A randomised clinical trial comparing interferon-α and intravenous immunoglobulin in polyneuropathy associated with monoclonal IgM

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Abstract

***Objectives*—The polyneuropathy associated with a monoclonal IgM directed to the myelin associated glycoprotein (MAG) is a specific entity with a putative causal link between the IgM and the neuropathy. The small benefit offered by alkylating agents or plasma exchanges in these patients justifies the search for alternative treatments.**

***Methods*—A 12 month multicentre, prospective, randomised, open clinical trial was carried out comparing intravenous immunoglobulin (IVIg; 2g/kg and then 1 g/kg every three weeks) and recombinant interferon-α (IFN-α; 3 MU/m^2 subcutaneously three times weekly). The main end point was a clinical neuropathy disability score (CNDS) after six months of treatment. Twenty patients were enrolled; 10 were assigned to IVIg and 10 to IFN-α.**

***Results*—At six months, one out of 10 patients treated with IVIg had a CNDS improvement of more than 20% whereas eight out of 10 patients treated with IFN-α had such an improvement (P=0.005). The mean CNDS worsened by 2.3 (SD 7.6) (8%) in the IVIg group whereas it improved by 7.5 (SD 11.1) (31%) in the IFN-α group (P=0.02). This improvement persisted after 12 months and was mainly related to an improvement of the sensory component (P=0.02) whereas the motor component was unchanged (P=0.39). Electrophysiological data did not show improvement of motor nerve conduction velocities whereas sensory nerve conduction velocities improved in the upper limbs. A decrease in the level of the monoclonal IgM was seen in two patients treated with IFN-α. At the end of the treatment, antibody activity to MAG was still detected in the serum of all patients.**

***Conclusion*—IVIg, as used in this study, did not improve patients with polyneuropathy and monoclonal IgM. By contrast, although its mechanism of action remains to be fully elucided, IFN-α was effective in eight out of 10 patients at six months.**

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A peripheral neuropathy may be associated with a serum monoclonal IgM in the presence or absence of an overt lymphoid proliferative disease such as Waldenström's macroglobulinaemia.[1–3] A causal link between the monoclonal IgM and the development of neuropathy is suggested by (1) the specificity of most of these IgMs for the myelin associated glycoprotein (MAG),[4 5] peripheral nerve glycolipids,[6–8] and low molecular weight polypeptides[9]; (2) the detection by immunofluorescence of IgM and complement deposits on the myelin sheaths of patients' nerve biopsies[2 10 11]; (3) the induction, in animal models, of the neuropathological process through the transfer of the anti-MAG IgM[12 13] or by the intraneural injection of the IgM in peripheral nerves.[14] Because IgM associated neuropathy usually has a progressive course and can be responsible for severe disabling sensory and motor symptoms, effective therapy is necessary. Chlorambucil is given in chronic B cell malignancies such as chronic lymphocytic leukaemia and Waldenström's macroglobulinaemia and could therefore be active on anti-MAG secreting B cells, even in the absence of a detectable lymphoid proliferation.[15] However, in a previous study of 44 patients with IgM associated neuropathy, treatment with chlorambucil was unsucessful in two thirds of the patients and yielded only a slight improvement in the others.[16] No benefit from plasma exchange was found in this study. Likewise, a double blind study of plasma exchange in patients with monoclonal IgM neuropathy failed to show any benefit.[17] Therefore, a more effective therapeutic approach is warranted. Two potential useful treatments need to be tested: intravenous immunoglobulins (IVIg), which have been used with some improvement in a few patients,[18 19] and interferon-α (IFN-α) which induces remission in Waldenström's macroglobulinaemia,[20] as well as in monoclonal gammapathies of undetermined significance associated with mixed cryoglobulinaemia[21] or cold agglutinins.[22] Moreover, IFN-α may inhibit the spontaneous in vitro differentiation of purified B lymphocytes to plasma cells which was found in monoclonal gammapathies of undetermined significance.[23] Instead of conducting two independent phase II trials with each of these two treatments, we designed a multicentre, prospective, randomised, open clinical trial

assessing IVIg and IFN-α. Due to its disappointing results,[16] chlorambucil was not used as a reference. As assessment of these treatments in this chronic disease requires long term therapy, it was considered that a placebo group would be unethical.

