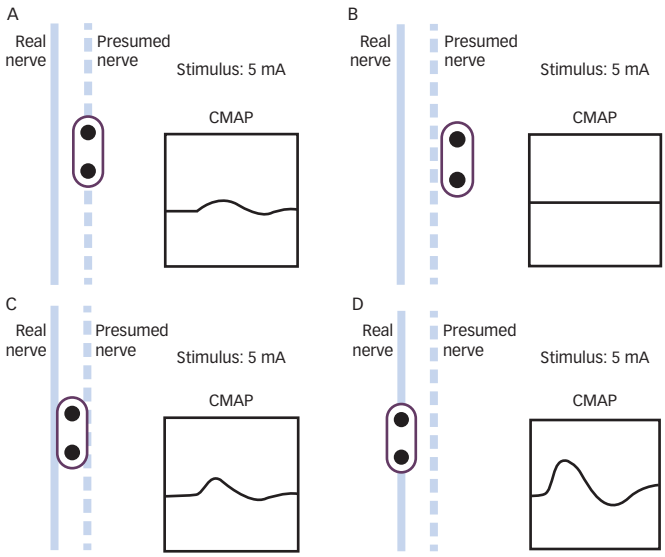
Supramaximal stimulation cannot always be achieved, especially at Erb's point. This may be due to obesity, anatomical features such as compact stature, or decreased nerve excitability due to the disease process. Two examples will be given. In the first example, the CMAP at Erb's point is 2 mV with stimulation at 60 mA, 3 mV with stimulation at 70 mA, 4 mV with stimulation at 80 mA, 5 mV with stimulation at 90 mA and 6 mV with stimulation at 100 mA. This indicates that neither maximal nor supramaximal stimulation was achieved, because the CMAP continued to increase when stimulus-current was increased. Since supramaximal stimulation was not possible, the CMAP at Erb's point cannot be properly judged. In the second example, the CMAP at Erb's point is 3 mV with stimulation at 60 mA, 4 mV with stimulation at 70 mA, 4 mV with stimulation at 80 mA, 4 mV with stimulation at 90 mA and 4 mV with stimulation at 100 mA. This indicates that maximal stimulation was achieved at 70 mA and that by adding 30 % of stimulus-current, supramaximal stimulation did not result in a further CMAP increase. Since supramaximal stimulation was achieved, this CMAP can be taken into account.

Recommended Protocol

In its most extensive form, the recommended protocol for NCS in the diagnosis of MMN consists of bilaterally performed motor and sensory NCS, using standard surface electrodes for stimulation and recording (see *Table 2*). Motor NCS are performed in order to detect motor CB, demyelinative slowing in motor axons, or loss of motor axons (see *Figure 2*). Sensory NCS serve two purposes:

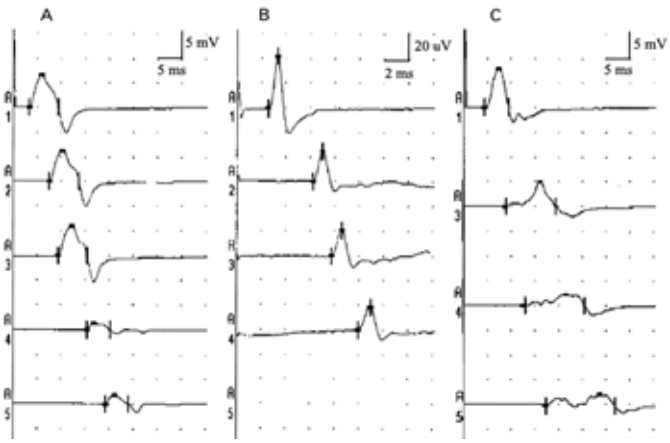
- sensory nerve action potentials (SNAPs) are recorded to rule out involvement of peripheral sensory axons. Decreased SNAPs may point to a sensorimotor neuropathy (e.g. Lewis-Sumner syndrome), brachial plexus involvement, or peripheral nerve pathology other than MMN; and
- normal sensory conduction over a nerve segment with conduction block or demyelinative slowing on motor NCS, strongly supports the diagnosis of MMN (see *Figure 2*).

