Chronic idiopathic polyneuropathy presenting in middle or old age: a clinical and electrophysiological study of 75 patients

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Abstract
The clinical and electrophysiological features were prospectively studied of 75 patients (46 men and 29 women) with chronic polyneuropathy presenting in middle or old age in whom a diagnosis could not be made even after extensive evaluation and a follow up of six months. The mean age at the onset of symptoms was 56±5 years. The clinical features of chronic idiopathic polyneuropathy were heterogeneous. On clinical grounds 44 patients had a sensorimotor, 29 patients a sensory, and two patients a motor neuropathy. The overall clinical course in chronic idiopathic polyneuropathy was slowly progressive. None of the patients became severely disabled. Electrophysiological and nerve biopsy studies were compatible with an axonal polyneuropathy. Antibodies against myelin associated glycoprotein, gangliosides, and sulphatides were assessed in 70 patients and found to be negative.

Methods
Between 1987 and 1991 we studied 75 patients with a polyneuropathy in whom no diagnosis could be made after extensive evaluation. Of these patients, 53 were directly referred by other neurologists to the department of neuromuscular diseases in Utrecht. From 1987 to 1991 approximately 500 patients with polyneuropathy were diagnosed in our department. Consequently, in our group of neuropathies 10% were idiopathic. The remaining 22 patients were referred to us after diagnosis in other University Hospitals (Rotterdam, Nijmegen, Amsterdam, so the total number from which they were drawn are not known. All patients were repeatedly examined by the same neurologist (NCN). A patient was eligible if: (1) neurological examination showed symmetrical signs of sensory or motor impairment of the limbs with a distal distribution; (2) the polyneuropathy had a slow onset and developed gradually in months rather than days or weeks; (3) electrophysiological investigations were compatible with a peripheral neuropathy; (4) the first symptoms of the neuropathy appeared between the age of 45 and 70 years. The limit of 45 years was chosen because the majority of inherited polyneuropathies presents at a younger age. The limit of 70 years was chosen to exclude any possible effect caused by the normal ageing process of the nervous system; (5) all laboratory tests were within normal limits, except for serum antibodies (see Laboratory section).

The following patients were excluded: (1) patients in whom a definite diagnosis could be made by clinical, laboratory or histological examinations; (2) patients with an elevated CSF protein level (>1 g/l) in combination with electrophysiological signs of demyelination, to prevent the inclusion of patients with a CIDP; (3) all patients with a history of any disease which could be associated with a neuropathy (for example, malignancy, intestinal surgery, thyroid disease).

PATIENT EVALUATION
After scrutinising all inclusion criteria the neurological interview and examination were carried out in a standardised fashion. This included an extensive interview to determine the nature and distribution of motor, sensory, and autonomic symptoms (blurred vision, orthostatic hypotension, ability to sweat, bowel and cardiac dysfunction, impotence, sphincter incontinence), the progression of the disease, the degree of physical disability,
the concurrence of other diseases or possible intoxications (medication, alcohol, occupational and environmental toxic agents). A detailed kinship history was taken to minimise the chance of including patients with a hereditary polyneuropathy; when there was any doubt, next of kin suspected of having a neuropathy were neurologically examined.5

Six muscles in both arms (deltoid, biceps brachii, triceps brachii, finger extensors, finger flexors, and interossei) and six muscles in both legs (iliopsoas, quadriceps, hamstring, anterior tibial, gastrocnemius, and peroneus) were tested, using the MRC grading system. Summation of the proximal or distal limb score could each lead to a maximum motor score of 30. Deep tendon reflexes in both arms (biceps jerk, triceps jerk) and in both legs (knee jerk, Achilles jerk) were tested and graded as follows: normal = 2, diminished = 1, absent = 0. Summation of the reflex scores of both sides could lead to the maximum score of 4 for each reflex. The following sensory modalities were examined: touch, pinprick, vibration, and joint position sense. The sensory system was graded as follows: touch and pinprick sense; normal = 4, distal to wrist/ankle abnormal = 3, distal half forearm/leg abnormal = 2, distal to elbow/knee abnormal = 1, distal to axilla/groin abnormal = 0. Vibration sense: tuning fork perception (128 Hz) on: middle finger/hallux = 4, ulnar styloid/medial malleolus = 3, elbow/knee = 2, calcavula/crista = 1, no perception = 0. Summation of each of these sensory modalities could lead to a maximum score of 16. Joint position sense of middle finger/hallux: normal = 2, diminished = 1, absent = 0. Summation could lead to a maximum score of 8. In addition all patients were assessed with the modified Rankin scale.14

