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# IVIg dose increase in multifocal motor neuropathy

## A prospective six month follow-up

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**Abstract** In this prospective, non-randomized 6-month observational study we evaluated the efficacy of intravenous immunoglobulin (IVIg) dose increase in patients with multifocal motor neuropathy (MMN). Diagnosis according to AAEM criteria, repetitive IVIg treatment for at least one year, persistent paresis and conduction block, stable symptoms and findings for at least six months were inclusion criteria. Nine patients (7 men) were identified and approved to standardized increase of IVIg dose. Patients were monitored using clinical scores and electrophysiological studies. Dose was increased from a baseline of 0.5 g/kg per month [mean, range: 0.1–1.1], given at variable intervals [4–12 weeks] to 1.2 g/kg per month given over 3 consecutive days planned for 6 cycles. If the patients' motor function did not improve after two cycles they entered step two: Dose was increased to 2 g/kg per month given over 5 consecutive days. The increased dose was maintained for

6 months. Assessments were performed by the same investigator, not involved in the patient's management, at baseline, after 2 and after 6 months. Following dose increase, motor function significantly improved in 6 patients ( $p=0.014$ ), 2 patients entered step two, 1 patient withdrew due to absent efficacy. Higher doses of IVIg caused more side effects, however, transient and rarely severe ( $p=0.014$ ). IVIg dose increase may improve motor functions in patients with stable MMN on long-term IVIg therapy independent of baseline dose. Improvement of motor function was associated with shorter disease duration ( $p=0.008$ ), but not with degree of muscle atrophy ( $p=0.483$ ). The treatment strategy to try to find the lowest effective dose and the longest tolerated interval might lead to underdosing in the long-term in many patients.

**Key words** multifocal motor neuropathy · MMN · immunoglobulin · IVIg · dose increase

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## Introduction

Multifocal motor neuropathy (MMN) is a rare neuropathy characterized by progressive asymmetric motor weakness with no sensory signs in the distribution of two or more nerves and electrophysiologically by motor nerve conduction blocks (CBs) outside compression

sites [6, 7, 15]. IVIg is today the only evidence-based treatment [16]. According to the guidelines of the European Federation of Neurological Societies, IVIg 2 g/kg given over 2–5 days should be considered as first line treatment, when disability is sufficiently severe to warrant treatment; level A recommendation [15]. Regarding maintenance therapy optimal dose and treatment interval are not established – consequently there is only a

level C recommendation. Therapy should be guided by the individual response, i.e., the best future treatment schedule is established through trial and error. Typical treatment regimes are (good practice point) 1 g/kg every 2–4 weeks, or 2 g/kg every 1–2 months [15]. One retrospective study in 10 selected MMN patients, suggests very high doses of 2 g/kg IVIg every 4 weeks (26 g/kg/year) to decrease the number of conduction blocks, the extent of axonal degeneration and to promote reinnervation [18].

The dose-response relationship in MMN has not been explored, neither in the short- nor in the long term. It is difficult to evaluate due to the rarity of the disease, individual variations in affected muscles, degree of paresis, disease duration, age, and treatment side effects, making randomization, e.g., difficult.

A retrospective analysis of 18 MMN patients followed at our department and treated with the strategy of trying to find the lowest effective dose and the longest tolerated interval had revealed slowly progressive muscle weakness over the long-term [4.3 years (mean (0.3–11.8))] despite IVIg treatment (submitted for publication). This was in contrast to other studies that showed a more stable course under regular treatment with IVIg [14, 18]. With 7.7 g/kg body weight IVIg in the first year of treatment and 4.8 g/kg body weight/year thereafter, our cumulative IVIg doses per year were considerably lower than those used by Van den Berg et al. (22.4 g/kg body weight in the first and 20.8 g/kg body weight in the following years) and Vucic et al. (21.1 g/kg body weight/year) [14, 18].

Therefore, we proposed increasing the dose to improve motor function in those patients with persistent paresis. Furthermore, we intended to determine predictors of response to IVIg dose increase.

Approval of ethical committee Institutional Review Board (IRB) was granted for this follow-up study.

## Methods

### ■ Patients

At our institution covering a population of approximately 1.5 million people, we follow 18 MMN patients with average disease duration of 8.8 years (range: 1.5 to 21.8).

