Acta orthop. Scandinav. 43, 4–18, 1972

Orthopaedic Hospital, University of Aarhus, Denmark.

ON THE PATHOGENESIS OF CHARCOT-MARIE-TOOTH DISEASE

A Study of the Sensory and Motor Conduction Velocity in the Median Nerve

VIGGO KAMP NIELSEN & SØREN PILGAARD

Accepted 20.ix.71

The pathogenesis of Charcot-Marie-Tooth disease (CMT) still remains unsettled. The different opinions of earlier writers have been extensively reviewed by England & Denny-Brown (1952), and more recently by Dyck & Lambert (1968 a, b). The concept that muscular dysfunction is secondary to a primary affection of the peripheral nerve or possibly the spinal cord has many proponents (England & Denny-Brown 1952, Dyck & Lambert 1968 a, Brodal et al. 1953. Schwartz 1963), but electromyographic studies and motor conduction velocity determinations have yielded conflicting results, considering the extent and distribution of muscular impairment. The Research Group on Neuromuscular Diseases (1968) leaves the question open, whether CMT should be classified under "spinal muscular atrophies" or "peripheral nerve disorders". Dyck & Lambert (1968 a, b) distinguish between three types of neurogenic disorders within the general category of CMT, the hypertrophic neuropathy, the neuronal type, and the progressive spinal type.

Sensory dysfunction is rarely prominent (England & Denny-Brown 1952, Dyck & Lambert 1968 a, Hoffmann 1893), and little information is available from the literature on the afferent nerve system in patients with CMT. Advances in the electrophysiological techniques (Buchthal & Rosenfalck 1966) have made it possible to discriminate sensory nerve action potentials of even low amplitude. This report presents the results of conduction velocity determinations in sensory and motor fibres of the median nerve in a series of severely affected patients with the hypertrophic neuropathy type of CMT*. Our data and

previously reported findings seem to fit in with the concept that the CMT disease may be due to a hereditary Schwannopathy.

MATERIAL AND METHODS

Fifteen patients, 6 women and 9 men, were selected from a large material collected by one of us (SP). The age ranged from 14 to 64 years, on the average 35 years. The patients belonged to seven families, two generations being represented in five. The following criteria for the selection were used:

1. A clear, dominant inheritance of CMT, established by analysis of the pedigree of the families. Personal examination (SP) of 114 of the 132 living members disclosed CMT in another 20 persons (Figure 1).

2. Cavus feet, loss of ankle and patellar jerks, and wasting and paresis of distal muscles in the legs. Wasting of the small hand muscles. The muscular affection in the lower extremity was severe in fourteen patients, and moderate in one (AT, female, 62 years old).

3. No clinical evidence of affection of the proximal muscles.

4. Severe reduction of the motor conduction velocity in the peroneal nerve, which ranged from 0 (i. e. no response in the extensor digitorum brevis muscle) to 26 m/sec.

5. No other neurological disorders *sui generis*, or due to internal medical diseases, intoxications, or trauma.

The earliest clinical symptoms or signs of the disease could be traced back to childhood or adolescence in all the patients.

The sensory and motor conduction velocity in the median nerve was measured with the technique described by Buchthal & Rosenfalck (1966). Supramaximal stimuli were applied to finger I through ring electrodes, and the evoked nerve action potentials were recorded at the wrist and when possible at the elbow through needle electrodes. These served as stimulating electrodes when motor fibres were activated. Muscle action potentials were recorded from the abductor pollicis brevis muscle through two concentric needle electrodes, 0.9 mm in diameter. The action potentials were displayed on and photographed directly from the oscilloscope of a three-channel electromyograph (DISA). Whenever necessary 15–20 potentials were superimposed on the same spot of the film. The temperature was about 35°C, recorded near the nerve with a thermoneedle (Ellap, Copenhagen). The interelectrode distances were measured percutaneously to the nearest 2 mm.

Results obtained from 60 examinations in normal persons between 16 and 62 years of age served as reference material (Nielsen, in preparation).

RESULTS

Clinical Findings

None of the patients had ever experienced sensory symptoms in the upper extremities, and clinical testing of sensibility yielded entirely

---

• Part of the study was presented at the 19. Scandinavian Congress of Neurology, Aarhus, 1970.

