

# Multifocal motor neuropathy: and then, 20 years later ... IVIg therapy

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## Summary

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Multifocal motor neuropathy is a distinct entity, whose treatment differs from that of other chronic immune-mediated neuropathies, mainly chronic inflammatory demyelinating polyradiculoneuropathy and its variant, multifocal acquired demyelinating sensory and motor neuropathy, although they share some electrophysiological characteristics. From the first descriptions intravenous immunoglobulins have been considered to be the gold standard of treatment for multifocal motor neuropathy. New therapeutic strategies are required, however, that focus on the effects and the costs of this therapy over long-term follow-up.

*Keywords: multifocal motor neuropathy; conduction block; anti-GM1 antibodies; intravenous immunoglobulins (IVIg)*

## Introduction

Multifocal motor neuropathy has been simultaneously identified from motor neuropathies in 1986 (for references see the review of F. Ochsner in the same issue), then has become a well-defined condition due to its distinctive clinical presentation and response to treatment, as well as to its characteristic laboratory and electrophysiologic features [1]. It is characterised by slowly progressive, predominantly distal, asymmetric limb weakness and wasting, predominant in the arms, with muscle cramps and fasciculations, within an anatomical

distribution of individual motor nerves, with minimal or no sensory involvement [2–4]. It is a rare condition affecting no more than 1–2 persons per 100 000, more frequent in men than women with an approximate sex ratio in reported patients of 2.6:1, as found in a recent questionnaire study conducted in France [5]. The electrodiagnostic hallmark is focal motor conduction block (CB) persisting for years at atypical sites. In the past 4 years, diagnostic criteria for multifocal motor neuropathy for use in clinical trials have been proposed by a workshop attended by European experts [6], and a second set of criteria has been edited by experts working under the umbrella of the American Academy of Electrodiagnostic Medicine [7]. The most typical laboratory findings are the presence of increased levels of serum IgM autoantibodies to the ganglioside GM1, and to a lesser extent, to other glycolipids including asialo-GM1, GD1a or GM2 [8]. More recently, a joint task force of the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS) has edited a Guideline on management of multifocal motor neuropathy, including diagnostic criteria, investigation and treatment [9]. From the first descriptions the effectiveness of high-dose intravenous immunoglobulin (IVIg) therapy has been reported; it is now considered as the gold standard of treatment for multifocal motor neuropathy. However, questions still remain about the specific position of multifocal motor neuropathy among the so-called chronic immune-mediated neuropathies [10] and its current therapies [11], together with its natural history and prognosis.

## Current therapies of multifocal motor neuropathy

Since the original report on the response to intravenous cyclophosphamide in 2 patients with multifocal motor neuropathy by Pestronk et al. [1], a number of immune therapies have been used on the assumption that multifocal motor neuropathy is an immune-mediated disease. However, there

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is firstly no clear-cut idea on the best outcome measures to be used in randomised controlled trials concerning multifocal motor neuropathy. In addition, if efficacy of intravenous immunoglobulins (IVIg) has been confirmed by several randomised, double-blind, placebo-controlled trials, only a few patients experience persistent improvement after a single or few courses of therapy, and the long-term efficacy of IVIg is currently debated. Consequently, there is a need for better assessing multifocal motor neuropathy in clinical trials and in patients' daily life, and for better knowing long-term management of this chronic disease.

### **Selection of outcome measures for assessment of multifocal motor neuropathy in clinical trials**

The selection of outcome measures to be used in therapeutic trials is difficult in the setting of multifocal motor neuropathy. The disability in multifocal motor neuropathy mainly affects the upper limbs, but may involve the lower limbs [2, 4]. In addition, outcome measures should also cover impairment and quality of life. They should be simple, valid, reliable and responsive, and correlate with disease severity. They should also allow comparison with those used in previous trials, to facilitate systematic reviews.

Published randomised controlled trials in multifocal motor neuropathy have used various motor outcome measures devised for the assessment of strength and were mainly based on the Medical Research Council (MRC) grading system. However, no outcome measures have been systematically evaluated in terms of being valid, reliable and responsive in multifocal motor neuropathy. Moreover, since multifocal motor neuropathy has an asymmetrical clinical pattern, an alternative motor sum score may be proposed covering at least 8 more affected muscles, corresponding to at least 2 affected motor nerves [6]. The Vigorimeter has been suggested for grip-strength assessment in immune neuropathies including multifocal motor neuropathy [12].

The conclusions of a European Neuromuscular Centre (ENMC) Workshop led by European experts in October 2004 [13] have favoured measures that would be meaningful for patients, with a preference for disability measures. Two of them have been proposed by these experts: the INCAT (for Inflammatory Neuropathy Cause and Treatment group) Overall Disability Sum Score (ODSS), which has been validated for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

[14, 15] and used in a published randomised controlled trial for CIDP [16], and the Amsterdam Linear Disability Status Scale (ALDS), which is currently being developed [17]. Another US impairment scale, the Mayo Clinic Neuropathy Scale (NIS), formerly called the Neurological Disability Scale (NDS), has successfully been used in some other trials for CIDP, but not for multifocal motor neuropathy (for review see [18]). Lastly, fatigue is a subjective parameter, but has been categorised by the WHO as an impairment entity and should be used as a secondary outcome measure.

