Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulin: a double blind, placebo controlled study

L H Van den Berg, H Kerkhoff, P L Oey, H Franssen, I Mollee, M Vermeulen, F G I Jennekens, J H J Wokke

Abstract
The effect of high dose intravenous immunoglobulin (IVIg) treatment was studied in six patients with multifocal motor neuropathy (MMN). All patients responded to treatment (0.4 g/kg for five consecutive days) in an open trial. The effect of IVIg treatment was confirmed for each patient in a single patient, double blind, placebo controlled trial. Four patients received two IVIg treatments and two placebo treatments, and two patients received one IVIg and one placebo treatment in a randomised order. Five out of six patients responded to IVIg but not to placebo. One patient responded to IVIg in the same manner as to placebo treatment. Thus IVIg treatment can lead to improvement of muscle strength in patients with MMN.

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Patients with clinical signs of progressive asymmetric weakness and muscle wasting without sensory loss usually have motor neuron disease; however, when electromyographical examination shows motor conduction block, multifocal motor neuropathy (MMN) should be considered.1,2 Patients with MMN may respond to immunosuppressive treatment,3–5 by contrast with those with motor neuron disease.6 A beneficial effect of high dose intravenous immunoglobulin (IVIg), which has few serious side effects, has also been reported in these patients.6,7 The aim of our study was to perform an open, as well as a double blind, placebo controlled trial to confirm the effect of IVIg in patients with motor neuron disease.

Patients and methods
PATIENTS
Six patients were diagnosed as having MMN based on the presence of progressive asymmetric weakness and atrophy without sensory involvement, and with electromyographical evidence of conduction block. Electromyography showed evidence of denervation in at least three extremities in muscles innervated by different segments. Sensory conduction was normal. No patients had upper motor neuron findings or met the criteria for the diagnosis of chronic inflammatory demyelinating polyneuropathy.8

ELECTRODIAGNOSTIC STUDIES
Conduction studies were performed with standard techniques of supramaximal percutaneous stimulation and surface electrode recording (Dantec Counterpoint or Nicolet Viking apparatus). During all recordings, skin temperature was maintained at 34°C with an infrared heat lamp. Motor conduction studies were performed in ulnar, median, and peroneal nerves. The ulnar and median nerves were stimulated at the axilla, at the elbow (median nerve), above and below the elbow (ulnar nerve), and at the wrist. The peroneal nerve was stimulated above and below the fibular head and at the ankle. F responses were recorded in a series of 20 with distal stimulation (wrist or ankle). Conduction block and temporal dispersion were defined according to the criteria of Lange et al7 and Rhee et al.8 Conduction block was considered to be present when the amplitude as well as the area of the negative part of the compound muscle action potential (CMAP) was reduced by more than 50% of proximal v distal stimulation.1 Abnormal temporal dispersion was considered to be present when there was an increase of more than 30% in the duration of the negative part of the CMAP on proximal v distal stimulation. According to these criteria, for a given nerve segment there can be evidence of conduction block only, temporal dispersion only, or a combination of conduction block and temporal dispersion. Evidence of demyelination included the following (a) abnormal temporal dispersion; (b) reduction of motor conduction velocities or increase of distal motor latency (DML) or F wave latency according to American Academy of Neurology criteria, (c) absent F waves.9

ANTI-GM1 ANTIBODIES
IgM and IgG anti-GM1 antibodies were measured as described previously.10 Serum samples were also tested for antibodies to the GD1b and asialo-GM1 gangliosides, which share the Gal(β1–3)GalNAc epitope with GM1. Briefly, microwells were coated with 100 μl methanol containing 5 μg/ml GM1, asialo-GM1, or GD1b (Sigma, St Louis, USA) and evaporated overnight. Uncoated wells were used as controls. Wells were
saturated with 100 μl phosphate buffered saline (0.15 M NaCl, 0.01 M NaH₂PO₄, pH 7.4) containing 1% bovine serum albumin (enzyme linked immunosorbent assay (ELISA) solution) for four hours. Serum serially diluted in 50 μl of ELISA solution beginning with a dilution of 1:100 was added in triplicate to ganglioside coated wells and uncoated control wells, and incubated overnight at 4°C. After washing, peroxidase conjugated rabbit antibodies to human IgM (Sigma) diluted 1:1000 in ELISA solution were added. After two hours, reaction products were visualised with o-phenylene-diamine as substrate and read spectrophotometrically at 492 nm in a multispec reader. The upper normal limit was set at the highest titre obtained from normal and diseased controls (200 arbitrary units (U)/l). Anti-GM1 titres in the serum of patients who entered the trial were measured before and after IV Ig and in a simultaneous ELISA.