Inclusion criteria for the present study were MMN diagnosed according to AAEM criteria, repetitive IVIg treatment for at least 1 year, stable IVIg dose during the last 6 months, persistent paresis and CB, and stable symptoms and findings for at least six months. Nine patients fulfilling these criteria consented to a standardized increase of IVIg dose and monitoring. Patients were monitored using clinical scores and electrophysiological studies.

### ■ IVIg therapy

Individual IVIg dose given over the last six months was retrospectively analyzed. In step one, dose was increased to 1.2 g/kg per month

given over 3 consecutive days planned for 6 cycles. If patients' motor function did not improve after 2 cycles, they entered step two: Dose was increased to 2 g/kg per month given over 5 consecutive days. Side effects and adverse events were assessed after each cycle. The following adverse events were considered to be serious: death, all events requiring hospitalization, myocardial infarction, stroke, thrombosis and embolic disease.

### ■ Follow-up evaluation

Clinical and electrophysiological assessments were performed at baseline, after 2 and 6 months. All clinical exams were performed by the same investigator, not involved in the patient's management.

The primary clinical outcome measure was change in motor function from baseline to 6 months scored according to the following scales:

The Medical Research Council (MRC) rating scale in 40 muscles or muscle groups (11 in each upper limb, 9 in each lower limb) was assessed resulting in a maximal score of 200 for a normal strength. Overall weakness was assessed by taking the difference between the maximal score and the individual clinical score which was called MRC paresis sum score, where 0 means no paresis and 200 complete loss of motor function.

Functional outcome was assessed, a) using the Guy's Neurological Disability Scale where 0 means no disability and 10 means no motor function in arms and legs [8, 14] and, b) according to our own non-validated Individual Disability Score where three motor activities of daily life (e.g., binding shoe strings) were defined individually for each patient at baseline. A score of 0 indicated no symptoms; 1 = function slightly slowed but qualitatively unimpaired, 2 = function severely slowed, 3 = function qualitatively severely impaired, 4 = function impossible, giving a total score of 0 with normal motor function and 12 if none of the three functions could be performed. To our knowledge, there is no validated individual disability score. Leger JM, et al. also used a non-validated own score [5].

Secondary clinical outcome measure was muscle atrophy which was assessed at baseline and after 6 months according to our own non-validated atrophy score. Twenty-four muscle groups (7 in each upper limb and 5 in each lower limb) were rated according to the following scale: severe = 3 points (no muscle belly can be seen and felt); moderate = 2 points (clearly reduced muscle belly); slight = 1 point (slightly reduced muscle belly for age and occupation and compared with unaffected muscles); no atrophy = 0 points. Thus a maximal score of 72 would indicate complete muscle atrophy.

### ■ Nerve conduction studies (NCSs)

NCSs were performed at baseline in clinically affected nerves and proximal stimulation (Erb's point) was only performed if CB was not detected distally. CB was defined according to the AAEM criteria [6]. Follow-up of NCSs were repeated only in nerves with proven CB.

### ■ Electromyography (EMG)

Needle EMG was performed at baseline and at the study end in one affected muscle in those patients who agreed to this investigation.

### ■ Definition of treatment response

Response was defined clinically: Improvement by at least 2 points in MRC paresis sum score and (in addition) by at least one point either in the Guy's Neurological Disability Scale or the Individual Disability Score. These cut-off values are in accordance to previous studies [5].

### ■ Statistical analysis

Statistical analysis was performed using Mann-Whitney test for unpaired and Wilcoxon Signed Ranks test for paired data between two groups.

## Results

### ■ Patients

Mean age at study onset was 59.4 years [range: 46–80]. Before study, mean disease duration was 11.2 years [range: 2–23], mean treatment duration with IVIg was 6.7 years [range: 1–14]. Anti-GM1 (IgM) antibodies were positive in 6 and negative in 3 patients (Table 1).

### ■ IVIg therapy

Stable average IVIg dose over the 6 months before entry into the study was 0.5 g/kg per month [range: 0.1–1.1 g/kg/month], given at variable intervals [4–12 weeks] (Table 1). Dose was increased as described in the method section.