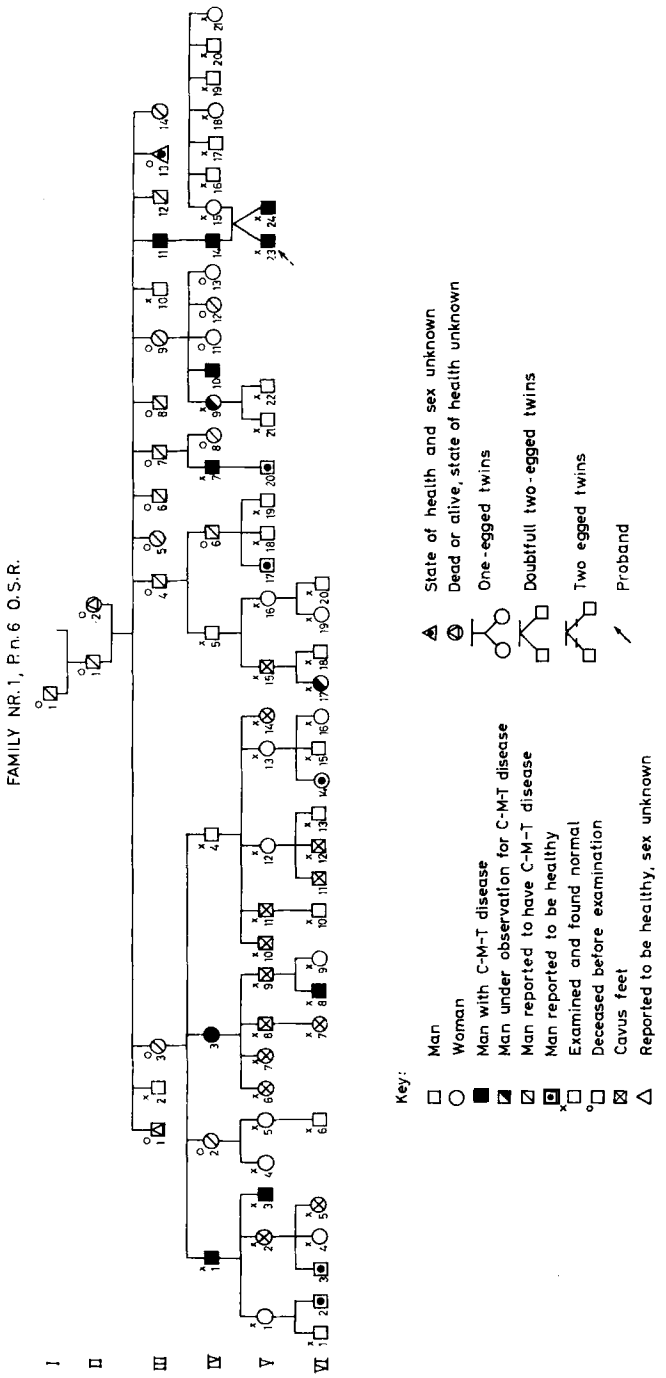

Figure 1. The pedigree of a CMT family. Roman numerals indicate the generations and Arabic numerals indicate the individual members. The following persons were included in the present study: IV–14 (KSR), V–23 (OSR), V–24 (PSR), and VI–8 (FJ).

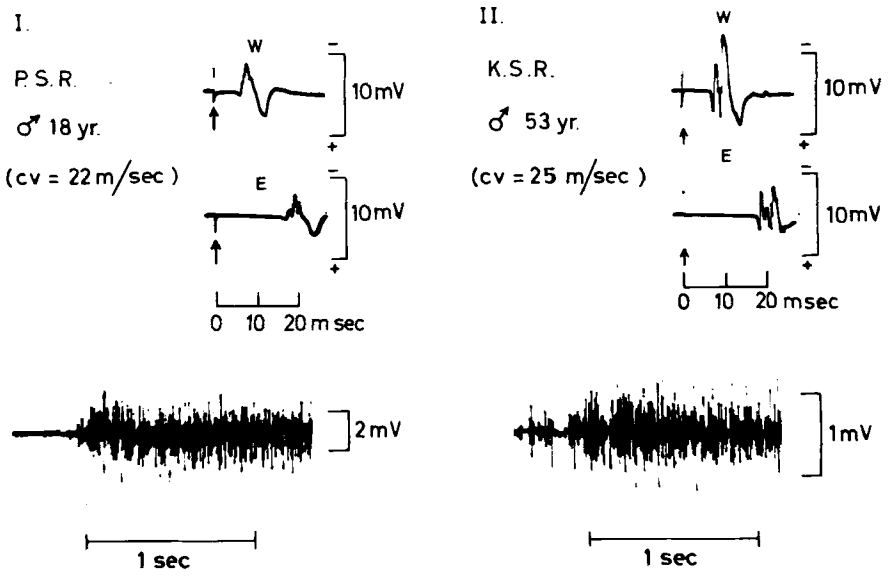

Figure 2. Muscle action potentials from the abductor pollicis brevis muscle evoked by stimulation of the median nerve at the wrist (W) and the elbow (E). Below: Electromyographic recording of the maximal voluntary contraction of the muscle, showing an interference pattern.

normal results. Slight to moderate paresis and atrophy of the thenar muscles were present in all patients.

