Diplomarbeit

Measurement of distal motor latencies versus measurement of nerve conduction velocities in classification of hereditary peripheral neuropathies

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Graz, am …….. (Unterschrift)

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Abstract

We performed an electrophysiological study in 67 patients with genetically proven hereditary neuropathies. Our intention was to establish electrophysiological criteria secondary to the measurement of distal motor latencies (DMLs), in addition to the well known motor nerve conduction velocity (MNCV) criteria that subdivides the Charcot-Marie-Tooth disease (CMT) into CMT1 and CMT2 by the cut-off value of 38 m/s. The 28 patients with CMT type 1A (CMT1A) showed uniform and marked reduction of MNCVs below 33 m/s in the four motor nerves and severe prolongation of median DMLs > 8 ms and ulnar DMLs > 5.4 ms in 93%. To compare DMLs in relation to MNCVs we calculated the terminal latency index (TLI). Mean median TLI with 0.32 and mean ulnar TLI with 0.42 in CMT1A were in the normal range, suggesting homogeneous conduction slowing along the entire length of the nerves. In the six CMT2-patients mean median TLI was 0.33 and mean ulnar TLI 0.4 with a low range. MNCVs and DMLs were in the normal range. We took the CMT2-patients as control group. The MNCVs and DMLs of X-linked CMT (CMTX) females and males did not differ significantly. Median TLI of the one female patient was 0.25, indicating distal accentuation of nerve conduction slowing, whereas ulnar TLI was in the normal range. In the six male CMTX-patients mean median TLI was 0.36 and mean ulnar TLI 0.43, suggesting rather homogeneous conduction slowing along the entire length of the motor nerves in the upper limbs in comparison to the female patients. The 14 patients with hereditary neuropathy with liability to pressure palsies (HNPP) were characterized by a sensorimotor background neuropathy. Median DMLs were moderately to severely prolonged disproportionately to MNCVs that were mostly in the normal range. This was supported by a low mean median TLI with 0.24. In contrast, ulnar TLI was with 0.41 in the normal range. The eight patients with mutations in the myelin protein zero (MPZ) gene showed a wide range of MNCVs from severely reduced to normal. DMLs were slightly-to-moderately prolonged in all cases, but were in contrast to CMT1A below 8 ms for the median nerve and below 6 ms for the ulnar nerve. Mean median TLI was increased with 0.41, with a wide range. In the two patients with mutations in the neurofilament light chain (NEFL) gene we observed a similar picture to that of patients with MPZ-mutations. We recommend for classification the ulnar DML because median DMLs may be prolonged due to the common carpal tunnel syndrome, independently of hereditary neuropathies, especially in CMTX females.

Zusammenfassung

Es wurde eine retrospektive elektrophysiologische Studie an 67 Patienten mit genetisch gesicherten peripheren hereditären Neuropathien durchgeführt. Die Idee dieser Studie war es elektrophysiologische Kriterien anhand der Messung der distal motorischen Latenz (DML) als Zusatz zur Nervenleitgeschwindigkeitsmessung einzuführen. Die 28 Charcot-Marie-Tooth Typ 1A (CMT1A) Patienten zeigten eine uniforme Reduktion der motorischen Nervenleitgeschwindigkeit (NLG) < 33 m/s in den vier motorischen Nerven und eine Prolongation der medianen distal motorischen Latenz (DML) > 8 ms und der ulnaren DML > 5,4 ms in 93%. Um die DMLs in Bezug auf die NLGs zu vergleichen, errechneten wir den terminal latency index (TLI). Der mittlere mediane TLI mit 0,32 und der mittlere ulnare TLI mit 0,42 der CMT1A-Patienten waren im Normbereich. Bei den CMT2-Patienten war der mittlere mediane TLI 0,33 und der mittlere ulnare TLI 0,4, beide mit einer geringen Streuung. NLGs und DMLs der CMT2-Patienten waren im Normbereich. Deswegen wurden die CMT2-Patienten als Kontrollgruppe benützt. Die männlichen und weiblichen X-chromosomalen CMT (CMTX) Patienten unterschieden sich hinsichtlich NLG und DML nicht signifikant. Der mediane TLI der weiblichen CMTX Patientinnen war mit 0,25 erniedrigt, was durch eine stark prolongierte mediane DML und im Vergleich dazu relativ normale NLG zu Stande kommt. Die ulnaren TLIs waren mit über 0,5 leicht erhöht. Die 6 männlichen CMTX Patienten hatten im Gegensatz dazu einen medianen TLI von 0,36 und einen ulnaren TLI mit 0,43, was auf eine Homogenität der Nervenleitung auf der gesamten Länge innerhalb der Nerven hinweist. In den 14 Patienten mit der hereditären Neuropathie mit Neigung zu Druckparesen (HNPP) fanden wir das Bild einer generalisierten sensomotorischen Polyneuropathie. Die medianen DMLs waren bei leicht verlangsamten bis normalen NLGs moderat bis stark prolongiert. Der mittlere mediane TLI war mit 0,24 erniedrigt, wobei der mittlere ulnare TLI mit 0,41 im Normbereich war. Bei den acht Patienten mit Myelin-Protein Zero (MPZ) Genmutationen beobachteten wir unabhängig von der NLG nur leicht bis moderat prolongierte mediane DMLs < 8 ms und ulnare DMLs 6 < ms. Die zwei Patienten mit Neurofilament light chain (NEFL) Genmutationen zeigten ein elektrophysiologisches Bild, das dem der MPZ-Patienten ähnelte. Wir empfehlen die Messung der ulnaren DML, da die mediane DML durch ein häufiges Carpaltunnelsyndrom unabhängig von einer hereditären Neuropathie verlängert sein kann.

