

Multifocal motor neuropathy: IVIg and other therapies

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Summary

Van den Berg LH. Multifocal motor neuropathy: IVIg and other therapies. Schweiz Arch Neurol Psychiatr. 2007;158:86–9.

Placebo-controlled studies showed that treatment with intravenous human immunoglobulins (IVIg) improves muscle strength of patients with multifocal motor neuropathy. The beneficial effect of IVIg lasts several weeks, and repeated IVIg are necessary to maintain muscle strength. Maintenance IVIg treatment is expensive and may not prevent long-term progression of motor deficits and axonal degeneration in multifocal motor neuropathy. Frequent infusions may also be burdensome to patients, but at present there is no therapeutic alternative to IVIg therapy. Plasma exchange is probably ineffective, and prednisone may worsen the disease course. Anecdotal reports suggest that cyclophosphamide may be effective as primary therapy or adjunctive therapy to IVIg, but its toxicity may preclude long-term use in relatively young patients. Evaluation in placebo-controlled trials of the efficacy of adjunctive (immunosuppressive) therapy that would allow reduction of IVIg doses is needed.

Keywords: multifocal motor neuropathy; intravenous immunoglobulins; immunosuppressive treatment

Multifocal motor neuropathy (MMN) has only been recognised as a separate disease entity in the late eighties [1,2]. It is characterised by progressive, asymmetric limb weakness, often related to the distribution of individual nerves, and usually affecting arms earlier and more severely than legs.

In contrast to most other neuropathies there is no sensory impairment. Before its recognition, patients were diagnosed as having a neurodegenerative (fatal) motor neuron disease (MND) or amyotrophic lateral sclerosis (ALS), as (early) signs and symptoms of MND/ALS resemble those of multifocal motor neuropathy. As multifocal motor neuropathy is a potentially treatable disorder, its differentiation from MND/ALS is important. The presence of persistent multifocal conduction block outside entrapment sites on motor nerve electrophysiological examination, which also occurs in patients with CIDP, is an important diagnostic hallmark of multifocal motor neuropathy [2]. Elevated serum antibodies to GM1 ganglioside, a potential autoantigen on the nodes of Ranvier and the surface of motor neurons, support an immune-mediated pathogenesis of multifocal motor neuropathy. Another diagnostic feature of multifocal motor neuropathy may be an abnormal (swollen nerves, increased signal intensity) MR imaging scan of the brachial plexus which is found in approximately half of the patients with multifocal motor neuropathy (fig. 1). Multifocal motor neuropathy is definitely more common in men than women (8:1) [3]. It is considered not ethical to perform a natural history study in patients with multifocal motor neuropathy as it would withhold patients from adequate immunological treatment. Two retrospective studies concerning the natural history of multifocal motor neuropathy have been published, both showing that multifocal motor neuropathy usually runs a slowly progressive course and that most patients are (severely) impaired in their daily life mostly by reduced dexterity in manual activities [4,5]. We performed a study to estimate the disease course of multifocal motor neuropathy by comparing features of disease progression in patients with a disease duration varying from 6 months to 34 years taking advantage of the fact that multifocal motor neuropathy has only recently been recognised as separate disease entity and many patients had been untreated before they were adequately diagnosed as suffering from multifocal motor neuropathy. Disease

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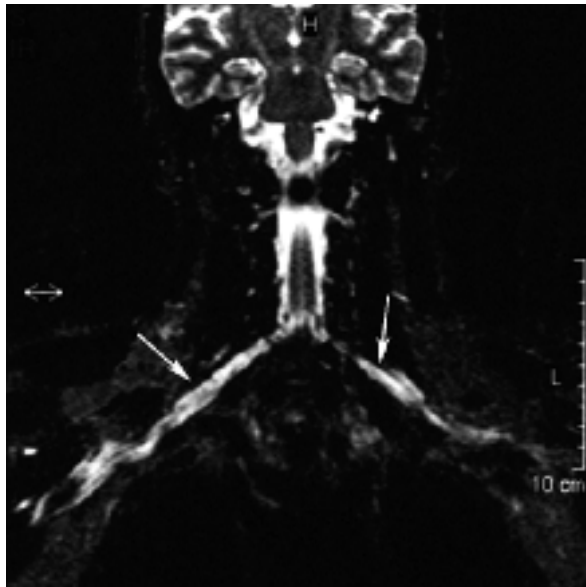
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Figure 1 MR imaging of the brachial plexus of a patient with multifocal motor neuropathy. Arrows indicate swellings and increased intensities on the T₂-weighted images of the brachial plexus.