Motor Conduction Velocity

Figure 2 shows typical examples of muscle action potentials following stimulation of the motor fibres at the wrist and the elbow. The distal latency (wrist-abductor pollicis brevis muscle) averaged 7.3 msec, ranging from 5.0 to 11.0 msec (Table 1). This was 2–3 times longer than in normal persons (3.1 ± 0.05 msec). The motor conduction velocity between elbow and wrist was on the average 23.6 m/sec, ranging from 16 to 35 m/sec. This represents a reduction of about 60 per cent (40–76 per cent) of the expected normal values for the age of the single patients (Figure 3). The conduction velocities, recorded in the two generations, were almost identical in four of the five families. Four patients had been examined by one of us (SP) 16 to 35 months prior to the present examination. The two sets of data showed variation, well within the range of *intra*individual variation in normal persons (Table 2).

Table 1. Neurophysiological data in patients with Charcot-Marie-Tooth disease.

Patient		Sex	Age (yr)	Motor: Distal latency Wr–APB (msec)	Motor: Conduction velocity El–Wr (m/sec)	Motor: Amplitude (APB) Stim: Wr (mV)	Motor: Amplitude (APB) Stim: El (mV)	Sensory: Conduction velocity Fg 1–Wr (m/sec)	Sensory: Amplitude (Wrist) Wr–El (m/sec)	Sensory: Amplitude (Wrist) Stim: Fg 1 (μV)
KSR	○*	♂	53	6.9	25	11	5	18	28	6
OSR	○	♂	18	8.1	22	12	6	17	?	2
PSR	○	♂	18	5.8	22	16	9	24	32	12
AT	△	♀	62	7.1	35	15	14	?	...	?
IJ	△	♀	34	9.7	19	12	5	13	22	2
ÅT	△	♂	28	9.0	16	7	4	16	...	1
HØ	■	♀	61	5.0	27	24	5	28	...	4
ELØ	■	♂	37	6.5	24	11	4	24	29	10
MLØ	■	♂	28	5.5	23	13	3	?	...	?
SNH	▽	♂	64	8.1	30	22	18	23	...	4
EH	▽	♀	23	5.6	30	8	6	22	...	2
HJ	□	♂	41	8.1	20	13	8	14	?	3
SJJ	□	♀	16	11.0	18	2	2	15	...	1
LHT	●	♀	26	6.5	23	12	5	24	...	1
FJ	▲	♂	14	6.5	20	8	2	?	...	?
Mean value			35	7.3	23.6	12.5	6.4	19.8	27.8	4.0
SD				1.7	5.1	5.4	4.5	4.9	4.2	3.6

* The symbols correspond to those in Figures 3, 4, and 5.

Motor conduction velocity (median nerve) in Charcot-Marie-Tooth disease.

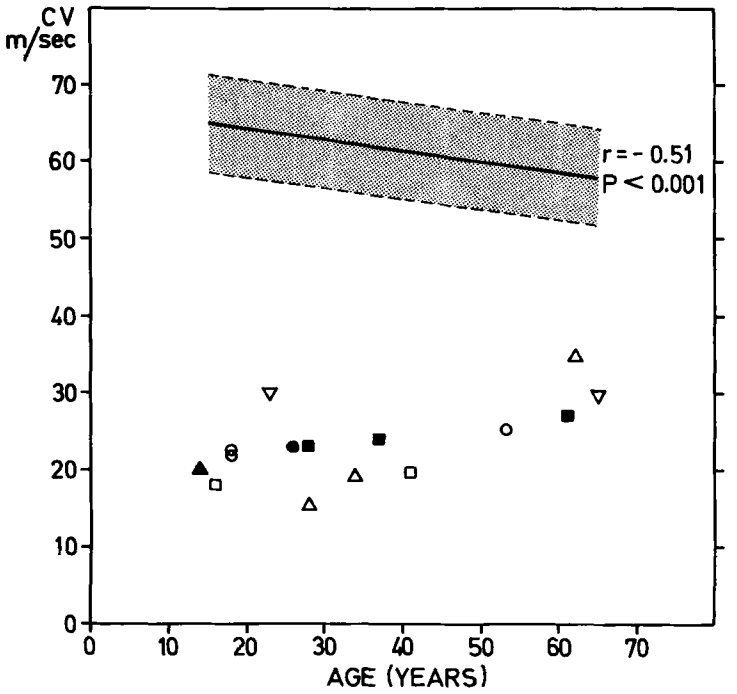

Figure 3. The motor conduction velocity in the median nerve related to the age of the patients. Members of the same family are indicated by the same symbol, as defined in Table 1. The shaded area indicates the 95 per cent range of normal variation.