Methods

PATIENTS AND CRITERIA FOR INCLUSION

Patients included in this study were recruited from five French departments of neurology and one department of immunohaematology. They had to fulfill the following criteria : (1) stable or progressive neuropathy for at least three months; (2) presence of a serum monoclonal IgM with anti-MAG antibody activity as detected by immunoblotting on delipidated human myelin[7]; (3) a clinical neuropathy disability score (CNDS) > 10 (see below); (4) exclusion of other causes of peripheral neuropathy, especially diabetes, alcohol misuse, cryoglobulinaemia, and amyloidosis; (5) absence of treatment in the past three months.

STUDY DESIGN AND TREATMENT

The study was designed to be a multicentre, prospective, randomised, open clinical trial comparing two treatments. The protocol was approved by the Hôpital Saint-Louis ethics committee. After providing written informed consent, patients underwent stratified randomisation according to the existence of a previous treatment, through a blind telephone assignment procedure. The patients were randomly assigned to receive either IVIg or IFN-α. IVIg (Laboratoire Français du Fractionnement et des Biotechnologies) was given at 500 mg/kg/day for the first four days followed by 500 mg/kg/day for two days every three weeks for a six month period and then, if improvement was found (more than 20% improvement in the clinical neuropathy disability score (CNDS)), every six weeks for the next six months. Recombinant IFN-α (Roferon, Roche) was administered subcutaneously at 3 MU/m^2 three times a week for six months and, if improvement occurred, at 3 MU/m^2 twice a week for the next six months. In cases of worsening of the neuropathy before the sixth month (more than 20% worsening of the CNDS) or of absence of improvement at six months, the patients were switched to the other treatment.

EVALUATION OF NEUROPATHY

The clinical neuropathy disability score (CNDS) (see appendix 2) resulted from a slightly modified score described elsewhere.[24 25] Briefly, selected items from the neurological evaluation were scored and summed. The function of 14 muscles (×2) was scored as 0 if normal and 1 if abnormal; sensation (touch-pressure, pin prick, warm-cold, joint motion, vibration) was scored in the same way; pain, paraesthesia and dysaesthesia were scored as 0 if absent and 1 if present; six muscle stretch reflexes (×2) were scored as 0 if present and 1 if absent. Scores could range from 0 to 93, summing 0 to 28 points for the motor component, 0 to 12 for the reflexes component, and 0 to 53 points for the sensory component. In addition, the patient was asked to rate the change in five symptoms : paraesthesia, dysaesthesia, ability to feel the floor, tightness, and walking in major improvement (−2), slight improvement (−1), stability (0), slight worsening (+1), major worsening (+2). This score termed "subjective assessment" ranged from −10 to +10 and was added to the previous one in follow up examinations. The examinations were performed by the same physician for each patient.

ELECTRODIAGNOSTIC STUDIES

Electrodiagnostic studies were performed at baseline and after six and 12 months of treatment with a Viking Nicolet electromyograph. Needle EMG examination was performed in all patients. The incidence of spontaneous activity at rest (fibrillation potentials and positive sharp waves) was recorded. The size of motor unit potentials and the pattern of recruitment during maximal effort were also analysed. Motor nerve conduction studies were performed with supramaximal percutaneous nerve stimulation, whereas compound muscle action potentials (CMAPs) were recorded with surface electrodes. Median, ulnar, and peroneal nerves were examined on both sides. The median nerve was stimulated at the wrist and the elbow. The ulnar nerve was stimulated at the wrist, below and above the elbow. The peroneal nerve was stimulated at the ankle, below and above the fibular head. During all nerve conduction studies, skin temperature was maintained at 36°C. Distal latencies, conduction velocity, and evoked motor response amplitudes (baseline to negative peak), were measured. Sensory nerve conduction and amplitude were measured in the median, ulnar, superficial peroneal, and sural nerves with surface recording and stimulating electrodes. The nerves were stimulated by orthodromic techniques in the upper limbs and antidromic techniques in the lower limbs. Amplitudes of the sensory nerve action potentials (SNAPs) were measured peak to peak.

