Disease Course of Charcot-Marie-Tooth Disease Type 2

A 5-Year Follow-up Study

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Background: Charcot-Marie-Tooth disease (CMT) type 2 is the axonal variant of an inherited, sensorimotor polyneuropathy. To our knowledge, the clinical course of CMT type 2 has never been prospectively studied in a large group of patients.

Objective: To prospectively evaluate the disease course of patients with CMT type 2.

Methods: We prospectively evaluated the disease course in patients with CMT type 2. Forty-three patients (24 men) of 27 families with CMT type 2 were included. All patients were analyzed by the same investigator at entry and after 5 years. The standardized protocol included manual muscle testing, which could lead to a motor sum score of 140 points, and quantification of sensory deficit. Disability was assessed using the modified Rankin scale, and quality of life was assessed using the RAND 36-item health survey questionnaire. Eighteen families were tested for known mutations in the MPZ, PMP22, and GJB1 genes.

Results: At entry, the mean ± SD age of the patients was 52 ± 14 years, and the mean ± SD duration of disease was 12 ± 8 years. The median motor sum score deteriorated from 135 to 128 points (P = .02). Progression was never rapid. There was no sensory deterioration. The Rankin score decreased by 1 point in 16 patients. At follow-up, more patients needed walking aids, but most patients remained ambulant. The number of patients with claw toes increased, whereas the number of patients with foot deformities such as pes cavus and short calf muscles remained stable. There was no correlation between deterioration and age. Analysis of quality of life did not show any changes. In one family, a mutation in the GJB1 gene was found.

Conclusion: This prospective study shows a slow deterioration of muscle strength and increase in disability in CMT type 2 during a 5-year follow-up period.

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CHARCOT-MARIE-TOOTH disease (CMT) type 2 or hereditary motor and sensory neuropathy type 2 is a genetically heterogeneous group of axonal neuropathies with motor and sensory abnormalities and signs of axonal degeneration on electrophysiologic investigation and in sural nerve biopsy specimens.1,3 Age of onset varies between the first and seventh decades of life, and the disease in asymptomatic, young affected individuals can remain undiagnosed.2,4,5 The inheritance mode is usually autosomal dominant, but autosomal recessive inheritance has also been described.6,9,10 Also, GJB1 mutations have been found in families with a CMT type 2 phenotype.4,11-13 In autosomal dominant CMT type 2, several candidate loci have been found,14 but only a few specific gene defects have been identified.15-20 Generally, CMT type 2 is considered to have a slowly progressive course that does not lead to severe disability, but this has never been prospectively studied in a large group of patients.21,22 To inform patients about their expected clinical course and disability, knowledge of the natural course of CMT type 2 is essential. We therefore prospectively examined 43 patients with CMT type 2, according to a standardized protocol, with a follow-up of 5 years. In addition, a search for mutations in the candidate genes PMP 22, MPZ, and GJB1 was performed in 18 families.

METHODS

PATIENTS

Patients were referred to the outpatient clinic of the departments of neurology of the University Medical Center Utrecht, Utrecht, the Netherlands (26 patients), and the University Medical Center Nijmegen, Nijmegen, the Netherlands (17 patients). A hereditary polyneuropathy was diagnosed if the patient and a first-degree relative had a polyneuropathy diagnosed...
by a neurologist. Electrodiagnostic investigation had been performed in all patients before inclusion, and the results had to be consistent with an axonal polyneuropathy, including a median nerve motor conduction velocity of more than 38 m/s. Of 55 patients examined at entry, 43 patients (24 men and 19 women) were seen after a mean follow-up period of 5 years (58 ± 5 months). Of the 12 patients who did not participate in the follow-up examination, 3 had died, 8 refused to participate (2 because they were not interested in the aim of the study and 6 because of personal problems), and 1 was lost to follow-up. The mean ± SD age of the participating patients was 52 ± 14 years (range, 17-78 years), age of disease onset was 40 ± 15 years (range, 3-67 years), duration of disease was 12 ± 8 years (range, 0-32 years), and duration of follow-up was 58 ± 6 months (range, 49-62 months).