### ■ Response to dose increase

Following step one, 6/9 patients improved, 2/3 non-responders entered step two and 1/3 non-responders withdrew due to absent efficacy and stopped IVIg treatment but consented to follow-up. In this one patient disease course was stable despite suspension of therapy. The two entering step two did not improve. One out of 6 responders (step 1) stopped after 4 months due to side effects (nausea). One patient required hospitalization due to infection of i.v. line with septicemia (serious adverse event). Seven patients completed the 6 months (5 responders at 2 months and 2 non-responders after 2 and 6 months). Mean MRC paresis sum score improved from 28.57 [range: 6–47] to 26.29 [range: 3–46] ( $p=0.048$ ), mean Guy's Neurological Disability Scale improved from 3.86 [range: 2–6] to 3.14 [range: 0–6] ( $p=0.030$ ), mean Individual Disability Score improved from 9.00 [range: 7–11] to 7.14 [range: 4–9] ( $p=0.014$ ) (Fig. 1).

Improvement was best reflected in the Individual Disability Score (6), and less in MRC paresis sum score (5) or Guy's Neurological Disability scale (4). One responder (case 5) reported marked improvement at month 2 but had deteriorated again at stable dose of IVIg at month 6, but was still better than at baseline.

Mean disease duration before study entry was longer in non-responders ( $n=3$ ; 15.67 years, [range: 14–17]) compared to responders ( $n=6$ ; 9.00 years [range: 2–23]) which was significant ( $p=0.008$ ). Difference in muscle atrophy between the 3 non-responders (mean atrophy

score 18.00 [range: 7–26]) and the 6 responders (mean atrophy score 16.67 [range: 2–30]) was not significant ( $p=0.483$ ).

### ■ Side effects

One of six responders (step 1) stopped after 4 months due to side effects (nausea). One patient required hospitalization due to infection of the i.v. line with septicemia (serious adverse event). Six patients had side effects: fatigue (5), headache (4), nausea (2), hypertension (2), vertigo (1) and abdominal pain (1). Overall in 35/48 (73%) of IVIg cycles with increased dose at least one side effect was reported; in the 6 months before dose-increase at least one side effect was reported in 5/39 IVIg cycles (13%) ( $p=0.014$ ).

### ■ Electrophysiological assessment

Follow-up of nerve of conduction studies was possible in 8/9 patients. One patient (case 5) refused assessment at termination visit. Interpretation of results is possible in 7/9 patients as in one patient (case 2) supramaximal stimulation at Erb's point was not possible. No CB completely disappeared. Response of CB's to treatment did not show a consistent pattern or correlation to clinical response (Table 2).

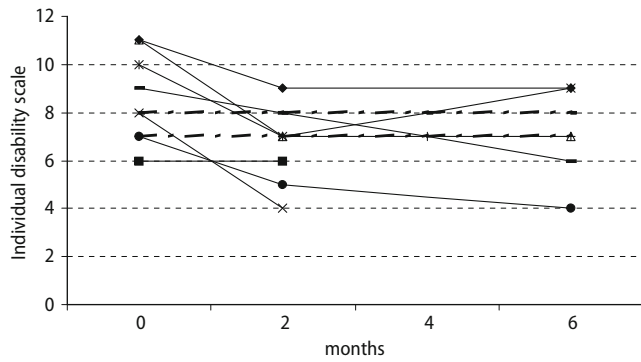
Five of nine patients consented to needle EMG at baseline and the end of the study. Four showed incomplete or discrete recruitment pattern of motor units (MUP) at baseline which after treatment had improved in three. Quantitative MUP analysis (Willison analysis) was performed in three and showed signs of chronic axonal damage without change after treatment in all; none had fibrillation potentials or fasciculations. Disease duration in these three patients was 3, 2 and 14 years, respectively.

## Discussion

In this small prospective, non-randomized, uncontrolled study, motor function significantly improved in 6/9 patients with MMN on long-term IVIg maintenance therapy by increasing IVIg dose. One patient transiently improved, then worsened again, but was still better than at baseline. A retrospective analysis of our 18 patients with MMN treated with the strategy of trying to find the lowest effective dose and the longest tolerated interval revealed progressive muscle weakness during the 4.3 years follow-up (mean, range: 0.3–11.8) under regular IVIg treatment. This outcome was in contrast to other studies that showed a more stable course under regular treatment with IVIg [14, 18]. With 7.7 g/kg body weight IVIg