Content

Abbreviations

AD	autosomal dominant
AR	autosomal recessive
BSCL2	Berardinelli-Seip-Congenital-Lipodystrophy-2 gene
CH	congenital hypomyelination
CMAP	compound muscle action potential
CMT	Charcot-Marie-Tooth disease
CNS	central nervous system
CV	conduction velocity
Cx32	Connexin 32
dHMN	distal hereditary motor neuropathy
DML	distal motor latency
DNA	deoxyribonucleic acid
DSS	Dejerine Sottas syndrome
GARS	glycyl-tRNA-synthetase
GJB1	gap junction protein, beta 1
HMSN	hereditary motor and sensory neuropathy
HNPP	hereditary neuropathy with liability to pressure palsies
HSAN	hereditary sensory and autonomic neuropathy
HSP 27	heat shock 27 kDa protein 1
HSP 22	heat shock 22 kDa protein 8
MFN-2	mitofusin-2 gene
mm	millimeter
MNCV	motor nerve conduction velocity
MPZ	myelin protein zero
m/s	meter per second
ms	millisecond
mV	millivolt
µV	mikrovolt
NCV	nerve conduction velocity
NEFL	neurofilament light polypeptide 68 kDa
P0	peripheral myelin P0 protein

PCR	polymerase chain reaction
PMP-22	peripheral myelin protein 22
RAB7	Ras-related GTPase 7 gene
RL	residual latency index
SNAP	sensory nerve action potential
SNCV	sensory nerve conduction velocity
SS	Silver Syndrome
TLI	terminal latency index

1 Introduction

1.1 Common facts and history

The study of inherited peripheral neuropathies has its origin more than a century ago in 1886. Jean-Martin Charcot and Pierre Marie [1] in Paris and Howard Henry Tooth [2] at Cambridge, independently described a few patients with a strikingly similar disease. Tooth postulated, as we know today, correctly that a neuropathy and not a myelopathy, as proposed by Charcot and Marie, is the apparent basis of this disorder [2].

Today the idea has been established that hereditary neuropathies are a genetically and clinically heterogeneous disorder [3]. The disease is characterized mainly by distal muscle weakness and atrophy predominating in the lower extremities, diminished or absent deep tendon reflexes, distal sensory loss and skeletal deformities such as pes cavus [4]. They are relatively common with an overall prevalence of 1 in 2500 [5] and the most common inherited disorder of the peripheral nervous system [6].

1.2 Definitions

The clinical literature tends to use the term hereditary motor and sensory neuropathies (HMSN), whereas the genetic literature uses the term Charcot-Marie-Tooth disease (CMT). HMSN I can be used interchangeable with CMT1 and HMSN II refers to CMT2 [7].

In the clinical literature HMSN is further divided into seven forms, HMSN I to VII. HMSN III refers to a severe demyelinating neuropathy with early onset. The other forms, HMSN IV or Refsum's syndrome, HMSN V with spastic paraplegia, HMSN VI with optic atrophy, HMSN VII with retinitis pigmentosa are rare [7].

Furthermore, traditional clinical classifications differentiate between hereditary neuropathies with its clear motor and sensory involvement called CMT or HMSN, hereditary sensory and autonomic neuropathy (HSAN) with much more sensory and autonomic but fewer motor features and distal hereditary motor neuropathy (dHMN), which has only motor symptoms and no sensory deficits [3].

1.3 Classification of the Charcot-Marie-Tooth disease

The Charcot-Marie-Tooth disease can be subdivided into the demyelinating form (CMT1) and the axonal form (CMT2). These two main types can be distinguished by nerve conduction velocity (NCV) measured by electroneurography. Patients with CMT1 show reduced nerve conduction velocities with a typically median motor nerve conduction velocity (MNCV) below 38 m/s. In contrast, patients with CMT2 offer normal or near normal MNCVs [8, 9]. Demyelinating CMT1 and axonal CMT2 can be further classified by the underlying genetic cause [10]. In some families with CMT patients were examined with median MNCVs in a range of 25 to 45 m/s; therefore it is difficult to classify these patients into CMT1 and CMT2 by using the cut-off value of 38 m/s for the median MNCV. Authors proposed to designate this type of CMT as intermediate CMT [3, 11, 12]. HMSN III refers to a demyelinating neuropathy starting in infancy with severely reduced nerve conduction velocities below 10 m/s. HMSN III is now considered to be a more severe form of CMT1 rather than a separate condition. In the genetic literature the term Dejerine-Sottas syndrome (DSS) is used for HMSN III [7]. CMT1 and CMT2 are further subclassified according to inheritance pattern (autosomal dominant = AD, autosomal recessive = AR, or X-linked) and the underlying molecular genetic cause [13].

In the genetic literature autosomal recessive forms of CMT1 are termed CMT4. They are characterized by early onset and more severe disease progression than the dominant types [10].

The following section refers to the different subtypes of the Charcot-Marie-Tooth disease that are subject of the following study. I will give here an introduction into the various CMT forms and their electrophysiological features and it should be mentioned what is already known in literature.