The shape of the muscle action potentials following stimulation at the wrist was somewhat split up, but never clearly polyphasic. The duration was increased, averaging 15 msec (8–22 msec). The amplitude was low normal or borderline, being markedly reduced in only one patient (2 mV). She (SJJ) had a distal latency of 11 msec and a motor conduction velocity of 18 m/sec, but an interference pattern could be recorded by maximal contraction of the muscle. The discrepancy between the distal latency and the amplitude is demonstrated in Figure 4.

Repeated replacements of the two needle electrodes in the search for a sharply defined onset of the action potential never aroused insertion activity, and spontaneous fibrillation potentials at rest were never

observed. Maximal voluntary contraction always showed an interference pattern (Figure 2).

Table 2. Double determinations of the motor conduction velocity (median nerve) in Charcot-Marie-Tooth disease.

Patient	Sex	Age (yr)	Time interval (months)	Conduction velocity (m/sec) 1. Exam.	2. Exam.
PSR	♂	18	16	22	22
OSR	♂	18	16	22	22
IJ	♀	34	20	18	19
AT	♂	28	35	18	16

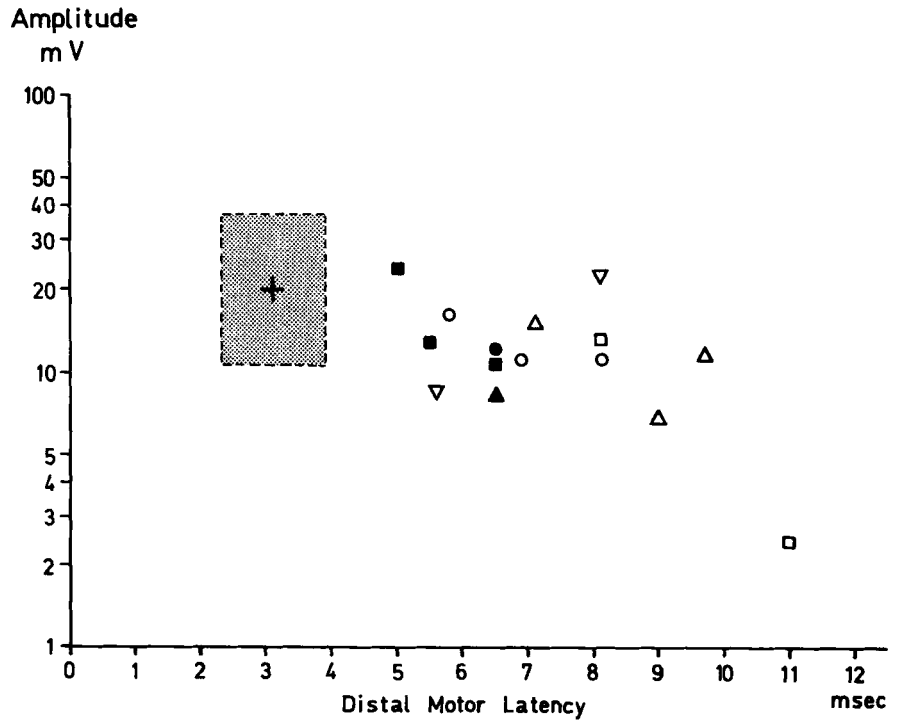

Figure 4. The relationship between the amplitudes (log scale) of action potentials from the abductor pollicis brevis muscle and the distal latency (following stimulation at the wrist). Symbols as indicated in Table 1. The shaded area indicates the 95 per cent range of normal variation in the two variables respectively.

Sensory conduction velocity (finger 1-wrist) in Charcot-Marie-Tooth disease.

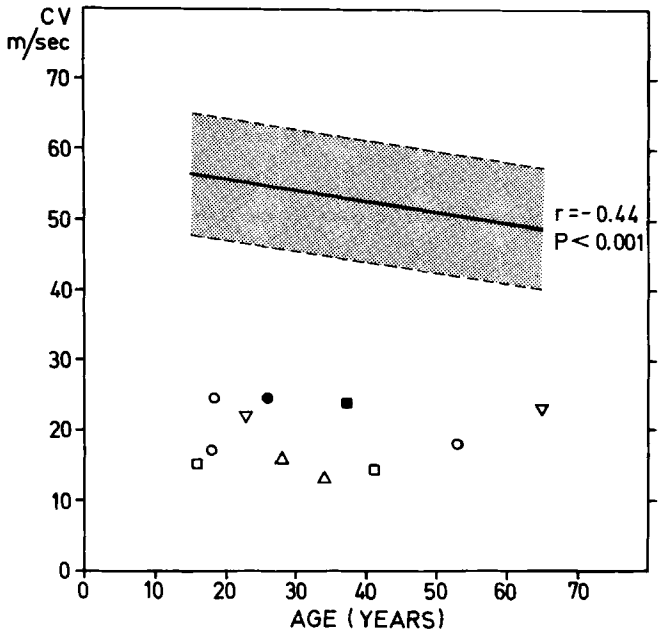

Figure 5. The distal sensory conduction velocity (finger 1—wrist) related to the age of the patients. Symbols as indicated in Table 1. The shaded area indicates the 95 per cent range of normal variation.

