Differences between hereditary motor and sensory neuropathy type 2 and chronic idiopathic axonal neuropathy
A clinical and electrophysiological study

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Summary
To evaluate whether chronic idiopathic axonal polyneuropathy (CIAP) should be considered as hereditary motor and
sensory neuropathy type 2 (HMSN type 2), we compared the clinical features of 48 patients with CIAP with those of 47
patients with HMSN type 2. In addition, we studied electrophysiological data in 20 patients with CIAP and in 20
patients with HMSN type 2. We found, in patients with HMSN type 2, that the initial symptoms were predominantly
motor and that weakness and handicap were more severe and skeletal deformities more frequent, compared with those
of CIAP patients. Electrophysiologically, the tibialis anterior muscle showed more denervation in patients with HMSN
type 2, consistent with the predominance of motor symptoms. There was no important effect of age of onset on clinical
features in HMSN type 2 patients. We conclude that in an individual patient with a sensory or sensorimotor idiopathic
axonal polyneuropathy and no family history of polyneuropathies, the diagnosis HMSN type 2 is unlikely. However, if
motor symptoms predominate, the diagnosis of HMSN type 2 should be considered.

Keywords: chronic; idiopathic; axonal; polyneuropathy; hereditary

Abbreviations: CIAP = chronic idiopathic axonal polyneuropathy; CMAP = compound muscle action potential;
DML = distal motor latency; HMSN = hereditary motor and sensory neuropathy; MCV = motor conduction velocity;
SCV = sensory conduction velocity; SNAP = sensory nerve action potential; VPT = vibration perception threshold

Introduction
In 10% of patients with chronic axonal polyneuropathy no etiology can be found even after extensive evaluation
(McLeod et al., 1984) and long term follow-up (Notermans et al., 1993, 1994). We have denominated this entity chronic
idiopathic axonal polyneuropathy (CIAP) (Notermans et al., 1993, 1994). Patients usually present in middle or old age
with mild sensory and/or motor symptoms, and show only slow progression. Severe disability does not occur (Notermans
et al., 1994).

Hereditary motor and sensory neuropathy (HMSN) type 2 is, in most cases, a dominantly inherited, sensorimotor
polyneuropathy also with slow progression. Nerve biopsies confirm the axonal nature of this neuropathy (Behse and
Buchthal, 1977; Harding and Thomas, 1980a). Although the peak age of onset is in the second decade, a substantial
number of patients may develop symptoms after the age of 40 years (Buchthal and Behse, 1977; Harding and Thomas,
1980a). In contrast with the demyelinating form of HMSN, type 1, where reduced nerve conduction velocities provide a
reliable diagnosis in at-risk individuals without apparent
symptoms (Harding and Thomas, 1980c), affected HMSN type 2 family members without overt clinical features cannot easily be traced with electromyography (Timmerman et al., 1996). The number of patients identified within HMSN type 2 families is therefore small and, although linkage studies have revealed a relation with chromosomes 1p36 (Ben Othmane et al., 1993) and 3q (Kwon et al., 1995), the gene has still to be found. As a consequence, in patients with CIAP, a diagnosis of HMSN type 2 should also be considered, even when detailed kinship history and neurological evaluation of family members do not reveal an inheritable disease (Dyck et al., 1981).

We set up a study to investigate whether extensive clinical and electrophysiological testing of patients with CIAP or HMSN type 2 with onset after the first decade could reveal significant differences between the two groups. If these differences exist, a hereditary cause in sporadic patients with CIAP becomes unlikely. To assess whether the results are possibly influenced by differences in age of onset between the groups, we compared CIAP patients with HMSN type 2 patients with age of onset >40 years. In addition, within the HMSN type 2 group, we compared patients whose age of onset was <40 years with those whose age of onset was >40 years. Furthermore, the clinical course of HMSN type 2 was studied by analysing the relationship between the duration of the disease and its severity.

**Patients and methods**

**Patients**

During 1995 and 1996, 48 patients with CIAP [31 male, 17 female; age 67 ± 7 years (mean ± SD)] and 47 patients with HMSN type 2 [25 male, 22 female; age 53 ± 14 years] were admitted to the study. Patients originated from the University Hospital Utrecht (40 CIAP, 29 HMSN type 2), the University Hospital Nijmegen (18 HMSN type 2) and the St Lucas-Andreas Hospital Amsterdam (eight CIAP). On entry, electrophysiological assessment confirmed the axonal nature of the neuropathy in all patients. In 20 CIAP patients and 20 HMSN type 2 patients electrophysiological testing was repeated at the University Hospital Utrecht according to procedures described below. All patients gave informed consent, and the study was approved by the Committee for Human Research, University Hospital, Utrecht.