**Table 1** Clinical baseline data and evolution following IVIg dose increase

Age/sex	Epidemiological data				Clinical response to IVIg-treatment				General remarks
	Duration (disease/IVIg treatment)	IVIg dose at baseline (g/kg body weight/month)	Clinically involved nerves	anti-GM1	Muscle strength	Motor function		Response (either muscle strength or motor function)	
						Guy's Neurological Disability scale	Individual Disability Score		
Case 1: 63 y/M	23 y/12 y	0.1	radial (L+R), ulnar (L+R), peroneal (L), tibial (R)	pos	47/41/yes	5/5/no	11/9/yes	yes	
Case 2: 52 y/M	16 y/3 y	0.7	radial (L+R), ulnar (L)	pos	11/10*/no	4/4*/no	6/6*/no	no	* with withdrawal after 8 weeks; due to lack of efficacy
Case 3: 47 y/F	4 y/3 y	1.1	median (L), radial (L), ulnar (L)	pos	26/16/yes	4/2/yes	11/7/yes	yes	
Case 4: 77 y/M	2 y/1 y	0.8	median (L+R), musculocutaneous (L+R), radial (L+R), ulnar (L+R), tibial (L+R), peroneal (L)	pos	17/8*/yes	3/1*/yes	8/4*/yes	yes	* with withdrawal after 4 months due to adverse events
Case 5: 80 y/M	17 y/12 y	0.3	median (L+R), radial (L), ulnar (L+R), peroneal (L+R)	neg	29/278/no	4/4/no	10/9/yes	yes	
Case 6: 63 y/F	3 y/2 y	0.4	ulnar (L), radial (L)	neg	6/3/yes	2/0/yes	7/4/yes	yes	
Case 7: 56 y/M	17 y/14 y	0.4	median (L), musculocutaneous (L), radial (L), ulnar (L+R), peroneal (L+R), tibial (L+R)	neg	40/46/no	6/6/no	7/7/no	no	Patient entered step two; no improvement
Case 8: 46 y/M	14 y/11 y	0.3	median (L+R), musculocutaneous (L+R), radial (L+R), ulnar (L+R), tibial (L+R)	pos	40/41/no	4/4/no	8/8/no	no	Patient entered step two; no improvement
Case 9: 51 y/M	5 y/2 y	0.3	radial (L+R), ulnar (L)	pos	12/9/yes	2/1/yes	9/6/yes	yes	



**Fig. 1** Outcome of motor function. Six patients improved in step one (solid line); two patients (dashed line) entered step two. Individual disability scale: 0 = best, 12 = worst performance (1 withdrawal after 4 months due to adverse events)

in the first year of treatment and 4.8 g/kg body weight/year thereafter, our cumulative IVIg doses were considerably lower than those used by Van den Berg et al. with 22.4 g/kg body weight in the first year of treatment and 20.8 g/kg body weight thereafter. Furthermore, Van den Berg et al. increased the dose even more in patients with a functional decline [14]. Vucic et al. in a study of 10 selected MMN patients showed significant long-term clinical and neurophysiological improvement during an observation time of 7.25 years. The IVIg dose used was 21.2 g/kg body weight/year [18]. Our results confirm that the efficacy of IVIg is dose dependent and that declining motor function can be restored by increasing IVIg dose, at least in 2/3 of MMN patients. Improvement correlated with short pretreatment disease duration indicating the need of higher doses of IVIg in early stages of the disease. However, dose increase does not work in all patients and might have a “ceiling effect” and thus must be titrated individually in each patient.

CB, the electrodiagnostic hallmark of MMN, was believed to underlie weakness in MMN. Treatment with IVIg may decrease the number of CB [3, 14, 18]. How-

ever, as confirmed by our results, most authors agree that CB status neither predicts nor runs parallel to clinical treatment response [9]. Recent studies showed that axon loss is also an important and early feature in MMN and correlates with muscle weakness [13, 17]. According to the study of Van Asseldonk et al., axon loss and not conduction block is the most significant independent determinant of weakness in corresponding muscles [12]. It is therefore unclear whether improvement of CB or reinnervation allows for improvement of motor function. The time course with quite rapid improvement within two months in our patients is in favor of IVIg reducing CBs. Furthermore, axonal degeneration was found to correlate significantly with both CB and with muscle weakness [12, 17]. Distal CMAP amplitude evolution is not optimal to determine axonal degeneration since a decrease in CMAP can either be due to distal CB, dispersion, or muscle atrophy due to inactivity or axonal degeneration. In our small sample, we found no spontaneous activity indicating ongoing denervation. Axonal damage could be only shown using quantitative analysis of motor unit potentials. We were not able to detect signs of axonal regeneration which probably would require a longer, high dose treatment phase and longer observation period [18]. Beneficial axonal regeneration is difficult to define and finally should lead to progressive and longstanding increase of CMAP amplitudes and reversal of atrophy. Vucic et al. in their highly selected patient group did not quantify their findings regarding axonal regeneration (e.g., using quantitative analysis of motor unit action potentials) and there is no statement about how many patients (instead of regions) had pretreatment axonal damage and in how many of them this finding disappeared. Furthermore, muscle atrophy, a frequent and even early finding [11, 12], is not commented and the high values for pretreatment distal CMAP amplitudes despite disease durations between 5 and 26 years is astonishing. The finding of axonal degeneration in only 16% of muscles as compared to 61% in the 20