Figure 1: Recommended Technique for Stimulation During Nerve Conduction Studies



CMAP = compound muscle action potential.

Figure 2: Conduction Studies in Patients with Multifocal Motor Neuropathy



A	DUR	AMP	AREA	DML MCV
A1 wrist	6.2	6.7	23.3	3.2
A2 elbow d	6.3	6.2	21.9	55
A3 elbow p	6.0	6.4	21.6	55
A4 axilla	4.8	1.4	4.4	23
A5 Erb	4.8	1.9	4.9	57
B	**AMP**	**SCV**		
A1 wrist	43.3	56		
A2 elbow d	25.1	61		
A3 elbow p	21.6	77		
A4 axilla	18.1	64		
C	**DUR**	**AMP**	**AREA**	**DML MCV**
A1 wrist	5.1	80	21.5	4.3
A3 elbow p	10.4	5.0	17.7	54
A4 axilla	12.4	2.6	17.9	49
A5 Erb	14.5	2.5	17.7	51

***A**: Motor conduction in the right ulnar nerve of Patient A, with recording from the abductor digiti V muscle; definite CB and MCV compatible with demyelination were found in the upper arm segment. **B**: sensory conduction in the same nerve, with recording from digit V; no abnormalities were found. **C**: motor conduction in the right median nerve of Patient B, with recording from the m. abductor pollicis brevis; increased TD and possible CB were found in the lower arm segment and possible CB in the upper arm segment. AMP = amplitude in mV or µV; DML = distal motor latency in ms; DUR = duration in ms; elbow d = stimulation 5 cm distally from elbow; elbow p = stimulation 5 cm proximally from elbow; MCV = motor conduction velocity in m/s; SCV = sensory conduction velocity in m/s. Area in mV.ms. Source: based on Van Asseldonk et al., 2003,[2] with permission and thanks to Oxford University Press.*

Table 2: Recommended Nerve Conduction Studies Protocol for Multifocal Motor Neuropathy

Motor NCS
• Median nerve (stimulation: wrist, elbow, axilla, Erb's point; recording m. abductor pollicis brevis and m. flexor carpi radialis)
• Ulnar nerve (stimulation: wrist, 3 cm distal to elbow, 5 cm proximal to elbow, axilla, Erb's point; recording m. abductor digiti V)
• Radial nerve (stimulation: elbow just lateral to biceps tendon, axilla posterior to place where the ulnar nerve was stimulated, Erb's point; recording: m. extensor carpi ulnaris)
• Musculocutaneous nerve (stimulation: axilla medial to place where median nerve was stimulated, Erb's point; recording: m. biceps brachii)
• Peroneal nerve (stimulation: ankle, 3 cm distal to fibular head; recording: 5 cm proximal to fibular head; recording: m. extensor digitorum brevis)
• Tibial nerve (stimulation: ankle, popliteal fossa; recording m. abductor hallucis)
Sensory NCS
• SNAPs on distal stimulation of the nerves affected by motor NCS abnormalities. These may include the median, ulnar, radial, musculocutaneous, peroneal and sural nerves
• Sensory conduction over those nerve segments that show conduction block or demyelinative slowing on motor NCS (in practice the latter is limited to median and ulnar nerve sensory NCS)

NCS = nerve conduction studies; SNAP = sensory nerve action potential.