1.4 Charcot-Marie-Tooth type 1

Dominantly and recessively inherited forms of CMT1 are known in literature [10]. In 1957, Gilliatt and Thomas [14] showed one form of the Charcot-Marie-Tooth disease with markedly reduced nerve conduction velocities (NCVs), which has been designated as CMT1. CMT1 is clinically characterized by distal muscular atrophy and weakness, minor sensory symptoms, and absent or significantly lowered deep tendon reflexes. The onset is usually in the first or second decade of life with a slow progression. Considerable phenotypic variability has been described, but in the majority of cases the disease is not severely disabling. NCV is typically below 38 m/s on all examined nerves, including those in mildly affected patients. Pathological findings in sural nerve biopsy include demyelination and remyelination with typically onion bulbs made up by Schwann cells and their processes with an increase of collagen, causing hypertrophy of the nerves [8, 15].

According to the different genetic defects and to the clinical phenotype, six types of dominantly inherited CMT1 (CMT1A, CMT1B, CMT1C, CMT1D, CMT1E and CMT1F) have been identified [16].

1.4.1 Charcot-Marie-Tooth type 1A (CMT1A)

1.4.1.1 Genetic background

The first form mapped using molecular technology was CMT1A in 1989 by Vance et al. [17]. A deoxyribonucleic acid (DNA) duplication on chromosome 17p11 was found to be the cause of the disease [18, 19]. Patel et al. [20] showed that the peripheral myelin protein 22 (PMP22) gene is located entirely within the CMT1A duplication region, leading to a gene dosage defect. Today we know that the PMP22 gene encodes a 22-kD protein that comprises 2 to 5% of peripheral nervous system myelin. It is produced primarily by Schwann cells and expressed in the compact portion of essentially all myelinated fibers in the peripheral nervous system, as shown by Snipes et al. [21].

1.4.1.2 Clinical features

In the literature is shown that CMT1A accounts for up to 60% of families with CMT. It is said that PMP22 point mutations are rare and usually present as a more severe phenotype, such as early-onset Dejerine–Sottas syndrome (DSS) [16].

The clinical hallmarks of patients with CMT1A are consistent with the CMT1 phenotype, as described above; absence of tendon reflexes, arching of the feet, distal muscle weakness and wasting, hypertrophic nerves, and slow motor nerve conduction velocity (MNCV). Nerve and muscle biopsy reveal chronic neurogenic muscle atrophy and segmental de- and remyelination with typically onion bulb formation [22].

Harding and Thomas [8] showed that patients with CMT1A usually have their onset in the first decade. Other authors showed that onset occurs in 50% of cases in the first decade and before the age of 20 years in 70% of patients [23].

Unusual phenotypes characterized by predominant proximal muscle involvement of the upper extremities were reported in an Austrian family [24].

1.4.1.3 Electrophysiological findings

The nerve conduction study in CMT1A shows predominantly demyelinating features with variable severity among individuals. Neurography reveals motor nerve conduction velocities (MNCVs) below 38 m/s, independently of age and disease duration. Axonal loss becomes evident by variably present decrease in compound muscle action potential (CMAP) amplitude, independently of NCV slowing [25]. These observations are in good agreement with other reports [23, 26-30]. It was postulated that CMAP reduction and axonal loss were more pronounced in advanced disease [25]. This severe CMAP reduction in advanced stages of the disease was also found in an electrophysiological study in 8 Croatian children with CMT1A [31].

The main electrophysiological features were elucidated in a group of 119 patients in a study by Birouk and Gouider et al. [23]. The results are consistent with previous studies [26]. Motor nerve conduction velocity (MNCV) is uniformly reduced in all nerves. The median nerve MNCV is $\leq$ 33 m/s and distal motor latencies (DMLs) are prolonged in all motor nerves, suggesting uniform slowing of nerve conduction velocity between proximal and distal proportions of the nerves. Previous authors found that sensory nerve action potentials (SNAPs) are abnormal in all cases, even where there is no clinical sensory loss [23, 24, 26]. It was postulated that electrophysiological penetrance of 17p11.2 duplication is complete even

in clinical asymptomatic patients, making median MNCV a reliable tool for screening affected at-risk individuals [23].

In the study by Birouk and Gouider et al. [23] the median nerve terminal latency index (TLI) [32] with 0.34 ± 0.1, which explores the ratio between distal and proximal conduction velocity, was not significantly different from that in controls.

The calculation of TLI is explained in the material and methods-section on page 21. Authors of previous studies showed that neither conduction block nor temporal dispersion of action potentials occur in CMT1A, further underlining homogeneous conduction slowing along the entire length of the nerves [23, 24].

1.4.2 Charcot-Marie-Tooth type 1B (CMT1B) and other MPZ-mutations

1.4.2.1 Genetic background

It has been shown that CMT1B accounts for 2-4% of CMT1 cases [16]. Bird et al. [33] showed linkage of demyelinating autosomal dominant Charcot-Marie-Tooth disease to the Duffy blood group locus (Fy) on chromosome 1. Hayasaka et al. and Oakey et al. mapped the myelin protein zero (MPZ) gene to 1q22-q23, the CMT1B locus [34, 35]. It is known that the MPZ gene encodes a 28-kDa integral membrane glycoprotein (MPZ), which is the major structural protein of peripheral nerve myelin. MPZ accounts for more than 50% of the protein in the sheath of peripheral nerves [36]. Expression of the MPZ gene occurs only in Schwann cells. MPZ is a member of the immunoglobulin gene superfamily of cell adhesion molecules [37]. It is thought to link adjacent lamellae by extracellular homotetramers and thereby stabilize the myelin assembly [38].

1.4.2.2 Clinical features

The clinical picture caused by MPZ mutations can differ widely, including early onset demyelination, mild adult onset neuropathies, and CMT2-like clinical presentations [39].