Both disability and impairment scales have recently been recommended as primary outcome measures in multifocal motor neuropathy by European and US experts who met in an International Workshop [19]. In addition, INCAT ODSS has recently been found as highly related to patients' own clinical judgement [20], and a new disability scale, Overall Neuropathy Limitations Scale (ONLS), was proposed by other authors [21] in assessment of peripheral neuropathy.

Electrophysiological outcome measures to be used in randomised controlled trials for multifocal motor neuropathy are not a matter of consensus. Electrophysiological difficulties include the debated significance of low amplitude compound action potentials (conduction block or axonal degeneration) and decreased recruitment pattern with normal motor unit potentials. Axonal degeneration is also difficult to quantify. Considering conduction block, there are differences between single and multiple stimuli. There might be a correlation between multiple stimuli detected conduction block and fatigue. However, it seems reasonable to consider the degree/number of conduction block and signs of axonal degeneration as secondary outcome measures in future randomised controlled trials for multifocal motor neuropathy [19].

### **Current IVIg therapy**

Numerous recent article reviews [2–4, 11, 22] and two Cochrane systematic reviews [23, 24] have summarised the status of immunomodulating treatments in multifocal motor neuropathy. Unlike CIDP, multifocal motor neuropathy does not respond to steroids, even when given at high-dose intravenously [25], whereas almost 20% were reported to worsen even dramatically on this therapy, as with plasma exchanges which may be followed by the appearance of conduction block in previously clinically unaffected motor nerves [26]. Immunoabsorption and CSF filtration are similar-

ly ineffective in most reported patients. These findings highlight the fact that the distinction between multifocal motor neuropathy and CIDP or its variant, multifocal acquired demyelinating sensory and motor (MADSAM) neuropathy (also called Lewis-Sumner syndrome: LSS) [27, 28], is not only of theoretical interest, as steroids and plasma exchanges, which are usually efficacious in CIDP and Lewis-Sumner syndrome, are ineffective and may be even dangerous in multifocal motor neuropathy.

The efficacy of IVIg in improving weakness in patients with multifocal motor neuropathy has early been pointed out in numerous case reports and small series [1]. IVIg infusions, given at 0.4 g/kg/day for 5 consecutive days were followed by an early and often dramatic improvement of the motor deficit in the affected motor nerves and sometimes a reduction of conduction block in the electrophysiological studies. However, the presence of definite conduction block is not a necessary condition to observe a response to IVIg therapy [29] and treatment does not appear to affect serum anti-GM1 antibody titres [2].

#### **IVIg in the short-term treatment of multifocal motor neuropathy**

Four controlled studies have been conducted with IVIg in the short-term treatment of multifocal motor neuropathy. Azulay et al. [30] gave a course of IVIg infusions or placebo, followed by the other treatment after crossover, in 12 patients with motor neuropathy and high anti-GM1 antibody titres, of whom 5 patients had conduction block and the others did not: they found that only the patients with conduction block responded to IVIg. Van den Berg et al. [31] published a double-blind, placebo-controlled study in 6 patients with multifocal motor neuropathy, all responders to IVIg in open treatment; 4 patients received two infusions of either IVIg 0.4 g/kg/day or placebo, and the two other patients received a single infusion. A significant clinical improvement, assessed by MRC score in 16 affected muscles, was observed in 5 of 6 patients with IVIg, and no clinical improvement was found with placebo. In addition, electrophysiological studies showed a significant reduction of only one conduction block in the median nerve in one patient. No significant change in serum anti-GM1 antibody titres was noted. Finally two double-blind, placebo-controlled studies [32, 33] confirmed the efficacy of IVIg versus placebo, given respectively during 2–6 months, in 16 and 18 patients, respectively. Furthermore, one of these studies [33]

showed no significant changes in conduction block and serum anti-GM1 antibody titres, but all 6 patients with high titres responded to IVIg. Van den Berg-Vos et al. [34], in a retrospective study, found that age at onset, the number of affected limb regions and the number of patients with a creatine kinase level >180 U/l were significantly lower in responders than in non-responders. In addition, elevated anti-GM1 IgM antibodies and definite conduction block were found significantly more often in responders.