LABORATORY

The following laboratory investigations were performed in every patient and had to be normal: haemoglobin, haematocrit, leucocytes, platelets, erythrocyte sedimentation rate, serum glucose, renal function and electrolytes, liver enzymes, serum calcium and phosphorus, urea, creatinine, serum protein transketolase, vitamin B12, folic acid, thyroid function, serum agargel and immunoelectrophoresis, antinuclear antibodies, cryoglobulins, rheumatoid factors. All patients had a routine chest x-ray and a total body bone scan. In addition, CSF was obtained in almost all of the patients. The presence of serum antibodies against myelin associated glycoprotein (MAG) was investigated by thin layer chromatography, using the glycolipid SGPG (kindly provided by Dr N Latov, Columbia University, New York, USA).19 Sera were tested for antibodies against GM1 gangliosides16 and against sulphatides (ELISA, measured by Dr N Latov).17 Whenever there was any suspicion on clinical or laboratory grounds of an inflammatory or infiltrating disorder (vasculitis, amyloidosis, sarcoidosis, and inflammatory demyelinating neuropathy), inherited storage disorder and abnormality of myelination, a sural nerve biopsy was performed.18-20 In all patients with a slightly elevated CSF protein (0.45-1.0 g/l) a biopsy was also taken and only those patients whose biopsy showed no signs of inflammation or infiltration were entered into the study.21

ELECTROPHYSIOLOGICAL ASSESSMENT

Electrophysiological investigations according to the procedure described below were carried out in 60 patients in order to confirm and classify the peripheral neuropathy. The first dorsal interosseus and tibial anterior muscles were examined using concentric needle investigation. Nerve conduction studies were performed with surface electrodes using standard techniques.22 We investigated the ulnar nerve (motor and sensory) in one arm, the tibial nerve (motor) and the sural nerve in one leg, and the H-reflex of the soleus muscle in the opposite leg. The following variables were measured: distal motor latency (DML), motor and sensory conduction velocity (CV), the compound muscle action potential (CMAP) amplitude (baseline to first negative peak), and sensory nerve action potential (SNAP) amplitude (first positive to first negative peak), the latency difference between H-reflex and M-response (H-M interval). The variables were considered abnormal when they exceeded the limits of normality at 2 SD level. These were: (1) tibial nerve CV 40 m/s, DML 5.9 ms, CMAP 2.0 mV; (2) sural nerve CV 39 m/s, SNAP 2.5 μV; (3) ulnar nerve (motor) CV 47 m/s, DML 3.7 ms, CMAP 1.7 mV; (4) ulnar nerve (sensory) wrist-fifth finger CV 44 m/s, SNAP 5.6 μV; (5) ulnar nerve sensory elbow-wrist CV 54 m/s. For the H-M interval the normal limits of Visser et al23 were taken. Criteria for demyelination were: (1) CMAP area on proximal stimulation less than 50% of the CMAP area on distal stimulation, indicating a conduction block4; (2) elbow to wrist CV less than 40 m/s in the ulnar nerve, or less than 30 m/s in the tibial or sural nerve; (3) ulnar DML longer than 7 ms or tibial DML longer than 10 ms.25 Axonal degeneration was possible diagnoses, criteria following was found: (1) spontaneous EMG activity such as fibrillation potentials, positive sharp waves or complex repetitive discharges on concentric needle examination; (2) reduced amplitude of CMAP or SNAP in the absence of conduction block.

RESULTS

Seventy five patients were studied (46 men and 29 women). The mean age at the onset of symptoms was 56.5 years (SD 6.4). The mean time from onset of symptoms to entry into the study was 6.3 years (SD 4.3). On clinical grounds 44 patients (21 men, 23 women) had a sensorimotor, 29 patients (23 men, 6 women) a pure sensory, and two men a pure motor polyneuropathy. In motor neuropathies the symptoms and signs were purely motor except for a diminished vibration sense
in the big toe which was not regarded as evidence for sensory involvement.