Sensory Conduction Velocity

A sensory action potential could be recorded at the wrist in all patients, but in three patients the potential could be discerned only when 15–20 potentials were superimposed. These potentials were omitted, since a reliable determination of the latency and amplitude was not possible. The latency was on an average 6.5 msec, corresponding to a mean distal conduction velocity of 20 m/sec, ranging from 13 to 28 m/sec. This represents a mean reduction of 65 per cent (53–76 per cent) of the expected normal value for the age of the single patients (Figure 5). As in the motor fibres, the sensory conduction velocity was almost identical in two generations within the same family. Action potentials at the elbow were recognizable in four of the six patients tested. The conduction velocities between wrist and elbow (Table 1) showed a reduction of 60 per cent of the normal mean value.

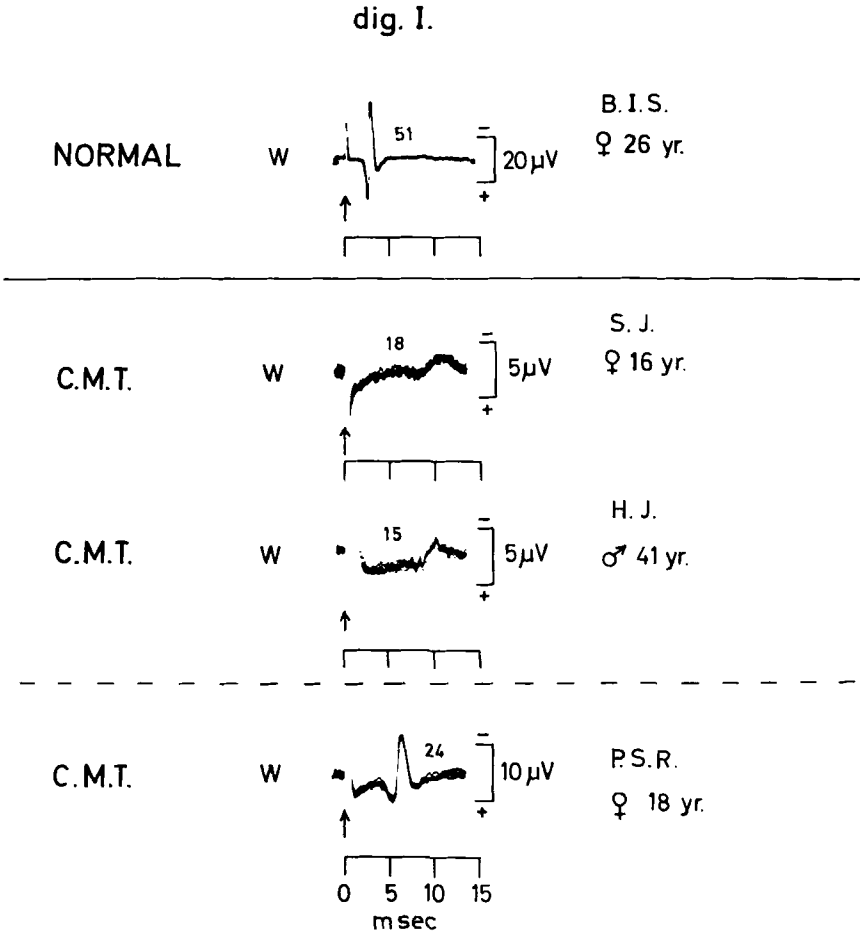

Figure 6. Sensory action potentials recorded at the wrist following supramaximal stimulation of finger 1. In the CMT patients, 10–20 single potentials were superimposed. Figures above the potentials indicate the conduction velocity (m/sec) in the distal segment. The markedly prolonged latency and potential duration constitutes the most significant deviation from the normal action potential (upper trace). Note the uniform shape of potentials recorded in SJ and her father, HJ, despite a difference in age and the duration of the disease of about 25 years. The lower trace (PSR) demonstrates a normally synchronized potential despite the severely reduced conduction velocity. The well-preserved amplitude does not indicate any significant loss of nerve fibres.

Typical examples of sensory nerve action potentials, recorded at the wrist, are demonstrated in Figure 6, which also includes an action potential from a normal person. The most significant deviation from the normal potential was a highly increased potential duration, which ranged from about 3 to 5 msec. The prolonged duration may in part account for the low potential amplitude, which varied from 1 to 12 μV, being 4 μV or lower in nine of the patients. The technique applied was insufficient for a detailed study of the shape of pathological potentials of the present degree.