Patients were diagnosed as having CIAP if no cause was found after extensive clinical and laboratory evaluation (Notermans et al., 1993). A detailed kinship history was taken and if suspicion of the existence of a polyneuropathy arose, suspected family members were analysed, both neurologically and electrophysiologically (Notermans et al., 1994). HMSN type 2 was diagnosed if patients had both an axonal polyneuropathy and a first degree relative with polyneuropathy, diagnosed by a neurologist. To exclude the demyelinating form of HMSN type 1, the median motor conduction velocity (MCV) had to be >38 m/s (Harding and Thomas, 1980a) and in cases of doubt chromosomal evaluation was performed for 1p17 or 1q lesions.

The 47 HMSN type 2 patients originated from 25 families. Autosomal dominant inheritance was most likely in 42 patients of 22 families. X-linked inheritance could not be excluded in 10 of these families with no clear male-to-male inheritance. However, in these 10 families males were never more severely affected than females, which makes X-linked HMSN less likely (Bergoffen et al., 1993). In three patients from two families, an autosomal dominant inheritance mode was suspected as one of the parents had had a history of walking difficulties, which could not be confirmed as both parents were deceased. In two patients from one family, autosomal recessive inheritance could not be excluded as both parents showed no abnormalities on neurological and electrophysiological investigation. Clinically, these patients differed from the patients with autosomal recessive inheritance described by Harding and Thomas (1980b) and by Gabreëls-Festen et al. (1991) since onset had not been in the first or early second decade and they were not as severely affected.

**Patient evaluation**

For this study, all patients were examined by the same neurologist (L.L.T.). History taking and clinical examination were carried out in a standard fashion, including an extensive interview to determine age and nature of complaints at onset, nature and distribution of motor and sensory symptoms, the concurrence of other diseases or intoxications (medication, alcohol abuse, occupational and environmental toxic agents) and a detailed kinship history. Age of onset was defined as the moment when patients consulted a physician for the first time with symptoms which were probably related to the polyneuropathy.

The neurological examination was performed according to a standardized protocol (Notermans et al., 1993). Seven muscles or muscle groups in both arms (deltoid, biceps brachii, triceps brachii, wrist extensors, finger extendors, finger flexors and interosseus) and seven muscles or muscle groups in both legs (iliopsoas, quadriceps, hamstrings, anterior tibial, gastrocnemius, peroneus and toe extensors) were measured using the MRC scale (Medical Research Council, 1976). Summation of the scores could lead to a maximum motor score of 140. The following sensory modalities were examined: touch, pin prick, vibration sense and joint position sense. The sensory system was graded as follows: touch and pin prick 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 for 15 s, or on the hallux (big toe) for 10 s = 4, decreased on middle finger/hallux = 3, ulnar styloid/medial malleolus = 2, elbow/knee = 1, clavicula/crista or higher = 0. Joint position sense of middle finger/hallux normal = 2, diminished = 1, absent = 0.
Summation of all sensory modalities could lead to a maximum total sensory score of 28 in the arms and 28 in the legs, i.e. 56 in total. In addition, we performed the Romberg test and noted if muscle atrophy of arms and legs, and skeletal deformities such as pes cavus, claw toes and shortening of the calf muscles were present.

Disability was scored using the modified Rankin scale (van Swieten et al., 1988). Ability to walk and the use of walking aids was noted.

Vibration perception treshold (VPT) was measured using a Vibrameter type 3 (Somedic AB, Stockholm, Sweden) (Goldberg and Lindblom, 1979). The measurements were performed on the dominant metacarpal 2 and corrected for age (Halonen, 1986).

**Laboratory investigations**
Serum creatine kinase-level (CK) was measured in 36 CIAP and 43 HMSN type 2 patients. In all patients, extensive laboratory investigations were performed to exclude other causes of polyneuropathy, including gammopathy.