#### **IVIg in the long-term treatment of multifocal motor neuropathy**

Several studies have tried to assess natural history and long-term effectiveness of treatments in multifocal motor neuropathy. A longitudinal study of 46 patients with multifocal motor neuropathy [35], followed for a median of 2.3 years, demonstrated that spontaneous improvement or resolution may not occur. Although this study did not focus on therapy, IVIg and cyclophosphamide appeared to be associated with neurological improvement, which was seldom complete or sustained. Other studies focused on long-term efficacy of IVIg, given as the only treatment in periodic infusions. Van den Berg-Vos et al. [36] performed a long-term follow-up of 11 patients with multifocal motor neuropathy who received maintenance treatment with IVIg during 4–8 years. During the follow-up period the frequency and dosage of IVIg infusions were determined for each patient and ranged from one infusion every one to 7 weeks and an average dose of 7 to 48 g per week. Muscle strength improved significantly within 3 weeks of the start of IVIg treatment and was still significantly better at the last follow-up examination than before treatment, even though it decreased slightly and significantly during the follow-up period. Conduction block disappeared in 6 nerve segments but new conduction block appeared in 8 nerve segments during the follow-up period. Changes consistent with improvement (remyelination or reinnervation) occurred in 13 nerves during follow-up and changes consistent with worsening (demyelination or axonal loss) occurred in 14 nerves. The authors concluded that IVIg maintenance therapy has a beneficial long-term effect on muscle strength and upper limb disability but may not prevent a slight decrease in muscle strength, and that IVIg treatment favourably influences the mechanisms of remyelination or reinnervation but that axon loss cannot be prevented. Same data and conclusions were outlined by Terenghi et al. [37] who reported

10 patients with multifocal motor neuropathy responding to an initial course of IVIg with periodic infusion for 5 to 12 years (mean 8.2 years). At last follow-up only 2 patients had maintained the maximal improvement achieved during therapy, while 8 worsened despite increasing IVIg dosage. This decline started after 3 to 7 years (mean 4.8 years) of therapy and correlated with a reduction of distal compound muscle action potentials amplitude ( $p < 0.019$ ). The authors concluded that effectiveness of IVIg in multifocal motor neuropathy often declines after several years, possibly due to the development of axonal degeneration.

On the other hand, Vucic et al. [38] reviewed medical records of 10 patients with multifocal motor neuropathy for outcome in muscle strength (MRC score), functional disability (Modified Rankin Disability score), conduction block and axonal degeneration. All patients had received IVIg (2 g/kg in 5 days for 3 consecutive months), followed by monthly maintenance therapy. Patients were followed for an average of 7.25 years (range 3.5 to 12 years). The authors noted that all patients kept a significant sustained improvement in muscle strength and functional disability while on IVIg therapy. In addition, there were significant improvement in conduction block decrease, decrease in axonal degeneration and evidence of reinnervation by the end of the follow-up period. They concluded that long-term IVIg therapy improves muscle strength and functional disability, decreases the number of conduction blocks and the extent of axonal degeneration, and promotes reinnervation. The difference from previous findings may be explained by the different regimen in giving IVIg, the patients in this study being treated with significantly higher IVIg maintenance doses. Lastly, our group has recently achieved a retrospective study of 40 patients with multifocal motor neuropathy treated mainly with IVIg infusions during a mean follow-up of 2.2 years (range from 0.5 to 6.6 years) [39]. At the last follow-up examination patients were classified in the following groups: group 1: patients who obtained remission (>6 months) without further treatment, after an initial IVIg periodic treatment of 6–18 months; group 2: patients with stabilisation depending on periodic IVIg courses, without (2a) or with (2b) additional immunosuppressor; group 3: non-responders. Eight patients (20%) were in group 1 at the end of the study, 25 (62.5%) were in group 2 (of whom 8 in group 2b) and 4 patients in group 3. Data were missing for the 3 last patients. In addition, none of the following potential predictive factors at the inclusion (age, sex, duration between diagnosis and onset of therapy, prominence of clinical involvement in

the upper/lower limbs, absent tendon reflexes, MRC sum score, mean amplitude of the motor-evoked potentials in the affected motor nerves, presence/absence of serum anti-GM1 antibodies) could predict to a significant degree the clinical response to IVIg. The two best predictive factors (although not significant) were female sex ( $p = 0.08$ ) and lower MRC sum score at inclusion ( $p = 0.07$ ).

## Conclusion

IVIg (2 g/kg given over 2–5 days) should be considered as the first line of treatment of multifocal motor neuropathy, when disability is sufficiently severe to warrant treatment (first treatment recommendation of the EFNS/PNS Guideline [9]). If an initial treatment with IVIg is effective, repeated IVIg treatment should be considered in selected patients (third treatment recommendation of the EFNS/PNS Guideline [9]). The frequency of IVIg maintenance therapy should be guided by the individual response. Typical treatment regimens are 1 g/kg every 2–4 weeks or 2 g/kg every 4–8 weeks. If IVIg is not (or not sufficiently) effective, there is probably a need for immunosuppressive treatments that could be used alone or in combination with IVIg to increase efficacy, increase the duration of response and reduce reliance on current therapies.

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