EFFICACY CRITERIA

The main end point was defined by the change in the CNDS between the randomisation and the sixth month of therapy or the time of withdrawal of treatment if the treatment had been modified or stopped before the sixth month. The number of patients in each group who experienced an improvement of the CNDS of more than 20% was determined. Other criteria were (1) the change in the CNDS between the randomisation and the 12th month of therapy; (2) the change in electrophysiological data; (3) the change in the level of the monoclonal component; and (4) the change in the serum anti-MAG antibody activity.

SAMPLE SIZE AND STATISTICAL ANALYSIS

Estimation of sample size was based on the main criterion, using a two sample t test. We were expecting a difference between treatment groups of 10 with an SD of 10, using the estimates derived from a previous trial.[16] Specifying a type I error of 0.05 and a power of 0.90, a

Table 1 Baseline characteristics according to treatment

	IVIg (n=10)	*IFN-α (n=10)*
Age (y)	66 (10) (52-85)	67 (5) (60-76)
Sex (M/F)	7/3	9/1
Patients never previously treated	6	6
Duration of neuropathy (y)	4.0 (5.3) (0.4-17.8)	3.1 (1.8) (0.3-6.1)
Detection of monoclonal gammapathy (y)	2.5 (5.1) (0.1-16.8)	1.6 (2.1) (0.1-6.1)
Patients with bone marrow lymphoid infiltrate	3	3
Clinical score	28.7 (11.5) (10-48)	24.4 (11.3) (12-49)

Values are means (SD) (range).

Table 2 Clinical evolution according to treatment

Clinical score	*Time (months)*	*IVIg (n=10)*	*IFN-α (n=10)*	*P value (Kruskal-Wallis)*
Global score	0	28.7 (11.5)	24.4 (11.3)	
	6	31.0 (11.3)	16.9 (13.3)	0.02
	6−0	2.3 (7.6)	−7.5 (11.1)	0.02
Motor score	0	3.5 (3.3)	2.9 (5.5)	
	6	3.4 (3.1)	2.2 (4.4)	0.09
	6−0	−0.1 (1.4)	−0.7 (1.9)	0.39
Sensory score	0	17.2 (7.2)	16.0 (5.7)	
	6	17.8 (6.4)	11.6 (5.0)	0.04
	6−0	0.6 (4.5)	−4.4 (3.8)	0.02
Reflex score	0	8.0 (4.0)	5.5 (3.9)	
	6	9.6 (4.1)	6.0 (4.9)	0.14
	6−0	1.6 (2.3)	0.5 (4.1)	0.10
Subjective assessment	6	0.2 (1.0)	−2.9 (3.2)	0.01
	6−0	0.2 (1.0)	−2.9 (3.2)	0.01

Values are means (SD).

two sided test required 22 patients per group. Given the low incidence of this disease, the protocol planned two interim analyses to minimise the sample size, using repeated significance tests with a nominal significance level of 0.029.[26] Investigators were not provided with interim results as long as treatment difference was non-significant. Statistical analysis used a modified intention to treat approach: all randomised patients were analysed in their arm of treatment assigned by randomisation. However, when patients dropped out, the six month score was estimated by the last examination before switch. Comparisons used the Kruskal-Wallis test for continuous variables and Fisher's exact test for binary variables. The relation between continuous variables was studied by the Spearman's test for rank correlation. To adjust treatment comparison for baseline prognostic variables (baseline CNDS, previous treatment, and disease duration), a regression model was used. All tests were two sided. The SAS (SAS Institute, Cary, NC, USA) software package was used.