The common Thr95Met mutation is clinically characterized by late onset neuropathy associated with pupillary abnormalities and hearing loss [40].

In 2004, Shy et al. [41] reported that two major phenotypes with mutations in the MPZ gene exist, namely an early (infantile) onset type with severely reduced NCVs below 38 m/s and a late (adult) onset type with NCVs in the CMT2 range > 38 m/s.

Recently a phenotype with late onset of disease at the age of 45 to 55 years, rapidly progressive course leading to the need for a walking aid within a few years and electrophysiological and pathological evidence of chronic axonal involvement with only minor myelin abnormalities was reported [42].

1.4.2.3 Electrophysiological features

As a rule, nerve conduction velocities of the motor median nerve can vary from under 38 m/s to normal values in patients with MPZ mutations. In 2004, Santoro et al. [43] showed slightly reduced nerve conduction velocities, severely reduced or absent compound muscle action potentials in the distal muscles of the legs, and clear signs of chronic denervation on EMG in all the muscles explored. In a large Sardinian CMT2 family, described by Marrosu in 1998 [44], median motor nerve conduction velocities (MNCVs) in the CMT2 range from 42.8 to 57.3 m/s were observed.

Patients with MPZ mutations with normal or near normal nerve conduction velocities were also reported by other authors [40]. The NCVs vary widely and could be severely slowed, as in CMT1, slightly reduced, as in CMT2, or even normal. But it was postulated that the values of NCV are higher than those usually observed in autosomal dominant CMT1A-patients [40].

The values of distal motor latencies and terminal latency index have not been evaluated in studies.

1.5 HNPP

1.5.1 Genetic background

Behse et al. [45] showed that hereditary neuropathy with liability to pressure palsies (HNPP) patients are characterized by recurrent pressure palsies and sausage-like swellings (tomacula) of the myelin sheaths by nerve biopsy. Other findings like hypo- and hypermyelination, myelin sheath irregularities and even nodes of Ranvier distortions complete the pathological picture [46]. Deletion of the chromosome 17p11.2-p12 region including peripheral myelin protein 22 (PMP22) is the apparent genetic basis of HNPP in most cases [47]. In rare cases, frame-shift mutations in the PMP22 gene lead to HNPP [48].

1.5.2 Clinical findings

HNPP is characterized by acute recurrent painless nerve palsies, triggered by conditions, such as trauma or compression [49]. Recent studies showed that a family history is not often useful because of the presence of sporadic cases and clinically asymptomatic carriers [50]. In the study by Hong et al. [51] sensory symptoms, such as recurrent paresthesia persisting for long periods of several days to weeks associated with physical activity were considered as symptoms of the condition, especially in family members of HNPP-patients.

1.5.3 Electrophysiological findings

Hong et al. [51] elucidated two characteristic aspects of the electrophysiological profiles of HNPP, namely a generalized sensorimotor neuropathy and superimposed focal conduction abnormalities, preferentially located at common entrapment or compression sites. HNPP is, in contrast to CMT1A with homogeneous conduction slowing along the entire length of the nerves, characterized by multifocal or segmental conduction abnormalities preferentially located at common entrapment or compression sites and distal nerve segments, as proposed by different authors [51-53].

Prevalence of conduction block varies in studies from author to author. In the study by Hong et al. [51] it was rarely found, whereas in other studies the frequency of conduction block in HNPP ranged from 6 to 22% [52, 53].

It was shown that sensory nerve conduction velocity (SNCV) is reduced in almost all nerves, which is much more frequently observed than motor nerve conduction slowing [51]. Amato et al. [54] and Hong et al. [51] found that distal motor latency (DML) is typically prolonged in almost all motor nerves, which is disproportionate to the relatively infrequent and minor decrease of MNCV.

This distal accentuation of motor nerve conduction abnormalities can be made clear by the low terminal latency index (TLI) of HNPP nerves in comparison to normal controls and CMT1A [51].

Some authors suggested that the background polyneuropathy is independent to the superimposed focal abnormalities [55]. In contrast, others proposed that pressure injury may contribute significantly to the development of the background neuropathy, because abnormalities of the conduction parameters, such as sensory nerve conduction velocities (SNCVs) and DMLs were more frequent and severe in the median and ulnar nerve that contain the common entrapment sites, such as carpal tunnel, Guyon's canal, respectively at distal segments, than in the other motor and sensory nerves [51]. Amato et al. [54] postulated that the myelinopathy has its origin in the terminal portion of the nerve fibers. Hong et al. [51] proposed that this assumption may not be compatible with the non-uniform distribution of electrophysiological abnormalities across different nerve groups.

1.6 X-linked Charcot-Marie-Tooth disease (CMTX)

1.6.1 Genetic background

X-linked Charcot-Marie-Tooth disease (CMTX) is the second most frequent form of CMT, accounting to more than 10% of cases, as shown by different authors [56, 57]. CMTX is caused by mutations in the Connexin 32 (Cx32) gene which is also called GJB1 (gap junction beta 1) gene, mapped to chromosome Xq13 [58].

1.6.2 Pathophysiology and clinical features

Pathological studies revealed evidence of paranodal demyelination and signs of a length-related axonal degeneration in motor and sensory nerve fibers [59].

The clinical hallmarks of CMTX-patients were found to be muscle weakness, muscle wasting, predominantly upper limb areflexia, loss of proprioception and pes cavus with a more severe affection of men than women [60]. Onset of CMTX occurs mostly in the second decade [61]. There are reports of central nervous system (CNS) involvement in CMTX [62, 63]. Sometimes sensineural deafness was observed by authors [64].