Table 3: Van Asseldonk Criteria for Conduction Block

	Segmental Area Reduction (%) Distal Duration (ms)		
Duration Prolongation (ms)	<9 ms	9–12 ms	>12 ms
0	25 %	25 %	25 %
0–1	35 %	35 %	30 %
1–3	45 %	40 %	40 %
3–5	55 %	45 %	40 %
5–8	60 %	50 %	45 %
8–14	65 %	55 %	45 %
>14	70 %	55 %	45 %

All variables are measured from the total negative phase of the compound muscle action potential (CMAP). For each combination of duration prolongation and distal duration, the required segmental area reduction for conduction block (CB) is given as a percentage. Segmental area reduction = ([area on distal stimulation] - [area on proximal stimulation]) x 100 % / (area on distal stimulation). Duration prolongation = increase in ms (not in percentage) of CMAP duration on proximal versus distal stimulation of this segment. Distal duration = duration of the CMAP in ms on distal stimulation of the segment. Source: table based on Van Asseldonk et al., 2006.[5]

In MMN patients, the diagnostic yield for finding CB or slowing compatible with demyelination was found to be greatest for nerves innervating hand muscles, followed, in order of decreasing diagnostic yield, by nerves innervating forearm or upper arm muscles and nerves innervating foot muscles.[2] In another study, using different criteria for CB and slowing, no differences between upper and lower limb nerves were found.[4]

Criteria for Conduction Block

CB is defined as the failure of action potential propagation at a given site of a single axon. In clinical practice, CB has to be detected by NCS rather than by recording from single axons. When considering criteria for CB, it is important to realise that the CMAP, as recorded by NCS, is the summation of the surface recorded motor unit action potentials (MUPs) arising in the muscle that is innervated by the investigated nerve. CB can be detected by NCS if CB occurs in a sufficient number of axons of a nerve segment. If a part of the axons within a nerve segment is blocked, the CMAP evoked by proximal stimulation of that segment will be smaller than the CMAP evoked by distal stimulation of the segment; this is known as segmental CMAP reduction (see *Figure 2*). This is because a part of the action potentials that are evoked at the proximal site will not pass the site where they are blocked, whereas all action potentials evoked at the distal site will reach the muscle.

At least three mechanisms other than CB may also give rise to an abnormally large segmental CMAP reduction:

- increased temporal dispersion, defined as an increased difference in conduction time between the axons within a nerve, leads to desynchronised activation of the MUPs that form the CMAP. Since this desynchronisation is more pronounced on proximal than on distal stimulation, the CMAP on proximal stimulation will be lower and broader than the CMAP on distal stimulation. In NCS, temporal dispersion is usually measured by comparing the duration of the CMAP evoked on proximal stimulation with the duration of the CMAP evoked on distal stimulation of a nerve segment;
- increased temporal dispersion gives rise to cancellation between positive and negative phases of the MUPs out of which the CMAP is built (phase cancellation). Because temporal dispersion is more pronounced after more proximal stimulation, phase cancellation is also more pronounced after more proximal stimulation; and
- if the MUPs that form the CMAP are polyphasic due to partial loss of motor axons followed by collateral sprouting, phase cancellation may become more prominent. This mechanism seems unlikely, however, as simultaneous recording of MUPs by surface and needle electrodes showed no polyphasic surface recorded MUPs, even when its needle-recorded counterpart is polyphasic.[5]

Because CB has to be distinguished from the other mechanisms causing increased segmental CMAP reduction, criteria are required. Some studies have derived criteria for CB by comparing segmental CMAP changes in MMN patients, chronic inflammatory demyelinating polyneuropathy (CIDP) patients, motor neurone disease (MND) patients, and normal subjects.[6–8] For several reasons, this approach is not justified. Comparing MMN patients with normal subjects will not result in criteria for CB, since an increased segmental CMAP reduction in MMN may be caused by CB, increased temporal dispersion, axonal degeneration, or any combination thereof. By the same token, comparing MMN patients with CIDP patients will not result in criteria for CB since, in both MMN and CIDP, an increased segmental CMAP reduction in both disorders may be caused by CB, increased temporal dispersion, axonal degeneration, or any combination thereof. The most suitable approach to derive criteria for CB is therefore by computer simulation studies. In an important simulation study, CMAPs were reconstructed from MUPs recorded from rat muscles and the effects of temporal dispersion on CMAP size calculated.[9] This showed that unfavourable temporal dispersion without any CB could result in a segmental CMAP amplitude reduction of up to 80 % and a segmental CMAP area reduction of up to 50 %. The conclusions were that a CMAP area reduction of more than 50 % indicates that at least a few axons are blocked and that CMAP amplitude is not suitable to assess CB. These findings led to the Rhee criterion for CB: a segmental CMAP area reduction of more than 50 %. This criterion features in the criteria sets for MMN

of the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS)[10] and Van den Berg-Vos and colleagues.[1]