Results

The statistical analysis at the first interim analysis showed a benefit of IFN-α over IVIg (P=0.02) and hence no more patients were added, according to the rule defined in the protocol (nominal significance level of 0.029).Thus 20 patients were enrolled from five hospitals in a three year period, 10 being assigned to IVIg and 10 to IFN-α. Eight patients (four in each group) had been previously treated with chlorambucil without improvement of the neuropathy. In three of them, plasma exchanges were also unsuccessful. The mean duration (SD) of the peripheral neuropathy was 3.6 (3.9) years. The randomisation procedure resulted in balanced treatment groups for patient characteristics and neurological abnormalities (table 1). We found a strong correlation between baseline CNDS and duration of disease (r=0.62, P=0.004 by Spearman's test) and a trend for a relation between baseline CNDS and existence of a previous treatment (P=0.10 by Kruskal-Wallis test).

In the IVIg group, four patients withdrew early from therapy; one because of toxicity (he developed a self limited erythroderma five days after the first course of IVIg), one for personal reason after one course of IVIg, and two after three and five courses of IVIg respectively for intercurrent diseases (acute decompensation of chronic bronchitis and traumatic fractures). None of these patients improved before they stopped IVIg. These patients were analysed in the IVIg group according to the intention to treat principle. One other patient of the IVIg group switched to the IFN-α group after four months of IVIg because of progression of the neuropathy. In the IFN-α group, no patients withdrew from therapy before the sixth month but the dosage of IFN-α was tapered to 2 MU/m^2 because of systemic adverse effects in three patients. No haematological toxicity was found in the IFN-α group. Flu-like symptoms occurred at the beginning of the treatment in all 10 patients treated with IFN-α but persisted in only three of them leading to tapering of the dosage to 2 MU/m^2. There were no local adverse effects.

After six months of treatment, one out of 10 patients treated with IVIg had a decrease—that is, an improvement in CNDS—of more than 20% whereas eight out of 10 patients treated with IFN-α had such an improvement (P=0.005 by Fisher's test). Table 2 presents the detailed results. The mean CNDS decreased (improved) by 7.5 (SD 11.1) (31%) in the IFN-α group whereas it increased (worsened) by 2.3 (SD 7.6) (8%) in the IVIg group (P=0.02 by Kruskal-Wallis test). The improvement in the IFN-α group was mainly related to an improvement of the sensory component of the CNDS (P=0.02 by Kruskal-Wallis test) whereas the motor component of the CNDS was unchanged (P=0.39 by Kruskal-Wallis test). The adjusted comparison for the three selected baseline variables (baseline CNDS, previous treatment, disease duration) also showed the benefit of IFN-α (P=0.001). Among the nine patients treated unsuccessfully with IVIg, four stopped the protocol, three for intercurrent events (see above) and one for progression to overt lymphoma, and five were switched to IFN-α. One of these five patients had an improvement of more than 20% with IFN-α. The two patients of the IFN-α group who switched to IVIg had no improvement of the CNDS. The only patient who improved transiently with IVIg was refractory to chlorambucil. The four patients refractory to chlorambucil in the IFN-α group improved with IFN-α at six months but one of them returned to baseline score at 12 months.

The difference between the two groups persisted after 12 months. The only patient who improved with IVIg at six months returned to baseline score at 12 months. Among the eight patients who improved with IFN-α at six

Table 3 Electrophysiological data according to treatment

	Time (months)	*IVIg (n=8)*	*IFN-α (n=7)*	*P value (Kruskal-Wallis)*
Patients with absence of peroneal CAMP (n)	0	5	3	
	6	4	3	
Patients with absence of ulnar CAMP (n)	0	1	1	
	6	1	1	
Mean ulnar MNCV (m/s)	0	32.1 (18.4)	33.1 (15.0)	
	6	32.2 (16.9)	33.3 (15.1)	0.94
Mean ulnar DL (ms)	0	8.8 (7.3)	5.4 (3.0)	
	6	7.4 (5.9)	6.6 (2.4)	0.73
Patients with absence of sural SNAP (n)	0	5	5	
	6	7	5	
Patients with absence of median SNAP (n)	0	4	5	
	6	7	2	