NEUROLOGIC EXAMINATION

Neurologic examinations at entry and follow-up were performed by the same investigator (L.L.T.). Patients were examined as described by Notermans et al: muscle strength was measured according to the Medical Research Council grading system. Grades between 0 and 5 of 7 muscle groups in each arm and 7 muscle groups in each leg could lead to a maximum motor sum score of 140. The following muscle groups were tested: in the arms, the deltoid, biceps brachii, triceps brachii, wrist extension, finger extension, finger flexion, and intrinsic hand muscles; in the legs, the iliopsoas, gluteus maximus, quadriceps, tibialis anterior, gastrocnemius, peronei, and extensor hallucis longus. Touch, pinprick, vibration, and joint position sense were rated according to the distal-to-proximal distribution of abnormalities in both arms and both legs. Summation of all modalities could lead to a maximum sensory sum score of 56. The Romberg test was performed to measure stability. Ataxia was quantified using the tapping test for the dominant arm and leg. The device consisted of 2 push buttons for the hands and 2 pedals for the feet, placed at a fixed distance of 35 cm and connected to an automatic counter. The patient was asked to alternately push the buttons or pedals as fast as possible. The number of hits in 15 seconds was counted. The vibration perception threshold was measured on the dominant metacarpal 2 using a Vibrameter type 3 (Somedic AB, Stock-

QUALITY OF LIFE

Quality of life (QoL) was measured using the RAND 36-item health survey questionnaire (RAND-36). The questionnaire had been administered earlier to 27 patients and to all patients at follow-up. The RAND-36 is a general QoL questionnaire. It assesses 8 domains: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, pain, mental health, vitality, and general health perception. For each domain, the item scores are coded, summed, and transformed into a scale ranging from 0 to 100, where 100 is the best possible rating. The Dutch version of the RAND-36 was used in this study. This version has been validated in a group of randomly chosen inhabitants of a medium-sized Dutch town, consisting of 1063 persons (33% men) aged 18 to 89 years (mean, 44 years). The results of this validation were used as a reference population. The internal consistency (Cronbach α, 0.71-0.93) and the test-retest correlation (0.58-0.82) of the various domains were determined in this population.

ELECTRODIAGNOSTIC INVESTIGATION

At entry, 20 patients underwent an electrodiagnostic examination according to a standardized protocol. An additional examination was performed at follow-up in 10 patients according to the same protocol and in the same limbs. The limbs were warmed in water at 37°C for 30 minutes before the investigation; during the investigation, skin temperature was maintained at 37°C. Nerve conduction studies were performed using surface electrodes according to standard techniques. Motor conduction and F waves were investigated in the median and tibial nerve and sensory conduction in the median and sural nerve. Concentric needle electromyography was performed in the tibialis anterior muscle.

STATISTICAL ANALYSIS

The t test for paired samples, the nonparametric Wilcoxon signed rank sum test, and the McNemar χ² test were used when appropriate to test differences between entry and follow-up. Squaring of the Vibrameter values was performed to obtain a normal distribution. To compare differences between men and women, patients with age of onset of 40 years or less and more than 40 years, and patients with disease duration 10 years or less and more than 10 years, subgroup analyses were performed. To compare the RAND-36 scores of the study population with the reference population, we calculated standard scores by dividing the differences between the study population and the reference population by the SD of the reference population. These standard scores indicate how many SDs the scores of the study population differ from those of the reference population. This can be plotted in a graphic profile (Figure). In addition, z scores were calculated of the mean scores and SDs of patients and the reference population. P < .05 was considered statistically significant.
increased loss of strength and stability. Twenty-three patients complained about increased sensory loss. There was a trend toward a decrease in the number of patients complaining of positive sensory abnormalities (tingling and pain) and muscle cramp and an increase in the number of patients complaining of numbness.

