Follow up of patients with signs and symptoms of polyneuropathy not confirmed by electrophysiological studies

N R Rosenberg, C W Slotema, J E Hoogendijk, M Vermeulen

The outcome and final diagnoses of patients with symptoms and/or signs suggestive of polyneuropathy, but with normal electrophysiological studies, were investigated. All patients who presented at the outpatient clinic between 1993 and 1998 with signs and symptoms suggestive of polyneuropathy, but in whom electrophysiological studies were normal, were included. We retrospectively collected data from the medical records and then interviewed the patients and used the Sickness Impact Profile scale to investigate functional status at least 2 years after presentation. We included 74 patients, of whom 39 had neurological signs at neurological examination at the first visit. A final diagnosis was made in 24 of the 39 patients with neurological signs, and in three of the 35 patients without neurological signs but with symptoms. One (3%) of the 35 patients without neurological signs at the first visit had a poor outcome versus 15 (39%) of the 39 patients with neurological signs. In 11 (41%) of the 27 patients in the group with a final diagnosis the outcome was poor versus 5 (11%) of 47 patients without a final diagnosis. In 11 patients we concluded that they probably had small fibre neuropathy. Patients presenting with symptoms of polyneuropathy but who have neither neurological signs of polyneuropathy nor electrophysiological studies confirming a polyneuropathy have a good outcome at least 2 years after presentation. Further investigations are not indicated, except for patients fulfilling the criteria of small fibre neuropathy. In patients with neurological signs, as the outcome depends on the diagnosis and an explanation for these signs is often found, repeated investigations in this group are mandatory.

Polyneuropathy is a syndrome with many different causes. Polyneuropathies are typically characterised by distal sensory loss and diminished or lost tendon reflexes, with or without distal weakness and wasting, and affect the lower limbs before the upper limbs. When these patients are investigated, electrophysiological studies play a role initially in confirming the diagnosis and subsequently in directing the search for the cause. It is known that electrophysiological studies may be normal in patients with a history and clinical features suggestive of polyneuropathy. Possible explanations are that these patients have another (neurological) disease, the polyneuropathy is in an initial phase, or only small fibres are affected. We could not find any report in the literature on the prognosis of such patients. The prognosis is of interest since, if it is good, there is no need for repeated and further investigations. Therefore, we investigated the functional status in such patients at least 2 years after presentation. Moreover, we investigated whether finally an explanation for the signs and symptoms was found and whether the neurological examination at presentation predicted the functional status at follow up.

METHODS
Patients
We retrospectively analysed all patients with electrophysiological test results incompatible with polyneuropathy. All patients had been sent to the outpatient department by general practitioners suspecting a neurological disorder and had electrophysiological tests because neurologists considered the diagnosis might be polyneuropathy. The electrophysiological tests were conducted between 1993 and 1998.

Details of symptoms, signs, medical history, age, and gender were obtained from the medical records. Patients were not included if they had no symptoms and/or signs of a polyneuropathy. Symptoms could consist of: tingling, burning, electrical or band-like sensations, pain, numbness, a feeling of muscle weakness, cramps, muscle stiffness, and trembling sensations in muscles. Signs could consist of impaired vibration perception, impaired reaction to pin prick and temperature, reduction of joint position and cutaneous touch pressure, hyperpathy, muscle weakness, wasting, fasciculations, and loss of tendon reflexes. Impaired vibration perception on the great toe, loss of the ankle jerk reflexes, and atrophy of the digitorum brevis muscles were considered to be normal in patients older than 65 years of age.

In all patients, the diagnosis of small fibre neuropathy was considered. If clinical symptoms and signs were compatible with small fibre neuropathy, thermo-sensory threshold tests were performed. Electrophysiological studies were performed using standard techniques, including motor and sensory conduction velocities in at least one arm nerve and two leg nerves, F responses of the median nerve and peroneal nerve, H reflex of the soleus muscle, and electromyography of distal arm and leg muscles.

All included patients were interviewed at least 2 years after presentation. They were initially contacted by phone by a neurologist of the outpatient department where they had been investigated. The patient was included in the study after written informed consent. The study was approved by the ethics committee of our hospital after completion of the study.

Follow up
To investigate long term functional outcome, we scored the physical section of the Sickness Impact Profile (SIP) scale at least 2 years after presentation. The physical dimension of the SIP scale consists of three subscales which refer to (instrumental) disabilities in terms of body care and movement (23 items), walking (12 items), and mobility (10 items).

Abbreviations: SIP, Sickness Impact Profile
items). Each weighted item is scored as present or absent. The SIP scale was corrected for age and gender. A total score of 100% indicates severe disability. The validity and reliability of the SIP score have been evaluated extensively.\textsuperscript{17–19} The SIP scores were categorised into: (1) good outcome: minor symptoms not interfering with activities in daily life (score \leq 75th percentile); and (2) poor outcome: (severely) disabled (score \geq 75th percentile).\textsuperscript{20–23} The final diagnosis of the neurologist in charge of the patient was obtained from the medical records.