1.6.3 Electrophysiological findings

Authors of recent studies [60, 61, 65, 66] showed that men and women can be distinguished by electrophysiological features. Motor nerve conduction velocities (MNCVs) are slower, distal motor latencies (DMLs) are longer and compound muscle action potentials (CMAPs) are lower in men in all nerves. In previous studies [60, 66] axonal and demyelinating features were mixed and closely related in CMTX patients.

Authors of recent studies postulated that MNCVs in upper limbs are heterogeneous among nerves because mean differences between the median and ulnar nerve MNCVs were great in CMTX-patients, particularly in females [60, 67, 68].

The reason for this internerve heterogeneity of MNCVs in CMTX females can be partly explained by the concept of Lyonization or X-inactivation, as postulated by Dubourg et al. [60]. When most of the Schwann cells in a nerve have the normal X chromosome inactivated, demyelination is severe and MNCVs are severely decreased, when the mutated X chromosome is inactivated, MNCVs remain normal or subnormal.

It was shown that the mean median nerve terminal latency index (TLI) with 0.37 ± 0.08 is the same in males and females with CMTX, but greater, although not significantly so, than in CMT1A patients and controls, indicating rather homogeneous conduction slowing along the nerves [60].

Previous studies have suggested that temporal dispersion might be specific to CMTX neuropathy [67, 68]. In the study of Dubourg et al. [60] this was demonstrated in only a few patients.

1.7 The axonal form of the Charcot-Marie-Tooth disease (CMT2)

1.7.1 Genetic background

The axonal form of the Charcot-Marie-Tooth disease (CMT2) is a genetically and clinically heterogeneous disorder. Several genes have been reported to be associated with CMT2, kinesin family member 1B-ß (KIF1B) in CMT2A [69], Ras-associated protein RAB7 in CMT2B [70], glycyl-tRNA synthetase (GARS) in CMT2D [71], neurofilament light polypeptide 68 kDa (NEFL) in CMT2E [72], heat shock protein B1 (HSPB1) in CMT2F [73], myelin protein zero (MPZ) in CMT2I [74] and heat shock protein B8 (HSPB8) in CMT2L [75].

1.7.2 Clinical findings

Most patients with autosomal dominant CMT2 present with a phenotype, indistinguishable from autosomal dominant CMT1, as described above [3]. The major cause of this phenotype was found to be in the mitofusin 2 (MFN2) gene causing CMT2A [76].

The typical clinical appearance of CMT2B consists of marked distal muscle weakness and wasting with a high frequency of foot ulcers, infections, and amputations of the toes because of recurrent infections. Sensory loss with all modalities equally affected and absence of pain are said to be typical [77, 78]. The causative genetic defect in CMT2B is in RAB7 [70]. The presentation of the CMT2B phenotype is very similar to that of patients with HSAN1 secondary to mutations in the serine palmitoyltransferase long chain (SPTLC1) gene. Patients with SPTLC1 mutations usually have in contrast to CMT2B neuropathic lancinating pain and less motor involvement [79].

Another form of axonal CMT, namely CMT2D, particularly affects the upper limbs with symmetrical or asymmetrical wasting and weakness of the small muscles of the hands with much later involvement of the distal lower limb muscles [80]. CMT2D and distal hereditary motor neuropathy (dHMN V) have been shown to be allelic conditions caused by the GARS gene [71].

1.7.3 Electrophysiological findings

It was shown that in CMT2A predominant distal muscle weakness and atrophy is due to the evolving length-dependent degeneration of motor axons [25]. Distally accentuated muscle weakness in CMT2A is strongly correlated with a reduction in the number of large axons. This pathophysiological feature can be assessed by low compound muscle action potentials (CMAPs), but not with nerve conduction slowing [81, 82]. In a study by Chung et al. [81], median nerve TLI of CMT2A was the same in controls.

In CMT2B nerve conduction studies support the diagnosis of a sensory axonal neuropathy, although the electrical features are said to be mild. In a study by Holden et al. [83] sensory conduction velocities were normal throughout the nerve, but some sensory nerve action potentials (SNAPs) were reduced in amplitude like the motor nerves.

1.8 Neuropathies due to mutations in the NEFL gene

1.8.1 Genetic background and pathophysiology

The NEFL gene coding the neurofilament light chain (NF-L) was originally associated with CMT type 2E (CMT2E), as reported by Mersiyanova et al. [84]. In other studies patients with signs of demyelination, such as markedly reduced MNCV were observed and so the NEFL-related neuropathy was also designated as CMT1F [85].

NEFL seems to be a subunit of neurofilaments maintaining the cytosceleton of axons [85]. Functional analysis of two published NEFL mutations revealed a disturbed assembly and accumulation of neurofilaments in the perikarya, degeneration of neurons, atrophic axons, and perturbed transport and localization of mitochondria, as shown by different authors [86-88].

1.8.2 Clinical findings

Mutations in the NEFL gene cause clinically heterogeneous phenotypes that vary in severity. Patients with early onset and severe evolution have been reported [85]. In contrast to this observation also phenotypes with mild-to-moderate impairment with onset ranging from the first to the fifth decade have been shown [89].