COMMENTS

Functional impairment of muscles in the upper extremity is not a spontaneous complaint of the patients with CMT, but in most patients wasting and mild pareses in the small hand muscles is demonstrable, and in older persons the atrophy may reach severe degrees.

Thus, the extreme slowing of the motor conduction velocity is out of proportion to the clinical picture. Marked slowing of the conduction velocity in the ulnar and median nerve in patients with CMT was originally reported by Henriksen (1956), working with Lambert (1956), and Gilliatt & Thomas (1957). Later reports have convincingly confirmed these findings (Dyck & Lambert 1968 a, Amick & Lemmi 1963, Blom et al. 1964, Cristie 1961, Dyck et al. 1963, Earl & Johnson 1963, Kaeser 1965, Myrianthopoulos et al. 1965). The reported conduction velocities range from 10–30 m/sec, i. e. of the same order as recorded in the present material. Slight reduction of the conduction velocity in unaffected children of affected parents (Myrianthopoulos et al. 1965) has been interpreted as an indication of an early subclinical stage of a progressive impairment of the muscular function; a progressive deterioration of the *motor conduction velocity* has never been demonstrated in individual patients. On the contrary, the stationary level observed in four of our patients for up to 35 months confirms similar observations made by Amick & Lemmi (1963).

The evoked muscle action potential has a surprisingly well preserved amplitude and shape. The pronounced difference in amplitude following stimulation at the wrist and the elbow (Table 1), presumably resulted from a marked increase in the temporal dispersion. We did not measure the duration of single muscle action potentials by slight voluntary contraction, and the absence of fibrillation potentials does

not disprove the presence of a neurogenic atrophy. However, an interference pattern could be recorded by maximal voluntary contraction of the thenar muscles, adding further evidence of a discrepancy between the motor nerve function and the functional state of the muscles. These observations are not at variance with the more pronounced findings in previously reported electromyographic investigations (Amick & Lemmi 1963, Myrianthopoulos et al. 1965, Hausmanowa et al. 1967), since they have mainly been confined to muscles in the lower extremity. Hausmanowa et al. (1967), however, comment that even in the legs the electromyographic pattern took "a rather peculiar position among the neurogenic atrophies differing considerably from the entire group of neuropathies, and resembling in many aspects the group of spinal diseases".

Quite a number of patients, even with severe CMT, deny sensory symptoms. Clinical sensory findings are rarely prominent, usually confined to the distal parts of the lower extremities, and predominantly late manifestations (England & Denny-Brown 1952, Dyck & Lambert 1968 a, Brodal et al. 1953, Schwartz 1963, Dyck et al. 1963, Myrianthopoulos et al. 1965). The literature is particularly short of reports on sensory dysfunction in the upper extremities, and the few cases reported have been recorded almost exclusively in old persons (England & Denny-Brown 1952, Brodal et al. 1953, Amick & Lemmi 1963). Hence, the lack of sensory findings in our patients forms no exception.

With a few exceptions (Kaeser 1965, Myrianthopoulos et al. 1965, Bram et al. 1965), earlier attempts to record action potentials from the sensory nerve fibres in CMT patients have failed, owing to difficulties in discerning action potentials of low amplitude from the background noise. Dyck et al. (1963) commented that this indicated an abnormal sensory nerve function, as sensory action potentials were easily recorded in all their normal persons. Kaeser (1965) recorded a sensory conduction velocity of 27 m/sec in one of four patients examined. Dyck & Lambert (1966) measured the sensory conduction velocity in three sural nerves *in vitro*. The peak velocity ranged from 12 to 23 m/sec.

The consistent observation of extremely slow conduction velocities in sensory fibres in the present material contrasts with the absence of clinical sensory findings. The percent reduction from the normal mean values shows that motor and sensory fibres were equally affected. The uniform results obtained in two generations within the

same family counteract the normal tendency towards a decrease in the conduction velocity with advancing age. Furthermore, since the age of onset of clinical manifestations was roughly the same in both generations, and all patients experienced a progressive clinical course, the conduction velocity does not appear to be correlated with the duration of the disease. In a large kinship, examined by Dyck et al. (1963), a positive correlation between the conduction velocity and age was apparent. This was also observed in the present material (e. g. for the motor conduction velocity: Y (m/sec) = 0.19 X (yr) + 23.6, $r = 0.64$, $P < 0.01$). On this account it has been suggested that succeeding generations become earlier and more severely affected (Dyck et al. 1963, Earl & Johnson 1963). We hesitate to draw this conclusion for reasons discussed in the following paragraph, and because a reduction of the conduction velocity with progressive severity of clinical signs has not been documented in single patients.