IV Ig TREATMENT PROTOCOL
The IV Ig treatment protocol included an open and a single patient double blind placebo controlled designed trial.

Open trial
Patients were treated with IV Ig (Central Laboratory Blood Transfusion, Amsterdam; 0.4 g/kg for five consecutive days). Patients who responded as defined later entered the double blind placebo controlled trial, which was started when the patient had returned clinically to the pretreatment state.

Double blind placebo controlled trial
The effect of IV Ig treatment was studied for each patient in a single patient randomised trial. Four patients (1–4) received two IV Ig treatments (0.4 g/kg for five consecutive days) and two placebo treatments (pasteurised plasma solution for five consecutive days) in a randomised order. Two patients (5, 6) received only one IV Ig and one placebo treatment for practical reasons (see results).

Treatments were blinded for the patient and the physician by the participating pharmacist. The interval between each treatment was determined by the time it took for the patient to return clinically to the pretreatment state. To prevent cumulative dose effects, the minimal time interval between two treatment courses was kept at one month. The code was revealed by the participating pharmacist after all treatment courses had been completed and all measurements evaluated.

ASSESSMENT OF TREATMENT RESPONSE AND CRITERIA FOR IMPROVEMENT
To ensure similar conditions for each treatment, patients were admitted to hospital for six consecutive days during each treatment course. Patients were examined before and after each treatment (days 1 and 6 of admission) and then weekly at the outpatient clinic by the same physician. Muscle strength (flexors and extensors of the neck, elbow, wrist, hip, knees, and feet; abductors of the upper arm; hand grip; abductor; and opponens of the thumb) was evaluated with a hand held dynamometer and the Medical Research Council (MRC) scale. We used the dynamometric measurements to define improvement of muscle strength: an increase of 50% or more had to be present in at least two muscles or muscle groups, without a decrease of at least 25% in more than one other muscle or muscle group. To study the correlation between these measurements and subjective improvement of the patient, the patients were asked to state the order in which they thought they had received IV Ig or placebo at the end of all treatment courses. Disability was measured with the modified Rankin scale.

Neurophysiological studies were performed before treatment and on days 6 and 14 after each treatment.

Results
PATIENTS (TABLE)
All six patients had a predominantly distal,
asymmetric limb weakness with gradual progression for two to eight years. The initial symptom was unilateral foot drop in two, grip weakness in three, and proximal arm weakness in one. At the time of IVIg treatment both upper and lower extremities were involved in four patients. The Rankin disability scale before treatment was 2 in all patients. Reflexes were poor in affected limbs in five patients and absent in one. In four patients (1–3, 6) fasciculations were seen. Two patients had a slightly raised concentration in protein in CSF. None of the patients had a serum monoclonal gammopathy.

ELECTRODIAGNOSTIC STUDIES
Evidence of conduction block only was found in three nerve segments on one side (lower arm segment of the median nerve in patients 3 and 4, upper arm segment of the ulnar nerve in patient 6). Evidence of conduction block and temporal dispersion was found in five nerve segments on one side (lower arm segment of the median nerve in patients 1 and 5, upper arm segment of the median nerve in patient 6, lower arm segment of the ulnar nerve in patients 2 and 5). Ulnar-median or median-ulnar anastomosis and accessory peroneal nerve were excluded. Demyelination on the basis of DML, conduction velocity, temporal dispersion, or F wave criteria was found in 18 nerves. In none of these nerves was there evidence of compression neuropathy on the basis of sensory conduction studies.

ANTI-GM1 ANTIBODIES
Patients 4 and 5 had raised IgM antibody activity to GM1 (350 and 230 AU/l). The fine specificities of these antibodies were, however, different. Patient 4 had raised antibody activity to asialo-GM1 (300 AU/l), but the antibody activity to GD1b was low (50 AU/l), whereas patient 5 had antibody activities to GD1b and asialo-GM1 within the normal range (15 AU/l and 0 AU/l). In patients 1, 2, 3, and 6 the antibody activity to GM1, GD1b, and asialo-GM1 was within the normal range. Anti-GM1 antibodies of the IgG isotype were within the range of normal and diseased controls for all patients with MMN.

RESPONSE TO IVIG TREATMENT: OPEN TRIAL
Muscle strength improved in at least two muscle groups in all patients with MMN. A maximum effect was measured one to two weeks after the onset of treatment. Subjective feelings of all patients were in agreement with the findings from myometry. Patients 1 and 2 were able to lift their right or left arm after treatment, a movement not possible before treatment, and they also experienced improved manual skills. For patient 2 these improvements resulted in the ability to lift and therefore drink a cup of coffee without assistance. Patients 3, 5, and 6 experienced improvement of manual skills. Patient 5, a bricklayer, could return to his work. Patient 4 was less tired after IVIg treatment. In patients 3, 5, and 6 improvement was detectable on the Rankin scale (from 2 to 1). Muscle strength returned to the pretreatment level within six weeks in patients 1, 2, and 4, within nine weeks in patients 3, and within 12 weeks in patient 6. In patient 5 the improvement of muscle strength after IVIg treatment lasted for 26 months. For that reason he received only one placebo and one IVIg treatment in the double blind placebo controlled trial. Patient 6 agreed to participate in only two treatment courses because of family circumstances, as well as the long distance between home and our hospital during the follow up period.