The clinical examination of NEFL patients revealed considerably heterogeneous phenotypes even within a family as shown by a study of Zuchner et al. [90]. The phenotype ranges from a symmetrical polyneuropathy with distally accentuated loss of motor and sensory nerve functions in the lower limbs similar to the typical CMT1 phenotype to other manifestations, such as prominent sensory ataxia as in Friedreich's ataxia [90]. Prominent sensory involvement and episodic ataxia in childhood triggered by feverishness were also reported in other previous studies [89, 90].

Sensineural deafness and pathologic brainstem auditory evoked potentials (BAEPs) may occur [89, 90]. But this is not specific for NEFL-mutations. The age of onset may vary significantly. The reflexes can be decreased to normal [90].

1.8.3 Electrophysiological findings

The neurophysiological findings are like the clinical heterogeneous. Nerve conduction studies reveal MNCV values below 38 m/s, indicating a demyelinating component in the early onset type. Axonal damage becomes evident by severely reduced compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) [85]. In other studies also values greater than 38 m/s were observed [90]. The values of distal motor latencies (DMLs) have not been evaluated in recent studies. As mentioned above, based on nerve conduction velocities by the cut-off value of 38 m/s, some families may be categorized as CMT1F and others as CMT2E. The presence of nerve conduction slowing and reduced CMAPs show that axonal and demyelinating features are closely related in patients with NEFL-mutations [89]. Intermediately slowed nerve conduction velocities to a range of 35 to 39 m/s were observed in a recent study [91].

1.9 dHMN and Silver Syndrome (SS)

1.9.1 Genetic background and clinical features

Traditional clinical classifications subdivide distal hereditary motor neuropathy (dHMN) or distal spinal muscular atrophy (dSMA) into seven subtypes. It is a heterogeneous group of disorders characterized by degeneration of motor fibers, mainly in the distal part of the limbs [92]. The clinical hallmark of dHMN type V is a predominant symmetrical or asymmetrical wasting and weakness of the small hand muscles, particularly of the thenar and first dorsal interosseus muscles, as shown by recent authors [93, 94]. Sensory disturbances have been reported to occur rarely in advanced stages of dHMN-V [95]. Patients with CMT2D due to mutations in the GARS-gene offer a similar phenotype to dHMN-V, as shown by Sambuughin et al. [96].

In 1966, J. R. Silver [97] described two families with a complicated form of hereditary spastic paraplegia (HSP). In both families, the disease was characterized by distal amyotrophy that started in the hands and spasticity in the legs.

The locus of this disease has been mapped to the chromosome region 11q12-14 [98, 99]. It was reported that two heterozygous mutations, namely N88S and S90L located in exon 3 in the Berardinelli–Seip congenital lipodystrophy (*BSCL2*) gene are the apparent genetic causes of Silver Syndrome (SS) and families with dHMN type V [100].

The presence of mild to severe pyramidal tract signs is common in dHMN-V and SS whereas they have rarely been observed in patients with CMT2D [96, 101]. Recent studies showed that the BSCL2 N88S substitution is most often associated with a dHMN-V phenotype and less frequently, additional prominent spasticity and mild sensory disturbances are found in the lower limbs [102, 103]. In contrast, the S90L substitution in the BSCL2-gene seems to result in a spastic paraplegia phenotype with marked weakness and wasting in the hands [94, 100, 104].

Furthermore, mutations in the HSPB1 and HSPB8 genes have been reported as a rare cause of autosomal dominant dHMN and CMT2 [73, 105].

1.9.2 Electrophysiological findings

In dHMN and Silver Syndrome, motor nerves can be severely impaired or CMAPs might even not be recordable, while the sensory nerves remain normal for a long time, whereas in HMSN both motor and sensory nerves are affected simultaneously from the beginning [95]. In an electrophysiological study by Auer-Grumbach et al. [95] the results showed predominantly chronic axonal damage in the motor nerves. The compound muscle action potentials (CMAPs) were largely reduced and pronounced chronodispersion of the CMAPs and conduction block occur in lower limbs. Distal motor latencies (DMLs) and motor nerve conduction velocities (MNCVs) can be normal to severely abnormal.

It was also shown that in the upper limbs the median nerve was significantly more severely damaged than the ulnar nerve, suggesting that the median nerve is most useful for screening of this type of HMN V. Only in advanced disease sensory changes, predominantly axonal, may occur, as reported in recent studies [95, 102].

1.10 Purpose of this study

We present here a retrospective study of the electrophysiological and genetic features of 67 patients with genetically proven hereditary peripheral neuropathies. As mentioned above, classification of hereditary neuropathies is based on motor nerve conduction velocity (MNCV). CMT1 refers to a demyelinating neuropathy with reduced nerve conduction velocities with a typically median motor nerve conduction velocity less than 38 m/s and CMT2 is an axonal neuropathy with normal or near normal motor nerve conduction velocities. In addition, most studies performed electrophysiological examination concerning motor nerve conduction velocities (MNCVs) and the results of distal motor latencies (DMLs) were listed but not discussed. The value of distal motor latencies in comparing the various hereditary neuropathies has not been elucidated. In our study attention was focused on electrophysiological features, in particular to assess whether measurement of motor conduction velocity or measurement of distal motor latencies better classifies the hereditary neuropathies for further genetic diagnosis. We assessed of the following two indices: residual latency index (RL) and terminal latency index (TLI) which can be calculated by routine nerve conduction studies, such as motor nerve conduction velocity and distal motor latencies, in order to analyze which parts of the nerves are affected in the different neuropathies. The idea was that the value of TLI classifies neuropathies further in distal, proximal and homogeneous conduction slowing types. We attempted to establish electrophysiological criteria secondary to the measurement of distal motor latencies, RL and TLI in addition to the nerve conduction velocity criteria. Like mentioned above, some hereditary neuropathies, i. e. MPZ-mutations, CMT2A secondary to MFN2-mutations and patients with NEFL-mutations might be clinically and also electrophysiologically, based on analysis only of MNCV, similar. Furthermore, the object of this study was not only to compare MNCVs and DMLs between the different groups of hereditary neuropathies, we also analyzed the variability of those parameters among the different nerves within one type using Kruskal-Wallis test.