NEUROLOGIC EXAMINATION

During follow-up there was a significant increase in the number of patients with muscle atrophy of the hands.

There was a significant increase in the number of patients with claw toes, whereas the number of patients with pes cavus and short calf muscles remained the same (Table 1). The scores on the tapping test for arms and legs were significantly decreased, whereas the vibration perception threshold scores remained the same (Table 1).

DISABILITY AND HANDICAP

In 11 patients, the Rankin score changed from grade 1 to grade 2, in 4 patients from grade 2 to grade 3, and in 1 patient from grade 3 to grade 4. During follow-up, there was a significant decrease in walking distance and an increase in the use of walking aids, but the number of patients (3) who used a wheelchair did not change. At entry, 9 patients were declared incapacitated for work, and 12 patients had retired. At follow-up, 6 more patients (mean age, 45 years; range, 28-64 years) were declared incapacitated for work because of deterioration of the disease (χ² test, P=.03, after exclusion of retired patients). Three patients retired, of whom 1 was considered incapacitated for work before retirement. Fourteen patients were not incapacitated for work.

QUALITY OF LIFE

There were no statistically significant differences between the QoL scores of the 27 patients who had answered the
questionnaires at entry and those who had answered at follow-up, but there was a trend toward improvement on the domains of pain and role limitations due to physical problems (Figure). There was a statistically significant difference in mean QoL on the domains of general health perception, physical functioning, role limitations due to physical problems, social functioning (P < .001), and vitality (P < .01, z scores) in all 43 patients with CMT type 2 compared with the reference population.

SUBGROUP ANALYSES

There were no differences between men and women in any of the analyzed variables. At entry, patients with age of onset older than 40 years (late onset) used fewer walking aids, but the use had significantly increased at follow-up. The number of patients with pain decreased significantly in patients with age of onset younger than 40 years (early onset). Patients in the early-onset group had significantly more pes cavus and short calf muscles. Patients with a disease duration of more than 10 years at entry deteriorated more in muscle strength during the 5 years of follow-up than patients with a shorter disease duration (decrease in motor sum score, 8.2 vs 4.1), although this was not statistically significant. No difference was found in rate of decline of motor strength in patients with higher or lower motor sum scores at entry. There was a trend toward a decrease in number of patients who complained about pain in the short-duration group but not in the long-duration group. There were no other differences between patients with short or long duration of disease.

ELECTRODIAGNOSTIC INVESTIGATION

An additional electrodiagnostic examination was performed in 10 patients. Of the other 10 patients who underwent the examination only at entry, 1 was dead, 1 was lost to follow-up, 5 refused to undergo the electrodiagnostic examination, and 3 refused to undergo both the electrodiagnostic examination and the neurologic examination. All patients had an axonal neuropathy on electrodiagnostic investigation. There were no statistically significant differences between the variables at entry and follow-up (Table 2). None of the patients had electrodiagnostic abnormalities consistent with demyelination.

INHERITANCE MODE AND DNA ANALYSIS

Patients originated from 27 families. Autosomal dominant inheritance was certain in 11 patients of 10 families because of established male-to-male inheritance. There were no large differences between severity in men or women in families where an X-linked inheritance mode could not be excluded, but the families were small. In 18 families, a DNA analysis was performed to establish if patients had mutations in the candidate genes PMP22, MPZ, and GJB1 (connexin 32). No mutations were found in the coding region and intron exon borders of the candidate genes PMP22 and MPZ. In one family without male-to-male inheritance, a mutation in the GJB1 (connexin 32) gene was present, which makes an X-linked inheritance mode likely. In this family, the median nerve motor conduction velocity in both men and women was within the normal range, and there were no clinical differences between men and women. There was no statistically significant difference in age at onset, age at entry, and disease duration at entry between this family and the other patients. In a separate analysis, without the 6 patients of this family (3 men, 3 women), no important differences were found in comparison with the analysis of all 43 patients.