RESPONSE TO IVIG TREATMENT: DOUBLE BLIND PLACEBO CONTROLLED TRIAL (FIGURE)
All six patients entered the double blind placebo controlled trial. Muscle strength in five patients (1–3, 5, 6) improved after IVIg and remained stationary or became worse after placebo infusion. In these five patients

Dynamometric measurements (in Newtons) of muscles showing the clearest improvement in the double blind, placebo controlled study.
(A; patient 1) ... = R elbow extensor; ... = R elbow flexor; ... = R wrist extensor.
(B; patient 2) ... = R wrist extensor; ... = L shoulder abductor; ... = R shoulder abductor.
(C; patient 3) ... = L shoulder abductor; ... = R wrist flexor; ... = R shoulder abductor.
(D; patient 4) ... = R hip flexor; ... = L wrist extensor; ... = R elbow flexor.
(E; patient 5) ... = R hand grip; ... = R foot extensor.
(F; patient 6) ... = L wrist flexor; ... = L elbow flexor; ... = L shoulder abductor.
the objective improvement in muscle strength paralleled the subjective judgement of the patients. At the end of the four treatment courses, all five patients succeeded in naming the correct order of IVIg or placebo treatments before the code was broken. Improvement in patient 4 occurred once after placebo and once after IVIg, but she remained stationary after the two other treatment courses. Electroneurographic follow up showed an effect of IVIg treatment in only one patient (3) with conduction block disappearing in the lower arm segment of the right median nerve. Anti-GM1 antibody titres showed no significant changes.

**Discussion**

In the present study the effect of IVIg was investigated in an open and in a double blind, placebo controlled trial. In the open trial, all six patients with MMN responded to IVIg treatment, which confirms the results of other open trials. In the double blind, placebo controlled trial, the response to IVIg and placebo treatment was similar in one of the six patients. These results indicate that IVIg may be beneficial but that the effect of IVIg treatment may also represent a placebo effect in some patients.

The effect of IVIg treatment has been studied by Azulay et al in a double blind placebo controlled trial of five patients with MMN. A beneficial effect of IVIg was shown in all five patients. The experimental design of that study differed, however, from ours. We conducted an open as well as a double blind, placebo controlled trial; from the results, it seems that IVIg responders should be selected in a placebo controlled trial, as some patients who improve after IVIg treatment in an open trial may not respond in a double blind, placebo controlled trial (patient 4). In the placebo controlled trial by Azulay et al patients received two treatment courses, whereas in our study most patients received four courses. This reduces the likelihood of the effect of IVIg being due to chance alone from 50% to 16-6%. Four treatment courses may, however, not always be practical. In the study by Azulay et al the second treatment was given eight weeks after the first, whereas in our study the interval between each treatment was determined by the time the patient took to return clinically to the pretreatment state. Three of the six patients with MMN in our study were still responding to IVIg treatment after a period of more than eight weeks; therefore, our design may be preferred to avoid residual effects of a previous treatment course. Also, it may be important to recognise the duration of the effect of IVIg treatment for each patient with regard to follow up treatment. Improvement lasting more than one year after IVIg treatment, as in one of our patients, has been reported in a previous study.

In an open trial on the effect of IVIg in 52 patients with chronic inflammatory demyelinating polyneuropathy, 30 patients (57%) improved. The results of studies on the effect of IVIg in MMN show a better response to IVIg in patients with MMN, which may suggest that MMN is distinct from chronic inflammatory demyelinating polyneuropathy. Other distinguishing features are the pronounced asymmetric weakness, the absence of sensory abnormalities, and the normal or only slightly raised CSF protein in MMN. The clinical features of progressive asymmetric weakness and atrophy without sensory involvement suggest the presence of motor neuron disease, the referring diagnosis of five of the six patients. Therefore, careful neurophysiological examination for the detection of conduction block is essential to differentiate MMN, a potentially treatable disease, from MND. Although several patients with MMN have raised anti-GM1 antibody titres, the detection of these antibodies is not specific for MMN, as raised titres are also found in motor neuron disease and Guillain-Barre syndrome.