**Electrophysiology**
To compare the electrophysiological features of HMSN type 2 and CIAP, a second electrophysiological investigation was performed on 20 patients of both groups. Before the investigation, the limbs were warmed in a bath of water of 37°C for 30 min (Franssen and Wieneke, 1994) and during the investigation skin temperature was maintained at 37°C by an infrared heating device. Nerve-conduction studies were performed using surface stimulation and recording electrodes according to standard techniques (Kimura, 1989). Motor conduction was investigated in the median nerve (recording from the abductor pollicis brevis muscle) and in the tibial nerve (recording from the abductor hallucis brevis muscle); the distance between the distal stimulation point and the active recording electrode was 7 cm and 10 cm, respectively. Sensory conduction was investigated in the median nerve (recording with ring electrodes from the second digit) and in the sural nerve (recording from the sural nerve at the ankle). To elicit F waves, 20 stimuli were applied to the median nerve at the wrist and to the tibial nerve at the ankle. Concentric needle recording was performed in the anterior tibial muscle.

The following variables were measured. (i) Motor conduction: distal motor latency (DML), maximal MCV, amplitude, duration and area of the negative part of the compound muscle action potential (CMAP) after distal stimulation, reduction of CMAP amplitude and area, and increase of CMAP duration after distal compared with proximal stimulation, minimal central latency (shortest latency of F wave minus latency of M response). (ii) Sensory conduction: maximal sensory conduction velocity (SCV), amplitude and duration of the negative part of the sensory nerve action potential (SNAP) after distal stimulation. For the median nerve, definite conduction block was defined as a reduction in the area of the CMAP of >50%, possible conduction block as a reduction in CMAP amplitude of >30%, abnormal temporal dispersion as an increase of duration of >30%. The following concentric needle variables were scored: presence or absence of spontaneous muscle fibre activity (fibrillations, positive sharp waves or complex repetitive discharges), presence or absence of signs of reinnervation (polyphasic or giant motor unit potentials on light voluntary effort), pattern (no activity, single, mixed or interference) on maximal voluntary effort.

**Statistical analysis**
Statistical analysis was performed using the non-parametric Wilcoxon signed rank test and the $\chi^2$ test. For the Rankin score and the pattern on maximal voluntary effort (concentric needle examination) a $\chi^2$ test for trend was done. Wilcoxon rank sum score was used for nominal variables. For the correlations between total motor and sensory scores and age, of onset and duration of disease, Pearson’s correlation coefficients were determined. The means in different subgroups were compared and tested with the unpaired $t$ test and ANOVA (analysis of variance). $P < 0.05$ was considered significant.

**Results**
Onset of symptoms was significantly later and, in spite of the age differences (mean 14 years), the duration of disease was shorter in CIAP patients compared with HMSN type 2 patients (Table 1, Fig. 1). Symptoms at presentation were more often sensory in CIAP patients and more often motor in HMSN type 2 patients (Table 1). In both groups the initial symptoms became manifest in the legs. Progression to the hands occurred more frequently in HMSN type 2 patients and consisted of weakness of the intrinsic hand muscles or numbness of the fingers. Muscle atrophy, mainly of the first interosseus and tibialis anterior muscle, and skeletal deformities were significantly more frequent in HMSN type 2 (Table 1). Severe scoliosis or other spine deformities were absent. Summed motor scores and summed sensory scores for the arms were significantly lower in HMSN type 2 than in CIAP (Table 1). The VPT was abnormal in 25 (52%) CIAP patients and 28 (62%) HMSN type 2 patients (not significant). Pseudoathetosis was absent. Fasciculations were present in 31% of the CIAP patients and 49% of the HMSN type 2 patients and were mainly seen in small hand muscles and quadriceps muscles. A tremor was seen in 15% of CIAP patients and in 28% of HMSN type 2 patients (not significant).

In a separate analysis no sex differences were found for clinical symptoms and signs. All data are presented as percentages, mean ± SD or median (range)

**Disability**
Disability, measured with the Rankin scale, was more severe in HMSN type 2 patients; in HMSN, nine patients scored 1,
Table 1  Clinical comparison of CIAP patients and HMSN type 2 patients