A detailed analysis of the shape of the sensory action potential may yield valuable information, but this would require an averaging technique (Rosenfalck & Buchthal 1970). In the present study the marked increase of the duration of the sensory action potential indicates a wide temporal dispersion between action potentials of individual fibres, whence follows that the low amplitude of the compound action potential does not provide conclusive evidence *per se* of a significant reduction in the number of sensory fibres. One of the characteristic findings in histopathological studies has been a large decrease in the number of myelinated fibres, but Dyck et al. (1970) emphasized that considerable reservations should be made due to the fact that demyelinated segments of myelinated fibres or totally demyelinated fibres were not counted. It may be added that their observations are restricted to the sural nerve, where the extent of axonal degeneration may be more prominent than in the median nerve, considering the pattern of distribution of clinical findings.

CONCLUSIONS

The consistent, yet conflicting results may be concentrated into three aspects: (1) A discrepancy was observed between the clinical findings, in particular the lack of sensory symptoms and signs, and the disproportionately extreme slowing of the impulse transmission. (2) The electrophysiological findings in the thenar muscles were minimal compared with the severe reduction of the motor conduction velocity

in the median nerve. (3) A negative correlation was absent between the conduction velocities and the duration of the CMT disease or the age of the patients. The common denominator is the slow conduction velocity. This made us raise the question: *Has the motor and sensory conduction velocity ever been normal in patients with CMT?*

At birth the conduction velocity amounts to about 50 per cent of the normal adult values, which are reached around the eighth year of life (Thomas & Lambert 1960, Gamstorp 1963). There is abundant evidence that the postnatal increase in conduction velocity is due to the myelinisation of peripheral nerve fibres during infancy and early childhood (Gamstorp 1963). This reflects the function of the Schwann cells.

Conduction velocities reported in this and previous studies came close to those measured in infants at birth. Hence, we advance the hypothesis that *the low conduction velocities in CMT patients reflect an impaired post-natal myelinisation of fibres.*

A normal sensory perception is acquired in early childhood by a process of learning. A CMT child who has experienced nothing but afferent impulses, conducted at a speed of 15–30 m/sec, may learn to interpret such impulses "normally" from experience. The *clinical* picture of CMT, characterized by a slowly developed muscular atrophy and paresis eventually followed by minor sensory defects, may result from a progressive axonal degeneration. Histopathological studies strongly suggest that the primary site of affection is the Schwann cell, as evidenced by an absent or incomplete myelinisation of almost all fibres and by an inability to maintain myelin (see Dyck et al. 1970). It is conceivable that such a condition may lead to degeneration of nerve axons, also demonstrable in nerve biopsies.

Thus clinical, neurophysiological, and histopathological observations seem to fit in with the concept that the pathogenesis of the CMT of the present type, is a dominant, hereditary "Schwannopathy".

SUMMARY

The motor and sensory conduction velocity (median nerve) was determined in fifteen patients with Charcot-Marie-Tooth disease. Two generations were examined in five families. Clinical sensory findings were absent, whereas slight to moderate atrophy and paresis were demonstrable in the small hand muscles. The average motor and sensory conduction velocity was 23.6 and 19.8 m/sec, i. e. about 40

per cent of the normal values. The values were nearly the same in the two generations, despite differences in age and duration of the disease of 30–40 years. No deterioration was observed in four patients after 16–35 months. Muscle action potentials had relatively normal amplitudes, and maximal contraction showed an interference pattern. Sensory action potentials showed great temporal dispersion, accounting partly for the low amplitudes. It is suggested that the pathogenesis of CMT may be an absent or incomplete post-natal myelinisation, due to a dominant, hereditary "Schwannopathy".

REFERENCES

Amick, L. D. & Lemmi, H. (1963) Electromyographic studies in peroneal muscular atrophy. *Arch. Neurol.* **9**, 273–284.

Blom, S., Hagbarth, K.-E. & Lundberg, P. O. (1964) Motor conduction velocities in amyotrophic lateral sclerosis, polyradiculoneuritis and Charcot-Marie-Tooth's disease. *Acta neurol. scand.* **40**, 6–12.

Bram, S., Fra, L., Gangiglio, G. & Bergamasco, B. (1965) Sensory nerve conduction in degenerative lesions of the posterior columns of the spinal cord. (8th Internat. Congr. Neurol. Vienna, 1965.) *Excerpta Medica* **94**-E, 77.

Brodal, A., Böyesen, S. & Frövig, A. G. (1953) Progressive neuropathic (peroneal) muscular atrophy (Charcot-Marie-Tooth disease). *Arch. Neurol. Psychiat. (Chic.)* **70**, 1–29.