Values in parentheses are SD.
CAMP = Compound muscle action potential, MNCV = motor nerve conduction velocity, DL = distal latency, SNAP = sensory nerve action potential.

months, one worsened returning to his initial score, one was stable with a 75% decrease in the CNDS, and six experienced a sustained improvement (five of these six patients had a decrease of CNDS of more than 50%). These six patients were willing to continue IFN-α treatment after the planned duration of the protocol. Four patients are still being treated with IFN-α at 2 million U/m^2 twice a week with 16, 16, 23, and 40 months of follow up. The two other patients were treated for 18 and 40 months and remained stable 28 and five months respectively after IFN-α was disrupted.

Electrophysiological data were available in 15 patients (eight in the IVIg group, seven in the IFN-α group; table 3). These 15 patients had the same clinical evolution as the whole group (data not shown). At onset, CMAP was absent in the peroneal nerve in five patients in the IVIg group and in three patients in the IFN-α group and remained undetectable under treatment. The mean value of ulnar motor-nerve conduction velocities and distal latencies were not different between the two groups at six months. SNAPs of the sural nerves were not obtained in five patients in the IVIg group and in six patients in the IFN-α group at entry, and did not improve in the two groups. However, SNAPs of the median nerve, which was absent in four patients in the IVIg group and in five patients in the IFN-α group at baseline, was not obtained in seven patients in the IVIg group at six months and in only two patients in the IFN-α group at six months. Due to the large number of patients with no SNAP at baseline in the two groups, it was impossible to compare the evolution of sensory nerve conduction velocities (SNCVs) and amplitudes in the two groups. Nevertheless, the three patients in the IFN-α group without any median SNAP at baseline who recovered SNAPs after six months of IFN-α therapy had SNCVs of the median nerve of 29, 33, and 28 m/s with amplitudes of 3.9, 2.4, and 3.0 mV respectively.

At the end of the treatment, the antibody activity to MAG and the monoclonal IgM were detected in the serum of all of the patients. In two patients who improved under IFN-α, the monoclonal component decreased by more than 50%. In the other patients, no significant decrease in IgM was noted.

Discussion

The peripheral neuropathy associated with a monoclonal anti-MAG IgM is considered to be specific.[2–4 27] The clinical features are different from those found with monoclonal IgG or IgA, with more sensory loss and ataxia. A causal link between the monoclonal IgM and the development of neuropathy is suggested by the antibody activity of the IgM to nerve polypeptides or glycolipids,[4–9] the detection of IgM deposits on the myelin sheaths of nerve biopsies from patients,[2 10 11] and the induction of the neuropathological process through the transfer of the anti-MAG IgM in animal models.[12 13] The low rate (30%) of clinical improvement with chlorambucil or plasma exchange in such patients[16 17] needs the development of new therapeutic strategies. A double blind double dummy trial could not be conducted because of the duration (one year) and the mode of administration of the treatment. The clinical score used in the present study was correlated with known predictive factors of the disease (duration of the neuropathy and need of a previous treatment) and therefore seems to be a satisfactory criterion for the evaluation of the neuropathy under treatment. The first interim analysis disclosed a benefit of IFN-α (P=0.02 by Kruskal-Wallis test) leading to no more inclusion of patients according to the rule defined in the protocol. Likewise, the adjusted comparison, which takes into account the baseline imbalances and the prognostic variables and allows for a better statistical power, rejected the null hypothesis with low significance levels (P=0.001 at six months) and strengthened the conclusion of a higher efficacy of IFN-α than IVIg.Treatment with IVIg has been found to be effective in several autoimmune diseases such as autoimmune thrombopenic purpura, polymyositis, and Kawasaki disease through a multiple potential mechanism (reviewed in Kazatchkine *et al*[28]). The use of IVIg has been proposed for the treatment of peripheral neuropathies suspected to be immune mediated such as Guillain-Barré syndrome,[29] chronic inflammatory demyelinating polyneuropathy,[30] and multifocal motor neuropathy.[31] Two open trials tested IVIg in the treatment of peripheral neuropathy associated with monoclonal IgM gammapathy; Cook *et al* reported two patients who had clinical improvement after IVIg therapy[18]; a slight clinical improvement (grade 1 decrease of the Prineas score) was also found by Léger *et al* in six of 13 patients treated with IVIg[19]; however, in this study, most of the patients worsened after several months despite further treatment with IVIg. In our study, a clinical improvement with IVIg was found in only one patient at six months which disappeared at 12 months. The treatment was also unsuccessful in two patients of the IFN-α group who switched to IVIg. However, only six of the 10 patients in the IVIg group completed six months of therapy with IVIg. Indeed, four patients dropped out of