severity was assessed by determining muscle weakness, disability, conduction block, and distal and proximal compound muscle action potential amplitude in 38 patients with multifocal motor neuropathy who had never received immunological treatment. Patients with long disease duration had significantly more severe weakness, disability and electrophysiological abnormalities than patients with short disease duration (fig. 2) [5]. None of the patients had experienced spontaneous improvement or a relapsing/remitting disease course. These results provide indirect evidence for a progressive disease course in multifocal motor neuropathy. Importantly, as a consequence adequate treatment may prevent disease progression in patients with multifocal motor neuropathy.

The hypothesis that multifocal motor neuropathy is an immune-mediated neuropathy has led to the trial of several immunological treatments. Initially, cyclophosphamide given intravenously at high doses, followed by oral administrations as maintenance therapy, was reported to be an effective immunological treatment in patients with multifocal motor neuropathy [6, 7]. A beneficial response to cyclophosphamide was shown in approximately 50% of patients with multifocal motor neuropathy. However, cyclophosphamide has serious side effects such as bladder or haematological cancer, especially when given at high doses or for long periods of time as the risk for side effects are cumulative. This makes it unsuitable for treatment of multifocal motor neuropathy as patients are relatively young, have a long life expectancy and a need for long-lasting treatment of the disease.

Treatment with corticosteroids appeared not to be effective in multifocal motor neuropathy. Over 60 patients with multifocal motor neuropathy have been treated with steroids alone or in combination with plasma exchange or immune suppressants [2, 8–11]. Only few of these patients were reported to improve after this therapy while at least 20% of them worsened, even dramatically, soon after starting taking steroids. Plasma exchange was also ineffective in most treated patients, and induced a rapid and severe clinical worsening in several patients [10, 11].

Over the last two decades, a large number of patients with multifocal motor neuropathy have been reported to respond beneficially to IVIg therapy [2]. Almost 80% of patients with multifocal motor neuropathy have been reported to improve after treatment with IVIg. It induces a rapid improvement which often occurs within one week of treatment but usually lasts only a few weeks and has to be maintained with periodic IVIg infusions for long periods of time, if not indefinitely. The improvement observed after each infusion of IVIg and its duration are almost invariably stereotypical for each patient and usually more evident in the recently affected limb districts. The effect of IVIg was confirmed in four double-blind placebo-controlled trials [12–15]. In recent studies on long-term IVIg treatment it has been shown that IVIg can induce and maintain improvement in most multifocal motor neuropathy patients but it does not eradicate the disease [16–18]. Criteria have been formulated that predict response to IVIg [19, 20]. In another study, we measured the response to one course of IVIg treatment in 34 patients and associated the response with disease severity [5]. Thirty of the 34 patients responded to IVIg treatment. Non-responsiveness to IVIg was not associated with any of the disease variables. Severe and widespread weakness was significantly associated with a response $>$ or $= 2$ on the MRC sum score. The good response to IVIg treatment in patients with severe and prolonged disease provides indirect evidence that progression of weakness in multifocal motor neuropathy is caused by an ongoing immunological process and implies that early treatment with IVIg may prevent future progression of weakness and disability in patients with multifocal motor neuropathy.

Other treatments than IVIg were tested in at least 11 uncontrolled studies concerning 33 patients with multifocal motor neuropathy. With the exception of cyclophosphamide, cyclosporine and to a lesser extent interferon β 1A that were relatively effective, all the other treatments (dexamethasone, prednisone, mycophenolate, plasma exchange,

immunoabsorption and CSF filtration) were inefficient [21–25]. In a Cochrane Database Search on the effect of immunosuppressive drugs in multifocal motor neuropathy [25] the authors did not find any randomised controlled or quasi-randomised trials of immunosuppressive agents for the

treatment of multifocal motor neuropathy. According to my view, immunosuppressive drugs are not effective enough and produce too much severe side effects. New drugs are coming that should be evaluated in randomised placebo-controlled trials but currently IVIg is the only realistic option.