SYMPTOMS
In all patients the symptoms had developed in the course of 6 to 12 months. All symptoms had become symmetrical within the first 3 months. In all but one patient the symptoms started distally in the legs. In one patient the symptoms started with tingling in the hands; after 6 months she also complained about tingling in her feet.

In the sensorimotor neuropathy the most common presenting symptoms were tingling in the sole of the foot (14 patients), a heavy, tired feeling or weakness in the feet (10 patients), and sensations of numbness in the feet (nine patients). Other initial complaints were band-like sensations around the ankles, a feeling of stiffness in the calf and the feeling of walking on cotton wool. In the sensory neuropathy the presenting symptoms were paresthesias in the feet (nine patients), numbness of the feet (12 patients), and a burning pain in the soles of the feet (seven patients) (table 1). The two patients with a clinically pure motor neuropathy developed a bilateral footdrop within a couple of months as initial symptom.

In 35 of the 75 patients the symptoms spread to the hands in an average course of 5 years. In the other 40 patients the symptoms were limited to the legs, from the knees downward. In none of the patients the arms were solely affected.

In the sensorimotor polyneuropathy cramps in the calf muscles were frequently noted, especially after walking (table 1). In due course almost all patients experienced muscle weakness in the legs causing a disturbance of gait due to a bilateral foot drop. The patients with sensory polyneuropathy frequently complained about numbness of the fingers, causing difficulty in opening or closing small buttons and in dropping small objects out of the hands. In four patients the symptoms also spread proximally in the legs, mainly causing burning or electrical sensations. These painful sensations were most disabling, disturbing sleep and causing restlessness. During the daytime these painful sensations were less pronounced. Patients with a sensory polyneuropathy also often had to look where they were walking to prevent them from falling and usually walked with a broad based gait. When standing still they could only maintain their balance by leaning against a wall or other solid object. Sometimes cramps in the calf muscles were noted, although no motor deficits were found on neurological examination. In the sensorimotor polyneuropathy none of the patients had autonomic symptoms, while two patients with a sensory polyneuropathy had symptoms of bladder dysfunction and impotence, as a possible manifestation of an autonomic neuropathy. None of the patients had cranial nerve involvement.

CLINICAL COURSE
In the years before entry into the study, the clinical course of the polyneuropathy showed two patterns. In 42 patients the clinical course was slowly progressive over the years, whereas in 33 patients the course was initially slowly progressive followed by a prolonged period of stable deficit. In the patients with a sensory polyneuropathy the clinical course more often had a tendency to stabilise (table 1). No relation could be found between the duration of the illness and the occurrence of stabilisation.

During a 6 month follow up period the sensory neuropathy patients tended to stabilise as assessed by our patient evaluation and the Rankin disability scores. Also no aetiological cause of the peripheral neuropathy was identified. Long term follow up is still in progress.

SIGNS
In all patients the dysfunction was most prominent in the legs.

In the sensorimotor polyneuropathy, the pinprick sense was diminished in a stocking-like distribution distal to the ankle in 40 patients, and distal to the wrist in six patients. Light touch sensation was diminished in the same patients and with the same distribution as the pinprick sense. In all patients the vibration sense was diminished in the legs, mostly not perceptible on the malleolus. Sixteen patients showed diminished vibration sense on the middle finger. The joint position sense was normal in the hands in all patients and absent on the big toe in four. Romberg's sign was abnormal in 18 patients. Diminished or absent deep tendon reflexes of the arms was only seen in combination with diminished or absent reflexes of the legs. In all patients Achilles' tendon reflexes were absent bilaterally. In 11 patients all reflexes were absent. There was wasting of the interosseus muscles of the hands in nine patients, although weakness was not a prominent feature. In the legs there was wasting of the extensor digitorum brevis muscle, and frequently of the peroneal and anterior tibial muscles. No wasting was seen in the proximal muscles of the arm and legs. Weakness (MRC grade 3 and 4) was most prominent in the peroneal muscle (72.7%), and in the anterior tibial muscle (61.3%). No fasciculations or tremor was seen.