In the present study, conduction block disappeared after IVIg treatment in only one patient despite the clear clinical improvement. A possible explanation of this discrepancy may be that electrophysiological examination is a quantitative study of a limited number of individual motor nerves, whereas the muscle strength measurements involve the sum of several muscles. A minor improvement of nerves may not be detected electrophysiologically, although the sum of nerve improvements may lead to muscle strength improvement. Another explanation may be that longer treatment is necessary for electrophysiological changes to be detectable. Long term IVIg or immunosuppressive treatment may elucidate the role of conduction block and the involvement of motor neuron loss in MMN. Motor neuron loss or axonal degeneration may be the primary underlying disease and immunological mechanisms, responsible for the conduction block and demyelination, could play only a secondary part in MMN. In that case immunosuppressive treatment would only be beneficial temporarily. Another possibility is that axonal degeneration is secondary to conduction block or demyelination. In that case long term IVIg or immunosuppressive treatment would stabilise or improve the disease. Little is known of the effect of treatment on the outcome and long term prognosis of patients with MMN.

In conclusion, IVIg can lead to improvement of muscle strength in patients with MMN. A placebo controlled trial is useful to select IVIg responders as the effect of IVIg treatment may be similar to placebo treatment in some patients. Careful evaluation of treatment and long term follow up of more patients with MMN is necessary, not only to justify the use of IVIg treatment, which is expensive, but also to know more about the pathogenesis and future treatment strategies of the disease.

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Medical manners

Although Mr Lydgate and other physicians mentioned here have established the art of patient communication and, perhaps manipulation, the Yorkshire doctor in Howarth has clearly abandoned any such effort—one suspects that he had never acquired it.

In case one thought that overspecialisation was a modern failing, Dostoyevsky quickly disabuse us. In the same extract he describes the disarming directness of a medical student!

Henry Fielding, 1749, Tom Jones
To say the truth, every physician, almost, hath his favourite disease, to which he ascribes all the victories obtained over human nature. The gout, the rheumatism, the stone, the gravel, and the consumption, have all their several patrons in the faculty; and none more than the nervous fever, or the fever on the spirits.

Gustave Flaubert, 1865-7, Madame Bovary
When Dr Lavrière was angry, the whole hospital quaked. His pupils revered him to the point of trying to imitate him in everything as soon as they set up in practice themselves;

Elizabeth Gaskell, 1857, The life of Charlotte Bronté
When my husband and I had checked the effusion of blood with a strap that one of the bystanders unconcealed from his leg, he asked if a surgeon had been sent for.

"Yoli."
"But we dunna think he'll come.

"Why not?"
"He's owd, yo seen, and asthmatic, and it's up-hill."
My husband, taking a boy for his guide, drove as fast as he could to the surgeon’s house, which was about three-quarters of a mile off, and met the sexton of the wounded lad leaving it.

"Is he coming?" inquired my husband.

"Well, he didna say he wouldn' come."
"But tell him the lad may bleed to death."
"I did."
"And what did he say?"
"Why, only 'D -- n him; what do I care?"

George Eliot, 1858, Scenes of clerical life
They had both been long established in Milby, and as each had a sufficient practice, there was no very malignant rivalry between them; on the contrary, they had that sort of friendly contempt for each other which is always conducive to a good understanding between professional men; and when any new surgeon attempted in an ill-advised hour, to settle himself in the town, it was strikingly demonstrated how slight and trivial are theoretical differences compared with the broad basis of common human feeling.

Charles Dickens, 1859, A Tale of Two Cities
Doctors who made great fortunes out of dainty remedies for imaginary disorders that never existed smiled upon their country patients in the ante-chambers of monseigneurs.

George Eliot, 1871, Middlemarch
Mr Lydgate had the medical accomplishment of looking perfectly grave whatever nonsense was talked to him and his dark steady eyes gave him impressiveness as a listener.

Fyodor Dostoyevsky, 1880, The brothers Karamazov
I happened to come across a very enthusiastic little medical student. "You may die," he told me, "but at least you’ll have a very good idea of what illness you’re dying of!" And, then again, the way they have of sending you to specialists, "We can only diagnose your disease," they tell you. "You’d better go to such and such a specialist and he’ll be sure to cure you." I tell you the old-fashioned doctor who used to cure you of all illnesses has quite disappeared. Now there are only specialists and they all advertise in the papers. If there’s something wrong with your nose, they will send you to Paris: There’s a European specialist there who cures noses. You go to Paris, he examines your nose. "I’m sorry," he tells you, "I can only cure your right nostril, for I don’t cure left nostrils, it’s not my specialty. You’d better go to Vienna. There you’ll find a special specialist who will cure your left nostril."

G D Perkin
Regional Neurosurgery Centre, Charterhouse Hospital, Fulham Palace Road, London W6 8RF, UK