To evaluate prospectively the clinical course of CMT type 2, 43 patients were examined twice with an interval of 5 years. Nearly all patients experienced deterioration, mainly loss of strength and walking instability. This is in accordance with the decrease in muscle strength and the increased use of walking aids. There was a remarkable trend toward a decrease in the number of patients with positive sensory symptoms and muscle cramps, especially in patients with a shorter duration of disease or an early age of onset. The trend toward improvement on the domain of pain of the RAND-36 QoL scale is in accordance with this observation. This could mean that pain and cramps are symptoms at onset and disappear during the disease. Pain in the feet and muscle cramps have been reported earlier as symptoms at onset in CMT disease.23 An

Table 2. Electrodiagnostic Investigation*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Entry</th>
<th>Follow-up</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (M/F)</td>
<td>10 (7/3)</td>
<td>10</td>
<td>NA</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>53 ± 16</td>
<td>57 ± 16</td>
<td>NA</td>
</tr>
<tr>
<td>Median motor nerve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DML, ms</td>
<td>4.4 ± 0.8</td>
<td>4.4 ± 0.7</td>
<td>.72</td>
</tr>
<tr>
<td>MCV lower arm, m/s</td>
<td>51 ± 4.8</td>
<td>50 ± 4.9</td>
<td>.10</td>
</tr>
<tr>
<td>MCV upper arm, m/s</td>
<td>56 ± 6.2</td>
<td>54 ± 6.0</td>
<td>.84</td>
</tr>
<tr>
<td>CMPWrist, mV</td>
<td>7.9 ± 2.9</td>
<td>8.5 ± 3.0</td>
<td>.26</td>
</tr>
<tr>
<td>Short F-M latency, ms</td>
<td>28.2 ± 2.8</td>
<td>28.7 ± 3.2</td>
<td>.86</td>
</tr>
<tr>
<td>Median sensory nerve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCV hand, m/s</td>
<td>42 ± 7.7</td>
<td>43 ± 6.3</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>SCV lower arm, m/s</td>
<td>51 ± 3.4</td>
<td>50 ± 5.1</td>
<td>.61</td>
</tr>
<tr>
<td>SNAP wrist, µV</td>
<td>5.3 ± 3.8</td>
<td>5.0 ± 3.2</td>
<td>.51</td>
</tr>
<tr>
<td>Tibial nerve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DML, ms</td>
<td>6.0 ± 1.6</td>
<td>5.7 ± 1.0</td>
<td>.89</td>
</tr>
<tr>
<td>MCV, m/s</td>
<td>34 ± 4.7</td>
<td>33 ± 6.7</td>
<td>.31</td>
</tr>
<tr>
<td>CMPWrist, mV</td>
<td>0.9 ± 1.1</td>
<td>0.7 ± 1.1</td>
<td>.71</td>
</tr>
<tr>
<td>CMPWrist, mV</td>
<td>0.5 ± 0.6</td>
<td>0.4 ± 0.4</td>
<td>.44</td>
</tr>
<tr>
<td>Short F-M latency, ms</td>
<td>56.9 ± 6.5</td>
<td>57.2 ± 5.2</td>
<td>.72</td>
</tr>
<tr>
<td>No response obtainable</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Sural nerve</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCV, m/s</td>
<td>37 ± 3.9</td>
<td>39 ± 6.3</td>
<td>.29</td>
</tr>
<tr>
<td>SNAP, µV</td>
<td>2.2 ± 3.1</td>
<td>1.8 ± 2.4</td>
<td>.50</td>
</tr>
<tr>
<td>No response obtainable</td>
<td>6</td>
<td>6</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Electromyography of anterior</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>tibial muscle</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous activity</td>
<td>7</td>
<td>9</td>
<td>.16</td>
</tr>
</tbody>
</table>

Abbreviations: CMAP, compound muscle action potential; DML, distal motor latency; MCV, motor conduction velocity; NA, not applicable; SCV, sensory conduction velocity; SNAP, sensory nerve action potential. *Data are presented as mean ± SD or number of patients. †Mann-Whitney U test.
interesting finding was that during the follow-up period the number of patients with these foot abnormalities did not change, whereas the number of patients with claw toes increased. This indicates that pes cavus and short calf muscles develop early, probably during growth, whereas claw toes can develop at any time. Nearly all patients mentioned a deterioration of their disease, but according to the RAND-36 measurements their QoL did not deteriorate. This discrepancy may be caused by the chronic nature of CMT type 2; most patients already had complaints for years before the first examination. Moreover, RAND-36 may lack sensitivity to reproduce small changes in QoL or the follow-up period was too short.