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<thead>
<tr>
<th></th>
<th>CIAP  (n = 48)</th>
<th>HMSN type 2  (n = 47)</th>
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<tr>
<td>Age (years)</td>
<td>67 ± 7*</td>
<td>53 ± 14</td>
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<tr>
<td>Age at onset (years)</td>
<td>60 ± 8*</td>
<td>39 ± 16</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>6.4 ± 5***</td>
<td>13.2 ± 8</td>
</tr>
<tr>
<td>Men : women</td>
<td>1.8 : 1</td>
<td>1.1 : 1</td>
</tr>
<tr>
<td>Summed sensory scores (arms)†</td>
<td>26 (22–28)*</td>
<td>24 (22–26)</td>
</tr>
<tr>
<td>Summed sensory scores (legs)‡</td>
<td>16 (12.5–19)</td>
<td>16 (12–19)</td>
</tr>
<tr>
<td>Total summed motor scores§</td>
<td>137.5 (127–140)*</td>
<td>130 (123–138)</td>
</tr>
<tr>
<td>Mean MRC score ratio (gastrocnemius muscle:tibialis anterior muscle)</td>
<td>4.5:4.0</td>
<td>4.6:4.1</td>
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Number (and percentage) of patients presenting:

Onset with
- Sensory symptoms: 29 (60)*** compared to 7 (15)
- Motor symptoms: 19 (40)** compared to 40 (85)

Symptoms of
- Weakness in the hands: 12 (25) compared to 25 (53)
- Sensory symptoms in the hands: 21 (44) compared to 25 (53)
- Weakness in the legs: 36 (75) compared to 40 (85)
- Sensory symptoms in the legs: 46 (95) compared to 41 (87)

Signs
- Atrophy arms: 14 (29)* compared to 25 (53)
- Atrophy legs: 21 (44)* compared to 36 (77)
- Biceps jerk absent: 7 (15) compared to 12 (26)
- Riceps jerk absent: 14 (29) compared to 21 (45)
- Knee jerk absent: 22 (46) compared to 25 (53)
- Ankle jerk absent: 36 (75) compared to 42 (89)
- Romberg sign abnormal: 29 (61) compared to 28 (60)
- Postural tremor: 7 (15) compared to 13 (28)
- Fasciculations: 15 (31) compared to 23 (49)
- Pes cavus: 6 (13)*** compared to 27 (57)
- Claw toes: 6 (13)* compared to 14 (30)
- Short calf muscles: 1 (2)*** compared to 22 (47)

Mean ± SD except where indicated otherwise. †Median with 25–75% percentiles in. *P < 0.05, **P < 0.001, ***P < 0.0001, χ² test and Wilcoxon signed rank test (otherwise not significant).

Age, duration and clinical course in HMSN type 2 and CIAP

Within the group of patients with HMSN type 2, older age and longer duration of the symptomatic stage were related to more severe disability as scored with the Rankin scale (P < 0.001, χ² test for trend). In CIAP patients, there was no relationship between age or duration of disease and Rankin score. Patients with pes cavus were younger (47 ± 10 years) than those without (60 ± 15 years) (P < 0.001). They also had an earlier age at onset [with pes cavus: 33 ± 13 years, without pes cavus: 47 ± 17 years (P < 0.05)]. In patients with longer duration of disease, pes cavus did not occur more frequently. Patients with claw toes were older (57 ± 11 years) than those without (52 ± 14 years) (P < 0.05). A relationship between claw toes and age at onset, or disease duration could not be established. Duration of disease was negatively correlated with summed motor score

Fig. 1  Age of onset in decades for HMSN type 2 patients (open bars) and CIAP patients (filled bars) in percentages.
HMSN type 2 and CIAP compared

Fig. 2 Summed motor and sensory scores of HMSN type 2 patients and CIAP versus duration of disease in years.

(Pearson’s correlation coefficient = -0.3, \( P < 0.05 \)) and summed sensory score (-0.3, \( P < 0.05 \)), but not with age or age at onset. In CIAP, no correlation was found between duration, age or age of onset, and motor and summed sensory score (Fig. 2).

**HMSN type 2 patients and age of onset (\( <40 \) years or \( \geq 40 \) years)**

Within the group of HMSN type 2 patients no effect of age (\( <40 \) years or \( \geq 40 \) years) could be demonstrated, apart from a shorter duration of disease and a lower prevalence of pes cavus in the late onset group (Table 2). A comparison of HMSN type 2 patients with age of onset \( >40 \) years and CIAP patients showed no other differences from those that were found in the comparison of the complete groups.

**Laboratory tests**

Serum CK levels were significantly higher in HMSN type 2 patients \( (207 \pm 179 \text{ U/l, } n = 43) \) than in CIAP patients, \( (127 \pm 87 \text{ U/l, } n = 36, P < 0.01) \), 95% confidence limits 15–180 U/l.