In the sensory polyneuropathy, the pinprick

Table 1 Symptoms and clinical course in patients with chronic idiopathic polyneuropathy

<table>
<thead>
<tr>
<th>Symptoms:</th>
<th>Sensorimotor PN</th>
<th>Sensory PN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>12 (27)</td>
<td>18 (62)</td>
</tr>
<tr>
<td>Tingling</td>
<td>30 (68)</td>
<td>29 (100)</td>
</tr>
<tr>
<td>Numbness</td>
<td>29 (66)</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Band-like sensations</td>
<td>8 (18)</td>
<td>8 (28)</td>
</tr>
<tr>
<td>Cotton wool</td>
<td>16 (36)</td>
<td>19 (66)</td>
</tr>
<tr>
<td>Stiffness</td>
<td>20 (46)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>27 (61)</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Weakness</td>
<td>36 (82)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Clinical course:
- Slowly progressive, stable: 12 (27)*, 21 (72)*
- Slowly progressive: 32 (73)*, 8 (28)*

*χ² test 14-4, p < 0.0001.
sense was diminished in a stocking-like distribution distal to the ankle in 24 patients and distal to the wrist in six patients. Light touch sensation was diminished in 29 patients in the legs and in six patients in the hands, with the same distribution as the pinprick sense. In all patients the vibration sense was diminished in the legs, usually below the knees. In 12 patients the vibration sense was diminished below the ulnar styloid process. In three patients the joint position sense was diminished on the middle finger and in 10 patients absent on the big toe. Romberg’s sign was abnormal in 13 patients. The pattern of tendon reflex abnormalities was similar to that seen in the sensorimotor polyneuropathy, although complete absence of tendon reflexes was less frequent (five patients). No fasciculations or tremor were seen.

In the motor polyneuropathy, there was wasting of the interosseus, the extensor digitorum, the peroneal, the anterior tibial and the calf muscles. The power was diminished in the hands (MRC grade 4) and distally in the legs (MRC grade 2 and 3). In the proximal muscles there was no weakness.

DISABILITY
Fifty three patients were independent in their daily activities. Eight patients needed the use of a walking stick and 13 an ankle brace. Only one patient was wheelchair dependent due to a severe bilateral arthrosis of both knees, and bilateral weakness of ankle dorsiflexion. On the Rankin scale 39 patients had a score of 1, 35 patients a score of 2, and one patient a score of 3.

ELECTROPHYSIOLOGICAL ASSESSMENT
Sixty four patients fulfilled the electrophysiological criteria of axonal sensory (reduced SNAP amplitude) and axonal motor (spontaneous EMG activity, reduced CMAP amplitude) neuropathy. Seven patients had an axonal sensory polyneuropathy. In two patients there was evidence of a demyelinating motor polyneuropathy as well as an axonal motor and sensory polyneuropathy. In the two patients with a demyelinating polyneuropathy the clinical course was slowly progressive over months, leading to a minor handicap only, with the age at onset being 58 and 64 years respectively. In none of the 75 patients was conduction block found. In two patients the polyneuropathy was unclassified (increased H-M interval). Some patients refused repeated electromyographic evaluation. The results of 60 patients who fulfilled the entire standardised EMG protocol are presented in table 2.

LABORATORY
CSF was obtained in 73 patients. The mean protein was 0.43 g/l (SD 0.16) (95% confidence limits 0.15–0.45). The two patients with electrophysiological evidence of demyelination had a normal CSF protein (0.41 and 0.44). Nerve biopsy was performed in 31 patients. No signs of demyelination, inflammation, vasculitis, or amyloidosis were found. All nerve biopsy specimens showed axonal degeneration. Sera from 70 patients were investigated for the presence of antibodies against MAG, GM1, and sulphatides; all were negative.

Discussion
Chronic idiopathic polyneuropathy presenting in middle or old age is a heterogeneous clinical syndrome. In the published reports only a few studies on neuropathies of unknown cause have been conducted. Most studies show the percentage in which the neuropathy remains idiopathic (table 3), although a few also mention aspects of the clinical picture of this group of neuropathies. None of these studies are strictly comparable as they use different exclusion criteria, are not all prospective in nature, and use different electromyographic criteria. The study by McLeod et al3 may be the best compared with the present study in this respect. In their review of 67 patients with an idiopathic polyneuropathy, McLeod et al3 found 43 mixed, 17 sensory and seven motor neuropathies. In almost all of their patients the polyneuropathy was axonal. They also found an overall predilection for men (3:1) (table 3).