The finding of a gap junction protein 1 (GJB1 or connexin 32) mutation in one family with an axonal polyneuropathy on clinical and electrophysiologic investigation is in concert with earlier findings in patients with a CMT type 2 phenotype and stresses the importance of a search for X-linked CMT type 2 in families with an axonal polyneuropathy and no established male-to-male inheritance. Since the patients of this family fulfilled the inclusion criteria, because they all had an axonal polyneuropathy on electrodiagnostic investigation, we did not exclude them from our study, and a separate analysis without these patients showed the same results. Although we did not find mutations in the MPZ gene in our patients, searching for mutations in this gene may be worthwhile, in view of the recently found point mutations in the MPZ gene in patients with a CMT type 2 phenotype. The MPZ gene encodes for myelin protein zero, which forms a part of the myelin sheet. Mutations in this gene usually lead to demyelinating forms of CMT. Other recently discovered mutations that lead to CMT type 2 are a mutation in the NF-L gene, which is involved in neurofilament organization, and a mutation in the KIF1B gene, which plays a role in axonal transport.

From clinical experience, CMT type 2 has come to be considered a chronic progressive disease. Follow-up studies in CMT type 2 have only been performed in combination with CMT type 1, the demyelinating form. In a follow-up study of patients with CMT type 1 and type 2, no deterioration in muscle strength at functional muscle strength testing could be established within 1 year. In a combined, longitudinal, 10-year study in patients with CMT type 1 or type 2, there was mainly a decline in muscle strength of the lower legs, but the rate of deterioration varied: the more weakness at entry, the greater the decline in strength during follow-up.

In conclusion, a decrease in muscle strength and an increase in disability but not in QoL could be established in patients with CMT type 2, even in a relatively short disease duration of 5 years. However, no sensory deterioration could be established. These observations can contribute to counseling and rehabilitation of patients with CMT type 2 and can be useful in the determination of end points and follow-up duration of clinical trials of patients with CMT type 2.

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Author contributions: Study concept and design (Drs Teunissen, Notermans, Franssen, van Engelen, and Wokke); acquisition of data (Drs Teunissen, Franssen, and Baas); analysis and interpretation of data (Drs Teunissen, Notermans, Franssen, and Baas); drafting of the manuscript (Dr Teunissen); critical revision of the manuscript for important intellectual content (Drs Notermans, van Engelen, Baas, and Wokke); statistical expertise (Drs Teunissen and Franssen); obtained funding (Dr Notermans); administrative, technical, and material support (Drs Teunissen, Franssen, van Engelen, and Baas); study supervision (Drs Notermans, Franssen, van Engelen, Baas, and Wokke).

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**Correction**

Error in Materials and Methods. In the Original Contribution by Fukumoto et al titled “β-Secretase Protein and Activity Are Increased in the Neocortex in Alzheimer Disease,” published in the September 2002 issue of the ARCHIVES (2002;59:1381-1389), an error occurred in the “Materials and Methods” section. On page 1382, the homogenization procedure was incorrectly described as being performed at “10 µL/µg (volume per wet weight),” and the BACE ELISA was performed at “0.004 wt/vol.” The correct protocol should have read that the tissue was homogenized in 10 µL/mg volume per wet weight (=0.1 mg wt/µL vol) of Tris buffer and that the samples for the BACE ELISA were loaded as “50 µL of 0.001 wt/vol.” All dilutions are in the following units: milligrams of wet weight per microliters of buffer volume.