**Electrophysiology**

In HMSN type 2, compared with CIAP, the tibial nerve DML was significantly longer, also the sural nerve SCV was significantly more reduced, and abnormalities on electromyography (spontaneous muscle fibre activity, signs of reinnervation, reduced pattern on maximal voluntary effort) occurred more frequently (Table 3). Only the median nerve MCV was more reduced in CIAP patients than in HMSN type 2 patients. For the other variables no significant differences were found between the groups. Values outside the normal limit were equally distributed over CIAP and CIAP patients showed no other differences from those that were found in the comparison of the complete groups. HMSN type 2 patients (\( \chi^2 \) test). Correction for height or sex did not alter the findings. In one patient only (from the CIAP group), there was evidence of possible conduction block (reduction in amplitude of 65% and area of 40%) and increased temporal dispersion (increase in duration of 133%) found in the lower arm segment of the median nerve.
Table 2 Clinical comparison of early and late onset groups of HMSN type 2 patients

<table>
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<tr>
<th>HMSN type 2 patients, disease onset at</th>
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<tr>
<td>&lt;40 years</td>
<td>&gt;40 years</td>
<td></td>
</tr>
<tr>
<td>(n = 24)</td>
<td>(n = 23)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>42 ± 9*</td>
<td>63 ± 9</td>
</tr>
<tr>
<td>Age onset (years)</td>
<td>25 ± 8*</td>
<td>53 ± 9</td>
</tr>
<tr>
<td>Duration (years)</td>
<td>16 ± 10*</td>
<td>10 ± 6</td>
</tr>
<tr>
<td>Men : women</td>
<td>1.4 : 1</td>
<td>0.9 : 1</td>
</tr>
<tr>
<td>Summed sensory scores (arms)</td>
<td>23 ± 3</td>
<td>23 ± 5</td>
</tr>
<tr>
<td>Summed sensory scores (legs)</td>
<td>17 ± 6</td>
<td>15 ± 5</td>
</tr>
<tr>
<td>Total summed motor scores</td>
<td>129 ± 10</td>
<td>126 ± 16</td>
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Number (and percentage) of patients presenting:

<table>
<thead>
<tr>
<th>Onset with</th>
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<tr>
<td>Sensory symptoms</td>
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<tr>
<td>Motor symptoms</td>
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<tr>
<td>Signs</td>
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<tr>
<td>Atrophy in the arms</td>
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<tr>
<td>Atrophy in the legs</td>
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<tr>
<td>Pes cavus</td>
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<tr>
<td>Claw toes</td>
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<td>Short calf muscles</td>
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Mean ± SD except where indicated otherwise. *P < 0.05, **P < 0.001. χ² test and Wilcoxon signed rank test (otherwise not significant).

Discussion

HMSN type 2 patients could be distinguished from CIAP patients by more severe features of the neuropathy and more electrophysiological abnormalities. Compared with CIAP patients, HMSN type 2 patients had lower summed motor scores and lower summed sensory scores for the hands, more atrophy and skeletal deformities and higher CK levels, indicating more muscle denervation. At onset, HMSN type 2 patients had motor complaints more often, and their mean age of first symptoms was earlier compared with CIAP patients. The higher incidence of skeletal deformities also indicates an earlier age of onset. Electrophysiological studies showed more denervation of the tibialis anterior muscle, a longer DML of the tibial nerve and a slower conduction velocity of the sural nerve in HMSN type 2 patients. This indicates a more severe polyneuropathy with more pronounced motor abnormalities in HMSN type 2 patients compared with CIAP patients. The slower MCV of the median nerve in CIAP patients could be explained by the older age of these patients. Dyck et al. (1981) found in their study on inherited and acquired polyneuropathies the same predominance of motor symptoms at onset and skeletal deformities in the group with inherited polyneuropathies. Their study consisted of a heterogeneous group of inherited polyneuropathies and was not focussed on HMSN type 2. Hereditary polyneuropathies were often not recognized at the first evaluation because kinship history was unclear. We therefore evaluated, in our index HMSN type 2 patients, whether the diagnosis ‘hereditary polyneuropathy’ had been considered after the first neurological evaluation. This was indeed considered in all patients, except in one in whom the diagnosis ‘idiopathic polyneuropathy’ was made since the family history only later became positive when a younger sister of the patient developed the same symptoms. Because CIAP patients are likely to have a heterogeneous aetiology, it is of course possible that there are HMSN type 2 patients among this group with no family history. This problem will not be solved until a genetic diagnosis of HMSN type 2 is possible.