**Table 2** Evolution of CB and distal CMAP

Patient	Nerve	Assessment of nerve conduction studies				Muscle
		Amplitude reduction (%) at site of CB		Amplitude CMAP (mV) with distal stimulation		
		baseline	after 6 months	baseline	after 6 months	
Case 1, 63 y/M	ulnar (R)	45	32	4.2	4.7	ADM (R)
Case 3, 47 y/F	ulnar (L)	63	67	3.5	4	ADM (L)
Case 4, 77 y/M*	ulnar (L)	32	27	3.8	4.9	ADM (L)
Case 6, 63 y/F	ulnar (L)	59	54	6.6	7	ADM (L)
Case 7, 56 y/M	ulnar (R)	99	98	7.2	6.1	ADM (R)
Case 8, 46 y/M	median (L)	72	77	4	4.7	APB (L)
Case 9, 51 y/M	radial (L)	80	100	2.5	1.5	Ext. dig. com. (R)

*ulnar* ulnar nerve; *radial* radial nerve; *APB* M. abductor pollicis brevis; *ADM* M. abductor digiti minimi; *Ext. dig. com.* M. extensor digitorum communis; \* assessment after 2 months



patients studied by Van Asseldonk [12] and to our results is also in favor of a selected patient population. We, as well as van Asseldonk, found axonal damage already in patients with short disease duration of less than 4 years. Determination of axonal damage should include quantitative analysis of motor unit action potentials.

Most adverse events of IVIg are mild and transient. The reported incidence varies widely between 1 and 81 % of patients treated or of applied infusions. Most studies report adverse events in 30 and 40 % of infusions [2, 4, 10]. The incidence is clearly dependent on the infusion rate, but it is unclear whether it is also dose dependent [1]. According to Dalakas the application of 2 g IVIg/kg over 2 days is not associated with more side effects than the application over 5 days [1]. We found a significantly higher incidence of reported adverse events with dose increase compared to the pre-study time with lower doses (73 % of cycles and 13 %, respectively; one withdrawal from study due to side effects and one septicemia which led to hospitalization). Aside the dose, age might play a role which was 59.4 years [46–80] in our patient population. The patient who did not tolerate the dose increase (case 4) was 77 years old.

The present study has several limitations: 1) non-randomized design (lack of a control group); 2) non-blinded evaluation; 3) non-linear scoring; 4) use of partly non-validated scores (atrophy score and individual disability score); 5) arbitrary defined criteria for treatment response; 6) small patient sample (e.g., for statistical analysis) and short time follow-up (6 months). However, randomization in this rare disease is difficult,

long-term clinical scoring given the individually quite variable features and slow progression is a challenge, Guy's and MRC scores are not very sensitive for focal weakness as frequently present in MMN, and a validated score for muscle atrophy is not available. In a double, blind trial of IVIg in MMN, disability self-reports proved in better agreement with overall clinical change than MRC estimates of strength [5].

## To summarize

Increasing IVIg dose can improve motor function in MMN patients with persistent deficits even after a prolonged seemingly stable disease course. Thus, instead of following the widely used treatment strategy of trying to find the lowest effective dose and the longest tolerated interval, it might be more successful to find the highest and most effective dose tolerated and the shortest interval with the highest gain of motor function. To what extent and for how long such a regimen can be pursued is unclear as well as whether it will work at any disease stage, e.g., regarding degree of axonal damage and muscle atrophy, or whether IVIg can prevent or even reverse axonal degeneration. Considering side effects and also economic aspects more and better designed multicenter studies with larger patient samples are necessary before such an expensive and burdensome treatment strategy can be widely recommended.

■ **Conflict of interest** The authors declare no conflict of interest.

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