Although the Rhee criterion is specific for CB, it lacks sensitivity and the result may be a missed opportunity to diagnose a potentially treatable neuropathy. Three different approaches have been used to avoid this problem:

- investigation of a large number of nerves according to a standardised protocol may reveal segments fulfilling the Rhee criterion;[1,2]
- more liberal criteria were formulated for so-called possible or probable CB. This is usually defined as a segmental CMAP amplitude or area reduction of at least 30 % in an upper limb nerve.[1,10,11] The criteria were based on the maximal segmental CMAP amplitude reduction that was encountered in patients with axon loss due to motor neurone disease. Therefore, they are not specific for CB, since they cannot distinguish between a segmental CMAP reduction due to block and a segmental CMAP reduction due to increased temporal dispersion. Nevertheless, they may help to identify patients with MMN because, if they are fulfilled, demyelination of motor axons is likely; and
- criteria for CB may be less stringent if temporal dispersion is limited. Based on consensus, the American Association of Electrodiagnostic Medicine (AAEM) formulated detailed criteria for CB that took temporal dispersion into account.[12]

There is, however, no scientific basis for the amount of detail in these criteria and the AAEM criteria identified fewer patients with proven MMN than simpler criteria.[1]

In another simulation study, CMAPs were reconstructed from surface MUPs recorded from human hand muscles and the effects of temporal dispersion in the relevant and adjacent segments simulated.[5] This showed that less stringent criteria for CB are indeed possible if temporal dispersion is limited (see *Table 3*). For instance, if the duration of the wrist CMAP is normal (<9 ms) and if there is no duration prolongation in the forearm segment where CB has to be assessed, the criterion for CB is a segmental area reduction of at least 25 %. However, with a duration prolongation of 3–5 ms in the forearm segment, the criterion for CB is a segmental area reduction of at least 55 %. *Table 3* also shows that criteria for CB become less stringent when wrist CMAP duration becomes longer. This is because temporal dispersion has already occurred in the segment between wrist and muscle so that its effects will be less pronounced in the forearm segment. The Van Asseldonk criteria[5] can be applied to median and ulnar nerve NCS with recording from hand muscles and require that CMAP area and duration are measured from the total area of all negative phases; this option can be installed on most commercial electromyography apparatus.

In conclusion, the above described evidence may suggest the following approach for the detection of CB (see also Practical Considerations): start with the Rhee-criterion; if this is fulfilled, definite CB has been diagnosed. If the Rhee criterion is not fulfilled, apply the Van Asseldonk criteria and if these are not fulfilled, apply the criterion for possible CB.

Criteria for Demyelinative Slowing

To distinguish nerve conduction slowing due to demyelination from slowing due to dysfunction of axons or loss of fast conducting axons, criteria are needed. Early criteria for demyelinative slowing were derived by comparing motor and sensory conduction velocity in demyelinating Charcot-Marie-Tooth (CMT) neuropathy with those in axonal CMT neuropathy.[13] Demyelinating and axonal forms were distinguished by findings on nerve biopsy. The cut-off value that distinguished both forms was 60 % of the normal mean; for an upper limb nerve this corresponds to approximately 38 m/s. In demyelinating CMT all conduction velocities were below this value and in axonal CMT they were above this value. Thus, in a patient with CMT neuropathy, a value below 60 % indicates demyelinating CMT and a value above 60 % axonal CMT.