treatment early because of intolerance (one patient), personal reasons (one patient), or intercurrent diseases (two patients). Moreover, the clinical score at baseline was higher in the IVIg group than in the IFN-α group (28.7 (SD 11.5) *v* 24.4 (SD 11.3)); and duration of neuropathy, usually associated with less reversible neuropathy, was longer (4 (SD 5.3) *v* 3.1 (SD 1.8)) years. IFN-α produced a significant clinical improvement in eight out of 10 patients at six months and in seven out of 10 patients at 12 months, six of these patients having a decrease of the global CNDS of more than 50%. Four of these patients are still being treated with IFN-α and two have stable disease 28 and five months after stopping IFN-α. Haematological and systemic tolerance of IFN-α were acceptable. Electrophysiological data did not show improvement of motor nerve conduction velocities. Although sensory nerve conduction velocities were not modified in the lower limbs, they significantly improved together with the potential amplitude in the upper limbs, which were less damaged at the onset. An electrophysiological improvement is likely to be detectable only if nerve demyelination is not too severe. As peripheral axonal neuropathy has been attributed to IFN-α, although very rarely,[32] the patients were followed up very carefully, but none of them experienced early worsening of their neuropathy.The mechanism of action of IFN-α is unclear. It induces a decrease in serum monoclonal IgM in almost half of patients with Waldenström's macroglobulinaemia,[20] but also in IgM monoclonal gammapathies of undetermined significance such as cold agglutinins.[22] On the other hand, IFN-α is also effective in mixed cryoglobulinaemia associated with hepatitis C viral infections, probably because of its action on the replication of the virus.[33] In this study, a decrease in the level of the monoclonal IgM was found in only two patients although the neuropathy improved in eight of 10 patients. The possibility that IFN-α led to an increase in polyclonal IgM antibodies which could have masked its effect on the monoclonal IgM is unlikely because IgM was still detected by immunofixation and anti-MAG antibody activity was still present in the serum of all patients after treatment. Therefore, the mechanism of action which has been anticipated seems to play a minor part, if any, in the improvement of the neuropathy. Unexpectedly, this holds true also for patients who improved with chemotherapy.[16] Of note, IFN-α has been found to be active in an autoantibody mediated neurological disease in mice—experimental autoimmune myasthena gravis—without decreasing the amount of pathogenic antibodies to the acetylcholine receptor.[34] Therefore, the potential beneficial role of IFN-α in some autoimmune diseases may be linked to mechanisms of action other than the decrease of production of autoantibodies. IFN-α has multiple functional effects on various cell types which might offer some clues.[35] It may decrease the level of mRNA for proinflammatory cytokines such as tumour necrosis factor TNF-α and the interleukins IL1 and IL6, downregulate MHC class II expression, upregulate the immunosuppressive cytokine TGF-β, and upregulate the expression of adhesion molecules. This last mechanism could be relevant in anti-MAG associated neuropathies. It is conceivable that IFN-α decreases the permeability of the blood-peripheral nerve barrier—for instance, by modulating the expression of adhesion molecules[36]—which could result in a more limited acces of anti-MAG IgM to the peripheral nervous system. In this setting, it is of interest that endothelial cells in the bovine nervous system express the glycolipid sulphoglucuronosyl paragloboside, which is a target of anti-MAG antibodies, and that human monoclonal anti-MAG IgM antibodies increase the leakage of ^{14}C-inulin and ^{125}I-IgM through brain microvascular endothelial cells monolayers.[37]