**RESULTS**

Between 1993 and 1998, 489 patients in whom a diagnosis of polyneuropathy was considered presented at our neurology outpatient department. In 397 of these 489 patients electrophysiological studies were performed to confirm or reject the diagnosis of polyneuropathy. In 139 of these 397 patients the electrophysiological examination was not compatible with polyneuropathy. Of these 139 patients, 27 were excluded because they did not fulfill the clinical criteria of polyneuropathy. The remaining 112 patients were eligible for the study. A total of 38 patients could not be investigated at least 2 years after presentation: 19 had died from various causes, five suffered from dementia or aphasia and were not able to answer the questions, 12 were lost to follow up, and two refused to be investigated.

Patients’ characteristics, outcome, diagnosis and co-morbidity are presented in table 1.

The only patient with a poor outcome in the group with symptoms only was a 54 year old man who suffered from several cerebral infarcts probably caused by atrial fibrillation. These multiple infarcts explained his poor outcome.

In 27 of the 74 patients a diagnosis could be established at follow up. In patients without a diagnosis, five (11%) of 47 patients had poor outcome; four of these patients had signs of polyneuropathy. In the group of patients with a diagnosis, 11 (41%) of 27 patients had poor outcome; all these patients had signs.

Eleven patients had symptoms and signs of isolated small fibre neuropathy. Of these 11 patients, eight had a thermo-sensory threshold test, the results of six of which were abnormal and two inconclusive. In the remaining three patients, the clinical diagnosis of small fibre neuropathy was highly probable, and therefore thermo-sensory threshold tests were not performed. Three of the 11 patients with small fibre neuropathy had diabetes mellitus, three were alcohol abusers, and one had both conditions. In the remaining four patients, one patient was suffering from Sjögren’s syndrome, while the other three had no explanation for the small fibre neuropathy.

In 15 of the patients we detected co-morbidity known to be associated with polyneuropathies: diabetes mellitus (seven), alcohol abuse (six), diabetes mellitus and alcohol abuse (one), and renal disease (one). In 13 of these patients the co-morbidity was already present at the first presentation. In the remaining two patients co-morbidity was found at follow up (one diabetes mellitus, one alcohol abuse).

Four of the eight patients with diabetes mellitus had no symptoms of small fibre neuropathy. Two of these had another final diagnosis (plexopathy, claudicatio intermittens). The remaining two patients had no diagnosis. One of these two patients had a good outcome after 3 year follow up. Electrophysiological examination was repeated and was again normal. The other patient had a good outcome after 5 year follow up and her complaints had disappeared.

Three patients with alcohol abuse did not have a diagnosis of small fibre neuropathy: two had another diagnosis (both canal stenosis), while the third had a good outcome after 5 year follow up with no complaints.

One patient with renal impairment without small fibre neuropathy had a good outcome after 5 year follow up with fatigue as the only symptom.

**DISCUSSION**

Our results show that in more than 60% of patients who present with objective signs at neurological examination, but without electrophysiological tests confirming polyneuropathy, a diagnosis can be established after at least 2 years of follow up. In contrast, less than 10% of patients without neurological signs finally had a diagnosis.

Almost two thirds of all included patients finally had no diagnosis. Of these patients, 11 probably had small fibre neuropathy.

In some patients with diabetes, alcohol abuse, or renal insufficiency we could not establish any diagnosis; these

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patients with symptoms and/or signs suggestive of polyneuropathy, but without abnormalities on electrophysiological examination</th>
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<tbody>
<tr>
<td></td>
<td>Only symptoms, no signs, ( n = 35 )</td>
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<tr>
<td>Female: male</td>
<td>15:20</td>
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<td>Age (years), mean (range)</td>
<td>51 (27–76)</td>
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<td>Good outcome on SIP</td>
<td>32 (0.91, 95% CI: 0.77 to 0.98)</td>
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<td>No diagnosis</td>
<td>3 (0.09, 95% CI: 0.02 to 0.23)</td>
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<td>Conversion</td>
<td>Erythromelalgia</td>
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*Frequency.
patients had neither polyneuropathy nor small fibre neuropathy.

Almost all the patients without signs at neurological examination had a good outcome. In the group of patients with neurological signs, more than one third had a poor outcome. The outcome in patients with neurological signs depends on the final diagnosis. In almost half of the patients with neurological signs in whom finally a diagnosis could be established, the outcome was poor. We are unable to compare our results with those of other centres since follow up data of similar groups of patients have not been published.

We conclude that in patients who present with symptoms of polyneuropathy but who have neither neurological signs nor electrophysiological studies confirming a polyneuropathy, further investigations are not indicated, except for patients fulfilling the criteria for small fibre neuropathy. In patients with neurological signs, but without electrophysiological evidence of polyneuropathy, further investigations are mandatory to establish a diagnosis as they may have a treatable disorder.

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