These criteria were later modified by defining a percentage below the lower limit of normal (or above the upper limit of normal) for various NCS variables that are affected by conduction slowing, including motor conduction velocity (MCV), distal motor latency (DML), shortest F-M interval and segmental CMAP duration prolongation. For instance, MCV was considered compatible with demyelination if its

Table 4: Criteria for Demyelinative Slowing for Nerves Investigated After Warming in Water at 37 °C

	Nerve			
	Median	Ulnar	Peroneal	Tibial
CMAP Variable				
DML (ms)	5.8	4.5	6.6	6.4
Shortest F-M latency (ms)	38	41	65	64
Distal duration (ms)	9.2	10.5	8.5	8.3
MCV forearm/leg (m/s)	38	40	35	35
MCV upper arm (m/s)	41	43	–	–
MCV shoulder (m/s)	46	46	–	–
Segmental duration prolongation forearm/leg (%)	30	30	100	100
Segmental duration prolongation upper arm (%)	30	30	–	–
Segmental duration prolongation shoulder (%)	40	40	–	–

Criteria are applicable for nerve segments where the compound muscle action potential (CMAP) on distal stimulation is at least 1 mV. Segmental duration prolongation = ([proximal CMAP duration - distal CMAP duration] × 100 %) / (distal CMAP duration).
DML = distal motor latency; MCV = motor conduction velocity.
Source: table based on Van Asseldonk et al., 2005.[15]

Table 5: European Federation of Neurological Societies and the Peripheral Nerve Society Criteria for Motor Conduction Block in Multifocal Motor Neuropathy[10]

1 Definite Motor CB*
Negative peak CMAP area reduction on proximal versus distal stimulation of at least 50 % whatever the nerve segment length (median, ulnar, 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 >1mV. Increase of proximal to distal negative peak CMAP duration must be ≤30 %
2 Probable Motor CB*
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 an increase of proximal to distal negative peak CMAP duration ≤30 %
Or: negative CMAP area reduction of at least 50 % (same as definite) with an increase of proximal negative CMAP duration of >30 %
3 Normal Sensory Nerve Conduction in Upper Limb Segments with CB

**Evidence for CB must be found at sites distinct from common entrapment and compression sites. CB = conduction block; CMAP = compound muscle action potential; Source: table based on the Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society, 2010.[10]*

Table 6: European Federation of Neurological Societies and the Peripheral Nerve Society Criteria for Multifocal Motor Neuropathy

Definite MMN	
Clinical criteria 1, 2 and 8–11 and electrophysiological criteria 1 and 3 in one nerve (see *Table 5*)	
Probable MMN	
Clinical criteria 1, 2 and 8–11 and electrophysiological criteria 2 and 3 in two nerves (see *Table 5*); clinical criteria 1, 2 and 8–11 and electrophysiological criteria 2 and 3 in one nerve and at least two supportive criteria 1–4 (see *Table 5*)	
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, clinical criteria 2 and 8–11 and electrophysiological criteria 1 or 2 and 3 in one nerve (see *Table 5*)	
Clinical Criteria	
Core Criteria (Both Must be Present)	
1	Slowly progressive or stepwise progressive, focal, asymmetric* limb weakness, that is, motor involvement in the motor nerve distribution of at least two nerves for more than 1 month.** If symptoms and signs are present only in the distribution of one nerve, only a possible diagnosis can be made
2	No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs***
Supportive Clinical Criteria	
3	Predominant upper limb involvement†
4	Decreased or absent tendon reflexes in the affected limb‡
5	Absence of cranial nerve involvement§
6	Cramps and fasciculations in the affected limb
7	Response in terms of disability or muscle strength to immunomodulatory treatment
Exclusion criteria	
8	Upper motor signs
9	No marked bulbar involvement
10	Sensory impairment more marked than minor vibration loss in the lower limbs
11	Diffuse symmetrical weakness during the initial weeks
Supportive Criteria	
1	Elevated IgM anti-ganglioside GM1 antibodies
2	Laboratory: increased CSF protein (<1 g/l)
3	MRI 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