2 Material and methods

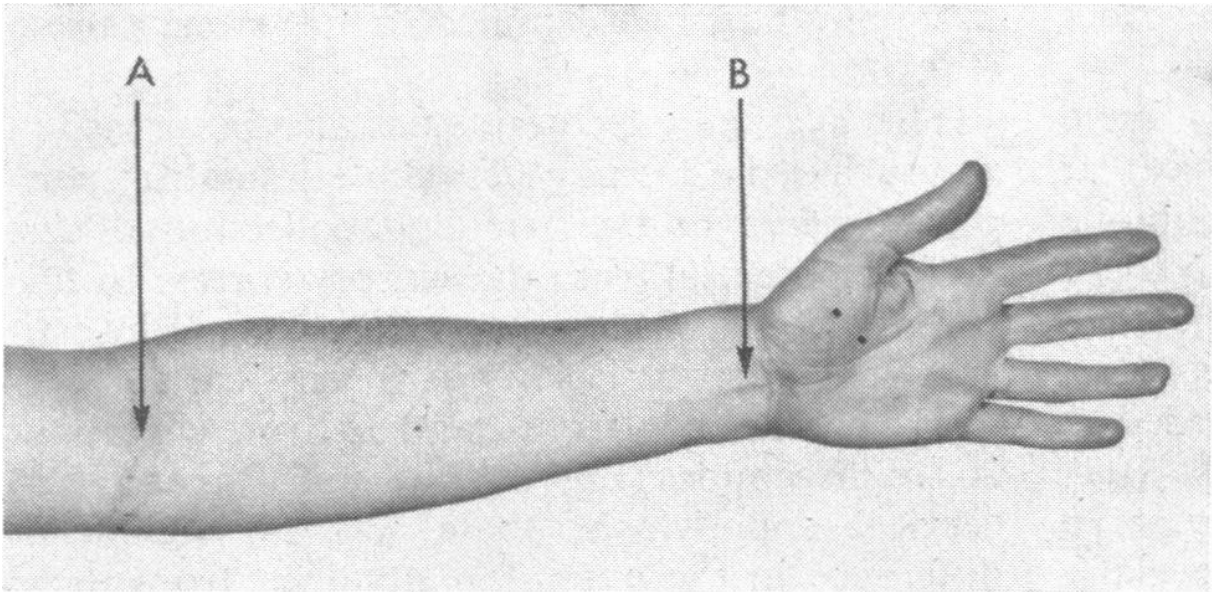
67 patients (28 CMT1A, 8 MPZ, 14 HNPP, 8 CMTX, 6 CMT2, 2 NEFL and one Silver Syndrome) with genetically proven hereditary neuropathies underwent a retrospective electrophysiological study.

2.1 Clinical assessment

All study subjects tested were patients at the Department of Neurology of the Medical University of Graz. Age at onset was determined by questioning the patients about the age of the first symptoms such as cramps, difficulty in running, jumping, climbing stairs and walking. Detailed family histories were obtained. To determine the mode of inheritance and disease manifestation in relatives or family members the patients were asked about the disease course and symptoms in several female and male family members. Male-to-male transmissions suggest autosomal dominant inheritance. An absent male-to-male transmission suggests X-linked neuropathy. Consanguity refers to recessively inherited neuropathies. Clinical information was assessed in a standardized manner, as described previously [25], including motor and sensory impairment, deep tendon reflexes, muscular atrophy or hypertrophy, muscle tone, gait, foot deformity, autonomic impairment and loss of proprioception. Weakness was assessed according to UK Medical Research Council (MRC) criteria (normal = MRC 5; mild = MRC 4, 4+; moderate = MRC 3, 4-; severe = MRC 0–2). Impairment was assessed for various sensory modalities, as described by previous authors [95] to distinguish the classical CMT phenotype with motor and sensory impairment from the dHMN-phenotype without sensory impairment in early stages of the disease, such as vibration, joint position, pain and light touch as mild, moderate or severe. Vibration sense was quantified with a graduated Rydel-Seiffer tuning fork (grades 0 to 8). The ability to recognize written numbers in the distal parts of the lower and upper limbs was also assessed. Associated findings, including deafness, pupillary abnormalities, ataxia, tremor, scoliosis, ulcera and mutilations, Babinski sign and dementia, were assessed. Tendon reflexes were assessed following the National Institute of Neurological Disorders and Stroke score (NINDS), and several tendon reflexes were selected for documentation: 0 = absent; 1+ = diminished; 2+ = normal; 3+ = brisk; 4+ = very brisk or clonus. Plantar responses were documented as flexor, extensor, or Babinski sign present.

2.2 Neurography

2.2.1 Technique for recording motor latencies and conduction velocities



Picture 1: Stimulation sites for the median nerve; A: proximal stimulation point; B: distal stimulation point; from Campbell 1971.