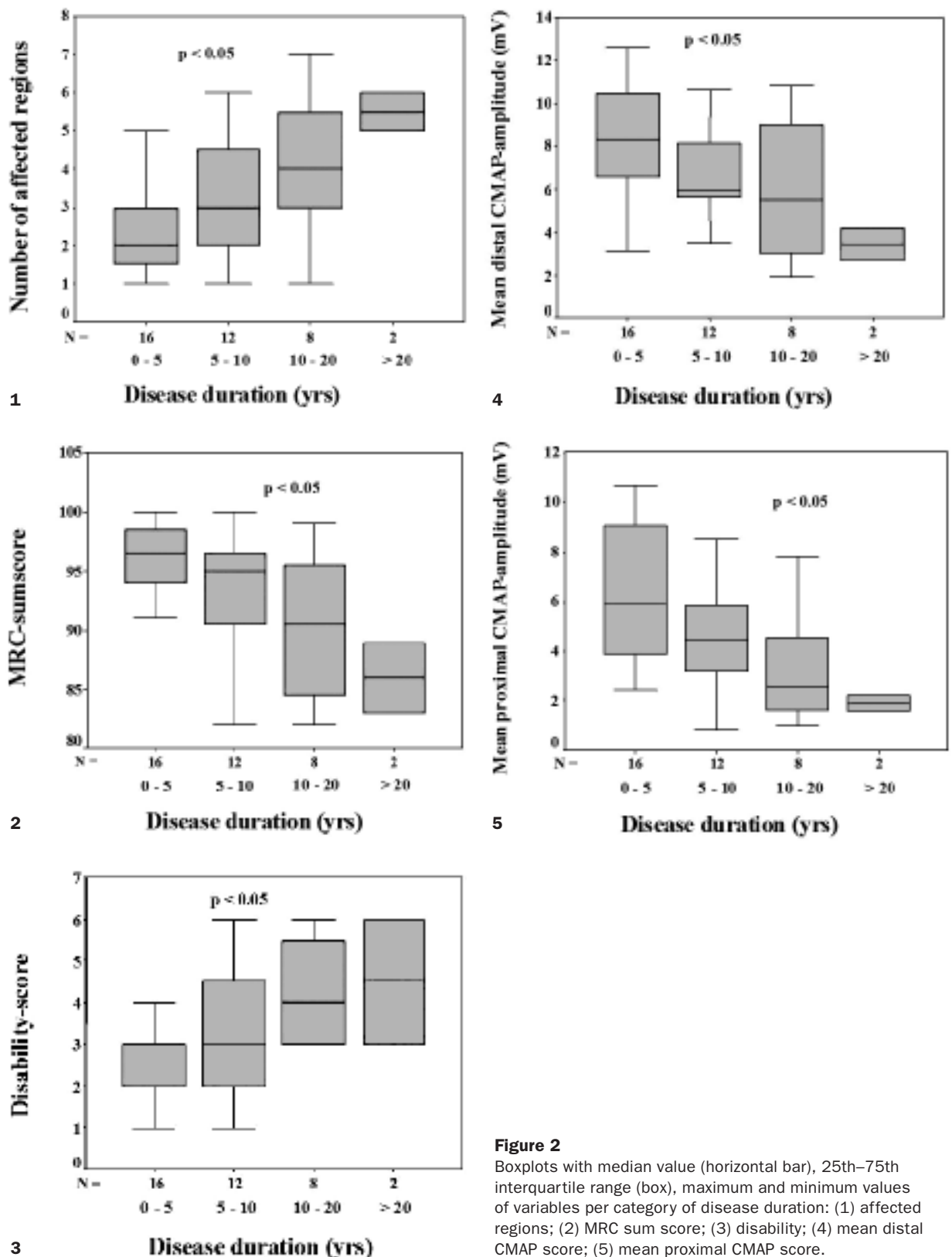


Figure 2 Boxplots with median value (horizontal bar), 25th–75th interquartile range (box), maximum and minimum values of variables per category of disease duration: (1) affected regions; (2) MRC sum score; (3) disability; (4) mean distal CMAP score; (5) mean proximal CMAP score.

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