**Asymmetric: a difference of 1 Medical Research Council (MRC) grade if strength is MRC >3 and 2 MRC grades if strength is MRC ≤3. **Usually more than six months. ***Sensory signs and symptoms may develop over the course of MMN. †At onset, predominantly lower limb involvement accounts for nearly 10 % of the cases. ‡Slightly 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. §Twelfth nerve palsy has been reported.*
CB = conduction block; CSF = cerebrospinal fluid; EFNS = European Federation of Neurological Societies; IVIg = intravenous immunoglobulin; MMN = multifocal motor neuropathy; MRI = magnetic resonance imaging; PNS = Peripheral Nerve Society; SNAP = sensory nerve action potential. Source: table based on the Joint Task Force of the European Federation of Neurological Societies and the Peripheral Nerve Society, 2010.[10]

value was below 80 % of the lower limit of normal for MCV. The reason for this modification is unclear and it was not based on new evidence. Furthermore, these criteria become unnecessarily strict if the standard deviation of variables in the normal population is large. Nevertheless, criteria defined by this approach still feature in many published criteria sets and their diagnostic yield was assessed in several studies.

In contrast to hereditary neuropathies, the MCV in an acquired demyelinating neuropathy such as MMN may have any value between normal and markedly slowed, depending on the degree of demyelination in the investigated nerve. As a consequence, the interpretation of MCV criteria becomes different. A value below 60 % of the normal mean indicates that the MCV cannot be explained by loss of fast conducting axons alone and that there must be at least some demyelination. An abnormal value above 60 % indicates either moderate demyelination or loss of fast conducting axons. Thus, a MCV of 55 m/s indicates no abnormality, 45 m/s indicates loss of fast-conducting axons or moderate demyelination that does not fulfil criteria and 35 m/s indicates that there must be demyelination because this value cannot be explained by loss of axons only.

Nerve temperature is an important variable to take into account, because both cold and demyelination may give rise to nerve conduction slowing (see 'Practical Considerations'). It is, therefore, more accurate to carry out NCS when nerve temperature is 37 °C. Criteria for demyelinative slowing are available when nerves are investigated after warming the limbs in water at 37 °C for at least 30 minutes; this procedure ensures that nerve temperature is close to 37 °C[14,15] (see *Table 4*). These criteria were made for several motor nerve conduction variables, including DML, MCV, minimal F-M latency and segmental CMAP duration prolongation and are applicable to the median, ulnar, peroneal and tibial nerves to hand or foot muscles. They were derived by assessing the maximal slowing due to axon loss patients with motor neurone disease and are based on the assumption that demyelination can be assumed if slowing exceeds the maximal slowing that may occur due to axon loss.

Criteria for Multifocal Motor Neuropathy

After studying the available evidence, a EFNS/PNS joint task force developed consensus electrophysiological criteria for the diagnosis of MMN (see *Table 5* and *6*).[10] However, the EFNS/PNS criteria may lead to underdiagnosis of MMN because they require at least two segments with possible CB, if definite CB cannot be shown. Our practice is to use criteria that are based on the response to intravenous immunoglobulin (IVIg), currently the gold-standard treatment of MMN.[1] A prospective study of 37 patients with lower motor neurone loss and features of demyelination on NCS showed that the response to IVIg depended on the electrophysiological findings. Patients were investigated according to the above described, extensive standardised NCS protocol. The percentage of patients who responded favourably to IVIg was 81 % if there was at least one segment with definite CB, 71 % if there was no definite CB, but at least one segment with possible CB and 11 % if there was demyelinative slowing without CB. The criteria, derived from these findings, are shown in *Table 7*.

IVIg did not induce improvement in five patients with a clinical picture of MMN without CB or demyelinative slowing.[16] Although this appears to suggest that MMN without CB or demyelinative slowing does not exist, the author investigated two patients with a lower motor neurone syndrome without CB or demyelinative slowing who responded favourably to IVIg. In one of these patients, subsequent NCS revealed CB. Another study described patients with a lower motor neurone syndrome who, despite lack of CB or demyelinative slowing, improved on IVIg treatment.[17] However, these patients did not undergo the extensive NCS protocol as described below. If the extensive NCS protocol does not show CB or demyelinative slowing in a patient with a clinical picture of MMN, a trial IVIg course of 2 g/kg

body weight may be warranted. Obviously, an objective response to treatment in terms of muscle strength and daily functioning should be measured before long-term maintenance treatment is started.