In conclusion, IVIg, as used in this study, did not improve patients with polyneuropathy associated with monoclonal anti-MAG IgM. By contrast, although its mechanism of action remains to be fully elucidated, IFN-α was effective in eight out of 10 patients at six months and in seven out of 10 patients at 12 months. Evaluation of sustained benefit in this chronic disease requires long term follow up.

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Appendix 1: The IgM associated Polyneuropathy Study Group

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Appendix 2: Clinical neurological disability score (Y = yes, N = no)

	Right		*Left*	
I Muscle weakness				
Upper limbs:				
Holding or keeping a pencil (between thumb and index)	Y	N	Y	N
Holding a glass	Y	N	Y	N
Wrist flexion	Y	N	Y	N
Elbow flexion (in supination)	Y	N	Y	N
Elbow flexion (in pronation)	Y	N	Y	N
Elbow extension	Y	N	Y	N
Lower limbs:				
Toes movements	Y	N	Y	N
Ankle dorsiflexion	Y	N	Y	N
Plantar flexion	Y	N	Y	N
Knee flexion	Y	N	Y	N
Hip flexion	Y	N	Y	N
Maintainance of legs against gravity (Mingazzini test)	Y	N	Y	N
Rising on toes		Y	N	
Rising on heels		Y	N	
Rising from chair (without any support)		Y	N	
Walking alone (without any support)		Y	N	
M = number of nos: /28				
II Reflexes				
Biceps	Y	N	Y	N
Triceps	Y	N	Y	N
Supinator (radial periosteal)	Y	N	Y	N
Pronator	Y	N	Y	N
Knee	Y	N	Y	N
Ankle	Y	N	Y	N
R = number of nos: /12				
III Sensory function				
Abnormal sensations:				
Paraesthesiae (tingling numbness, pins and needles)				
In the hand	Y	N	Y	N
Between wrist and elbow	Y	N	Y	N
Above elbow	Y	N	Y	N
In the foot	Y	N	Y	N

	Right		*Left*	
Between ankle and knee	Y	N	Y	N
Above knee	Y	N	Y	N
Dysaesthesiae (pain, burning, "electric discharge")				
In the hand	Y	N	Y	N
Between the wrist and elbow	Y	N	Y	N
On the elbow	Y	N	Y	N
In the foot	Y	N	Y	N
Between ankle and knee	Y	N	Y	N
On the knee	Y	N	Y	N
Is there inability to feel the floor?	Y	N	Y	N
Do you feel tightness?				
In the wrist	Y	N	Y	N
In the ankle	Y	N	Y	N
Examination:				
Joint position sense problems				
Upper limbs	Y	N	Y	N
Lower limbs	Y	N	Y	N
Vibratory sense problems				
Upper limbs	Y	N	Y	N
Lower limbs	Y	N	Y	N
Pinprick test problems				
Upper limbs	Y	N	Y	N
Lower limbs	Y	N	Y	N
Thermal sensation problems				
Upper limbs	Y	N	Y	N
Lower limbs	Y	N	Y	N
Are there difficulties in identifying objects with fingers (astereognosis)?	Y	N	Y	N
Hand tremor	Y	N	Y	N
Ataxia (Romberg's sign)		Y	N	
Gait instability				
Using a walking stick		Y	N	
Without a walking stick		Y	N	

S = number of yes: /53

IV Subjective assessment

From the beginning of the treatment what are the changes in the following symptoms:

Paraesthesiae	−2: major improvement
Dyaesthesiae	−1: slight improvement
Inability to feel the floor	0: no change
Tightness	+1: slight worsening
Walking problems	+2: major worsening

SA = (from −10 to +10)

For the initial score, SA = 0

Score: M+R+S+SA = /103