In our patients the cause of the chronic neuropathy remained unknown even after extensive evaluation. By definition of its unknown cause it may be misleading to divide undiagnosed neuropathies into subsets. On clinical grounds, however, it appears that chronic idiopathic polyneuropathy can be divided into groups. Leaving the motor neuropathy out of scope, two groups remain which can be distinguished by means of their different clinical presentation: sensorimotor and sensory polyneuropathy. There is a tendency for the sensorimotor polyneuropathies to run a slowly progressive course, whilst the sensory polyneuropathies have an initially slowly progressive course, followed by a prolonged phase without progression (table 1). A clear difference is found in the sex distribution. The sensorimotor polyneuropathies are equally distributed among the sexes, whereas in sensory polyneuropathies there is a strong predilection for men (4:1). Contrary to these differences concerning the clinical course and sex distribution, both groups share an overall

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Electrophysiological findings in chronic idiopathic polyneuropathy</th>
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<tbody>
<tr>
<td>Needle examination</td>
<td>Sensorimotor polyneuropathy</td>
</tr>
<tr>
<td>Fibrillations/Pos spikes</td>
<td>26 (65)</td>
</tr>
<tr>
<td>Nerve conduction studies</td>
<td>CMAP/SNAP</td>
</tr>
<tr>
<td></td>
<td>decr</td>
</tr>
<tr>
<td>Ulnar nerve (motor)</td>
<td>0</td>
</tr>
<tr>
<td>Ulnar nerve (sensory)</td>
<td>12 (30)</td>
</tr>
<tr>
<td>Tibial nerve</td>
<td>19 (48)</td>
</tr>
<tr>
<td>Sural nerve</td>
<td>5 (13)</td>
</tr>
</tbody>
</table>

*In two patients the CV of tibial nerve is <30 m/s.
Decr = CMAP/SNAP is decreased below normal values (see methods).
Decr = CV is decreased below normal values but CV is faster than 40 m/s of ulnar nerve, faster than 30 m/s of the tibial and sural nerve (see Methods).
benign course reflected by the minimal degree of disability found in our patients. The electrophysiological examination and nerve biopsy specimens show axonal degeneration in almost all our patients with chronic idiopathic polyneuropathy.

In only two patients electromyographic evidence of demyelination was found (table 2). The clinical course of these two patients was not consistent with a CIDP and their CSF protein was not elevated. In 95% of patients with a CIDP, the CSF protein is found to be higher than 0.45 g/l. In addition, our patients showed distal weakness predominantly in the legs, while patients with a CIDP usually have more extensive weakness.

Patients with a CSF protein in the range of 0.45–1.0 g/l underwent a sural nerve biopsy. A nerve biopsy was not performed in all patients as the neuropathy was not sufficiently severe enough to warrant an invasive investigation which may produce persistent dysesthesia. Theoretically speaking, some cases of inflammatory neuropathies and vasculitis could have been overlooked in our study, however, none of the laboratory findings or the clinical course gave any clues for an inflammatory or vasculitic cause of the polyneuropathy.

In the above analysis, the two patients with a pure motor neuropathy were left out. The more progressive and disabling clinical course of these patients appears quite distinct from the sensorimotor and sensory neuropathies which show a more benign course.

Table 3  Review of studies on neuropathies of unknown cause

| Reference            | Number of patients | % unknown cause | Mean age at onset (years) | Neuropathy at onset (N/m2/mm/s/motor/other) | Patients with elevated CSF protein (%) | Neurophysiological abnormalities (%) | Biopsy (%) cerebral/mucic
|----------------------|--------------------|----------------|---------------------------|--------------------------------------------|----------------------------------------|-----------------------------------|-----------------
| Prineas              | 278                | 36             | 40–50                     | 86/6/1/0/0                                  | 50                                     | CVI 100                           | —                |
| Drink~7,13            | 205                | 24             | —                         | —                                          | —                                     | ax 18; dem 15; mix 67              | —                |
| Fagius~7             | 91                 | 74             | 59                        | 99/1/0/0                                   | —                                     | CVI 84; dem 94                    | —                |
| Konig~7,13            | 14                 | 14             | 72                        | 42/30/0/28                                 | 26                                    | —                                 | —                |
| McLeod~7,13           | 519                | 13             | 51                        | 64/27/9/0                                  | 145                                   | CVI mot; sens imp                  | 100/0/0          |
| Corvisier~7,13        | 432                | 11             | 65                        | 66/0/0/34                                  | 55                                    | 41/48/11                          | —                |