Duration of disease was longer in HMSN type 2 patients than in CIAP patients. This may explain the differences found at the time of our study since for both CIAP and HMSN type 2, deterioration over time has been described (Harding and Thomas, 1980a; Bercianio et al., 1986; MacMillan and Harper, 1994; Notermans et al., 1994). In a comparison of CIAP patients with a subgroup of HMSN type 2 patients, disease CIAP HMSN type 2

<table>
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<th>Median nerve, motor</th>
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<tr>
<td>DML (ms)</td>
</tr>
<tr>
<td>MCV lower arm (m/s)</td>
</tr>
<tr>
<td>MCV upper arm (m/s)</td>
</tr>
<tr>
<td>Central latency (ms)</td>
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<tr>
<td>CMAP amplitude (mV)</td>
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</table>

Mean ± SD. The median nerve in the upper arm was investigated in 14 CIAP patients, NR = no response obtainable. In two CIAP and five HMSN patients, a median nerve SNAP could not be elicited on stimulation of the wrist. In four CIAP patients and six HMSN patients, F waves could not be elicited, despite an obtainable CMAP. DML = distal motor latency, MCV = motor conduction velocity, SCV = sensory conduction velocity, CMAP = compound muscle action potential, SNAP = sensory nerve action potential. Electromyography was performed in 18 CIAP and 19 HMSN type 2 patients. O/S/M/I = number of patients, respectively, without motor unit activity, or with single, mixed or interference patterns in the tibialis anterior muscle on maximal voluntary effort. *P < 0.05, **P < 0.001 (otherwise not significant).
2 patients with onset at >40 years and shorter duration of disease, the same differences were found as in the comparison of the total group. This suggests that duration of disease only cannot account for the differences between HMSN type 2 and CIAP. The findings cannot be attributed to differences in sex or age at onset either, since separate analyses did not show differences between men and women or between patients with early or late onset. If an effect of age, or age of onset, on the results of the neurological examination existed, then correction of this effect would enlarge the differences between CIAP and HMSN type 2 patients, since CIAP patients were older.

In this study, there was a relation between the Rankin score, age, and duration of disease in HMSN type 2. A weak correlation between duration and summed motor and sensory scores was found, but to evaluate the clinical course of HMSN type 2 more extensively, a follow-up study would be necessary. HMSN type 2 seemed a disabling disease in a considerable number of the patients, since walking aids were used frequently and the Rankin score was often 2 or 3; however, only two patients had become wheelchair-bound, and that was partly because of concomitant diseases. No difference in severity of features was found between the groups with early and late onset. Only pes cavus was more common in patients with early onset, which can be explained by an effect of the disease during growth. Claw toes were more common in the older HMSN type 2 patients.

HMSN type 2 patients were clinically heterogeneous, with age of clinical onset varying from the early second decade to as late as the seventh decade. Harding and Thomas (1980) demonstrated that onset at >40 years is not unusual. Linkage studies also suggest genetic heterogeneity in HMSN type 2 (Ben Othmane et al., 1993, Kwon et al., 1995, Timmerman 1991; 114: 1855–70. Harding et al., 1996). Harding and Thomas (1980) could not make a subdivision in terms of MCV in their patient group. It is difficult to assess heterogeneity in a relatively small patient group with small families in which only symptomatic members were evaluated. In our study, more similarities were found within families than in the total group. In 14 families of which two or more members were evaluated, pes cavus was either present in every family member or absent in every family member. Claw toes occurred in half of the families, mainly in older patients. Age of onset was equal among brothers and sisters, but in the older generation, where all the probands originated, it was generally one or two decades later. The younger generation was less affected, suggesting no anticipation but earlier recognition of symptoms. The severity among first grade family members of one generation was approximately the same.

In conclusion, patients with HMSN type 2 differ from patients with CIAP. In an individual patient with a sensory or sensorimotor idiopathic axonal polyneuropathy with late onset, without a family history, the diagnosis HMSN type 2 is unlikely, especially if, at onset, sensory symptoms predominate. If, however, motor symptoms predominate, the diagnosis of HMSN type 2 should be considered.

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