Buchthal, F. & Rosenfalck, Annelise (1966) Evoked action potentials and conduction velocity in human sensory nerves. *Brain Res.* **3**, 1–122.

Cristie, B. G. B. (1961) Electrodiagnostic features of Charcot-Marie-Tooth disease. *Proc. roy. Soc. Med.* **54**, 321–324.

Dyck, P. J., Lambert, E. H. & Mulder, D. W. (1963) Charcot-Marie-Tooth disease. Nerve conduction and clinical studies of a large kinship. *Neurology (Minneap.)* **13**, 1–11.

Dyck, P. J. & Lambert, E. H. (1966) Numbers and diameters of nerve fibres and compound action potential of sural nerve: Controls and hereditary neuromuscular disorders. *Trans. Amer. neurol. Ass.* **91**, 214–217.

Dyck, P. J. & Lambert, E. H. (1968 a) Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. I. Neurological, genetic, and electrophysiologic findings in hereditary polyneuropathies. *Arch. Neurol. (Chic.)* **18**, 603–618.

Dyck, P. J. & Lambert, E. H. (1968 b) Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. II. Neurologic, genetic, and electrophysiologic findings in various neuronal degenerations. *Arch. Neurol. (Chic.)* **18**, 619–625.

Dyck, P. J., Ellefson, R. D., Lais, A. C., Smith, R. C., Taylor, W. F. & Van Dyke, R. A. (1970) Histological and lipid studies of sural nerves in inherited hypertrophic neuropathy: Preliminary report of a lipid abnormality in nerve and liver in Dejerine-Sottas disease. *Mayo Clin. Proc.* **45**, 286–327.

Earl, W. C. & Johnson, E. W. (1963) Motor nerve conduction velocity in Charcot-Marie-Tooth disease. *Arch. phys. Med.* **44**, 247–252.

England, A. C. & Denny-Brown, D. (1952) Severe sensory changes and trophic disorders in peroneal muscular atrophy (Charcot-Marie-Tooth type). *Arch. Neurol. Psychiat. (Chic.)* **67**, 1–17.

Gamstorp, Ingrid (1963) Normal conduction velocity of ulnar, median, and peroneal nerves in infancy, childhood, and adolescence. *Acta pædiat. (Uppsala)*, **146**, 68–76.

Gilliatt, R. W. & Thomas, P. K. (1957) Extreme slowing of nerve conduction in peroneal muscular atrophy. *Ann. phys. Med.* **4**, 104–106.

Hausmanowa, Irena, Emeryk, Barbara, Wasowicz, Barabara & Kopec, Aniela (1967) Electromyography in neuromuscular diagnostics. *Electromyography* **7**, 203–225.

Henriksen, J. D. (1956) Conduction velocity of motor nerves in normal subjects, and patients with neuromuscular disorders. Thesis, Mayo Foundation.

Hoffman, J. (1893) Ueber chronische spinale Muskelatrophie im Kindesalter, auf familiärer Basis. *Dtsch. Z. Nervenheilk.* **3**, 427–470.

Humphrey, J. G. & Shy, G. M. (1962) Diagnostic electromyography. *Arch. Neurol.* **6**, 339–352.

Kaeser, H. E. (1965) Veränderungen der Leitgeschwindigkeit bei Neuropathien and Neuritiden. *Fortschr. Neurol. Psychiat.* **33**, 221–248.

Lambert, E. H. (1956) *Clinical examination in neurology*, p. 313. Saunders, Philadelphia.

Myrianthopoulos, N. C., Lane, M. H., Silberberg, D. H. & Vincent, B. L. (1965) Nerve conduction and other studies in families with Charcot-Marie-Tooth disease. *Brain* **87**, 589–608.

Nielsen, V. K. & Pilgaard, S. (1970) Sensory and motor conduction velocity in the median nerve in the Charcot-Marie-Tooth disease. *Acta neurol. scand.*, Suppl. **43**, 197.

Nielsen, V. K.: In preparation.

Research Group on Neuromuscular Diseases (1968) Classification of the neuromuscular disorders. Appendix. J. neurol. *Sci.* **6**, 165.

Rosenfalck, Annelise & Buchthal, F. (1970) Demyelination and axonal degeneration. *Acta neurol. scand.*, Suppl. **43**, 199.

Schwartz, A. R. (1963) Charcot-Marie-Tooth disease. A 45-year follow-up. *Arch. Neurol.* **9**, 623–634.

Thomas, J. E. & Lambert, E. H. (1960) Ulnar nerve conduction velocity and H-reflex in infants and children. *J. appl. Physiol.* **15**, 1.

Correspondence to:

Dr. Viggo Kamp Nielsen
Medical Dept. P.
Rigshospitalet
Blegdamsvej 9
2100 Copenhagen
Denmark