sens = sensory; sm = sensorimotor; mot = motor; oh = other neuropathies (for example, asymmetric neuropathies, mononeuritis multiplex); CVI = slowing conduction velocity; denerv = denervation; imp = impairment; — = no data available.

*Including patients with CIDP. Including patients with CIDP, systemic disease, paraproteinaemia, hereditary neuropathy. In four of the six patients with an elevated CSF protein 1 > g/l, a malignancy was found during follow up. Inclusion criteria age over 60.

arms. None had facial symptoms. Therefore, it is unlikely that chronic sensory neuropathy is a variant of the acute sensory neuropathy.

Basically a polyneuropathy can only be classified as idiopathic after exclusion of all known possible causes. Sometimes patients with a sensorimotor neuropathy appear to have a dominant or recessive hereditary form of HMSN 2, or alternatively represent cases of sporadic HMSN 2. In up to 15% of patients with a dominant form of HMSN 2 the onset of symptoms presents after the age of 50. In our study a detailed family history was negative and next of kin suspected of having a polyneuropathy did not have neuro- logical abnormalities on examination. These results imply that the dominant form of HMSN 2 is an unlikely diagnosis for most of our patients. Moreover, HMSN 2 usually does not present with tingling or numbness in the feet, as did most patients in our group. Another intriguing question is whether ageing of the nervous system plays an important role. In that case we would expect an increase of the number of affected patients with an increase with age which is not the case. The mean age of onset of the idiopathic neuropathies is in middle age (table 3).

We have to consider the possibility of toxic neuropathy and chronic alcoholism. Environmental influences may be responsible for chronic idiopathic polyneuropathy. However, in our study the presence of, or contact with, any known toxic agent was a reason for exclusion. A second common cause was the use of drugs or were on a diet. Considering chronic alcoholism, our inquiries on this topic have been extensive (including hetero-anaamnestic data, data of the patient’s general practitioner). McLeod et al revealed initially unsuspected causes in their long term follow up study. At present, our short time follow up study gave no clue for any toxic neuropathy or alcoholism.

Malignancy is an unlikely explanation for causing the neuropathy. Almost all our patients had a polyneuropathy for many years (mean 5 years) before entry into the study without any evidence of a malignant disease.

Finally, Sjögren’s disease and the possibility of another immunological aetiology of chronic idiopathic polyneuropathy have to be considered. Polyneuropathy may be the initial manifestation of Sjögren’s syndrome. The mean interval between the onset of polyneu-
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... and the occurrence of Sjögren’s syndrome in a large series was 24 months.31 In the present study, however, the mean follow up period was about 5 years, signs of xerophthalmia and xerosis were absent, and serological tests for Sjögren’s syndrome were negative. Dalakas found in his study in patients with chronic idiopathic ataxic neuropathies that nine of the 15 patients had a monoclonal or polyclonal serum gammopathy.32 In our study the presence of serum monoclonal proteins was a reason for exclusion. Patients with primarily axonal neuropathies rarely have antibodies against MAG.33 Since the majority of our patients have an axonal polynueuropathy, it is not surprising, that antibodies against MAG were absent. Recently, Pestronk et al.17 described eight patients with an idiopathic sensory neuropathy who had antibodies against sulfatides; these antibodies were absent in sera from our patients with a sensory neuropathy.

In conclusion, chronic idiopathic polyneuropathy presenting in middle or old age is a heterogeneous clinical syndrome. It is interesting that all patients have an axonal polynueuropathy and only minimal disability even after a long duration of symptoms. A follow up of at least 6 months did not provide an answer concerning the aetiology of these peripheral neuropathies. Long term follow up is still in progress.

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