Practical Considerations

When conducting electrophysiological studies in a patient suspected of having MMN, the above suggests the following practical considerations :

- use the simple Rhee criterion for definite CB: segmental area reduction of >50 %. As this criterion already takes temporal dispersion into account there is no justification in requiring limited temporal dispersion as suggested in some consensus criteria;
- start with motor NCS, on both sides, of the median, ulnar, radial, and musculocutaneous nerves up to Erb's point. The median nerve should be assessed to the thenar and forearm muscles;
- if there is at least one segment with definite motor CB and sensory conduction over this segment is normal, the electrophysiological investigation is consistent with MMN;
- if only possible CB is found in the median or ulnar nerve to the hand, assess if the segmental CMAP reduction is consistent with CB according to the Van Asseldonk criteria (see *Table 3*). If so, the diagnosis of MMN is more likely;
- if no CB is found in upper limbs, extend motor NCS to the peroneal and tibial nerves on both sides. Note that for these nerves only the Rhee criterion is applicable and that evidence-based criteria for possible CB are not available;
- judge CB from measurement of CMAP area and not from CMAP amplitude;
- do not judge CB and do not judge demyelinative slowing if the CMAP on distal stimulation of the segment is below 1 mV (baseline-negative peak);
- needle electromyography in patients with MMN may show prominent signs of denervation and re-innervation, also in non-atrophic muscles.[3] Thus, the finding of prominent needle EMG abnormalities does not favour motor neurone disease over MMN;
- if the NCS protocol does not show CB or demyelinative slowing in a patient with a clinical picture of MMN, repeat NCS after one year or after progression of weakness; and
- it is strongly recommended to warm the limbs in water at 37 °C for at least 30 minutes before NCS to ensure that the investigated nerves reach a temperature of 37 °C.[14,18–21] Warming nerves to this temperature increases the detection of CB because nodal sodium channels have a shorter open time at higher temperatures, increasing the probability that conduction at critically demyelinated internodes will become blocked.[19,22] Furthermore, CV slowing due to cold can be distinguished from CV slowing due to demyelination. Correcting a measured CV value for limb temperature by recalculating it for 37 °C (using the relation 2.2 m/s/°C) is not appropriate since correction factors in diseased nerves differ from those measured in normal subjects.[20,21] Warming limbs by infrared heaters is not recommended since it takes an extraordinary amount of time to reach the desired nerve temperature.[18] The usefulness of warming by blankets has not yet sufficiently been proven.

Table 7: Electrophysiological Criteria for Multifocal Motor Neuropathy that Predict the Response to Intravenous Immunoglobulin

Definite MMN
At least one segment with definite CB according to Rhee-criterion (segmental CMAP area reduction ≥50 %)
Probable MMN
At least one nerve segment with possible CB (segmental CMAP amplitude reduction >30 % in an upper limb nerve)
Possible MMN
No CB, but at least one segment or nerve with demyelinative slowing
Required for Definite, Probable and Possible MMN
Distal CMAP >1 mV in a segment with CB or demyelinative slowing
Sensory NCS in segment with CB or demyelinative slowing normal
SNAP amplitude in nerve with CB or demyelinative slowing normal

CB = conduction block; CMAP = compound muscle action potential; IVIg = intravenous immunoglobulin; MMN = multifocal motor neuropathy; NCS = nerve conduction studies; SNAP = sensory nerve action potential.

Conclusion

MMN is a rare, acquired, immune-mediated neuropathy that responds to treatment with IVIg. Accurate differential diagnosis using electrophysiological investigation is essential in patients presenting with clinical signs and symptoms suggestive of MMN. By following the practical steps outlined in this article, the relevant NCS can be carried out by any appropriately trained neurologist. ■

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