Peripheral nerve conduction studies were performed by using previously published techniques [106]. In short, the peripheral nerve is stimulated supramaximally, otherwise we will record falsely long latencies, at the two separated points A and B for the median nerve, as shown in picture 1. The muscle action potential is recorded from the same site on each occasion and the nerve conduction velocity (NCV) between the two points A and B in picture 1 can be calculated by the formula AB/(PML-DML), where AB is the distance between the two points of stimulation expressed in millimeters (mm), proximal motor latency (PML) is the conduction time from the proximal point of stimulation and distal motor latency (DML) is the conduction time from the distal point of stimulation to the onset of the action potential expressed in milliseconds (ms). For PMLs and DMLs, neurologists do not calculate conduction velocities seperately because of neuromuscular transmission. At the same time as the motor nerve fibers are stimulated, also the sensory fiber components of the mixed peripheral nerves are stimulated and the antidromic sensory nerve action potentials (SNAPs) can be recorded by surface electrodes on the finger and displayed simultaneously with the muscle action potential [106].

2.2.2 Methods and points of stimulation

Nerve conduction studies followed standard techniques by using the Electromyograph MS60 (Medelec, Old Woking UK) or a Myohandy portable EMG (Micromed Neurodata, Mogliano Venetto Italy), as described previously [102]. Median, ulnar, peroneal, and tibial motor nerves were measured unilaterally or bilaterally in the 67 individuals, and sensory nerve conduction studies were performed on the median, ulnar and sural nerve on at least one side in the majority of patients.

Median, ulnar, peroneal, tibial and sural conduction studies were performed using standard recording techniques at a skin temperature of 34 °C. Stainless-steel disk electrodes (9 mm) were applied over the thenar and hypothenar in the common belly-tendon configuration, as described previously [107]. Distal stimulation sites at the wrist were located at a distance ($D_{wrist\text{-}to\text{-}thenar}$) 70 mm proximal to the G1 electrode. Proximal stimulation site was at the elbow for the median nerve and 4 cm distal from the medial epicondyle for the ulnar nerve. For peroneal and tibial nerve distal stimulation site was 80 mm proximal to the G1-electrode. The proximal stimulation point was slightly above the fibular head for peroneal nerve and in the popliteal fossa for the tibial nerve. MNCV was then assessed in the following segments: wrist to elbow for the median and ulnar nerves, ankle to fibular head for the peroneal nerve, ankle to popliteal fossa for the posterior tibial nerve.

F-waves were obtained from distal and proximal stimulation sites for both median and ulnar nerves [107], but not assessed systematically. Minimal F-wave latency was determined from at least 10 stimulations.

Compound motor action potential (CMAP) amplitudes were measured, using previously published methods [107], peak-to-peak or baseline-to-baseline, but they were measured baseline-to-peak to record conduction blocks.

Sensory nerve studies were performed antidromically by using surface or ring electrodes. Electrophysiological measurements from one arm per patient in the disease groups were used for statistical analysis. If responses were unrecordable, they were excluded from statistical analysis.

The next section refers to indices we used for analysis in the study and which can be calculated by routine nerve conduction studies, such as motor nerve conduction velocity (MNCV) and distal motor latency (DML).

2.2.3 Calculated indices

The following two indices were calculated using previously published formulas. They can be calculated from routine nerve conduction measurements [107].

Residual latency index (RL) [107, 108] assesses the distal portion of the nerve:

$$RL = DML\ (ms) - [D_{wrist\text{-}to\text{-}thenar}\ (mm) / MNCV\ (m/s)]$$

Terminal latency index (TLI) [107] compares wrist-to-thenar with elbow-to-wrist motor nerve conduction velocity (MNCV). In the upper extremity, TLI allows comparative assessment of the conduction time along the distal (wrist-to-thenar) nerve segment with that of the intermediate segment (elbow-to-wrist).

$$TLI = [1 / DML\ (ms)] * [(D_{wrist\text{-}to\text{-}thenar}\ (mm) / MNCV\ (m/s)]$$

High values of TLI result when DML is low and MNCV is low, which means that demyelination occurs in the more proximal nerve segments, whereas low values result when DML is prolonged and MNCV is high, indicating distal conduction slowing process.

2.3 Genetic examination

Peripheral blood samples were obtained from patients after they had given informed consent. DNA isolation from leucocytes was performed according to standard methods.

In CMT1A molecular diagnosis of the 17p11.2 duplication was performed by using RFLP (restriction fragment length polymorphism) probes and Southern blot hybridization based methods, as previously described [109].

In the CMT2A patients MFN2 mutation screening was performed by polymerase chain reaction (PCR) based amplifying all 17 coding exons of MFN2 gene using intronic primers, as described by Zuchner et al. [76]. After PCR amplification the PCR products were sequenced and analyzed.

In patients with HNPP molecular diagnosis was obtained by using PCR and marker based methods, as described elsewhere [110].

In CMTX patients mutation screening was performed by using non-radioactive SSCP (single-strand conformation polymorphism) as described previously [60, 66]. Variants were characterized by sequencing the entire coding region of both strands of the *CX32* gene. For each mutation, restriction sites by using RFLPs that distinguished the normal from the mutated sequence were found by computer analysis.

In patients with mutations in the MPZ gene amplification of all coding exons of the MPZ gene was performed by using standard PCR techniques. After PCR-amplification direct sequencing was performed by using previously published techniques [111].

In patients with mutations in the NEFL gene DNA was amplified by using PCR based methods. Mutation screening was performed by SSCP (single-strand conformation polymorphism) analysis, which was reported to be most efficient when short fragments of DNA are analysed. Additionally, long PCR products were fragmented by restriction endonucleases before SSCP analysis, as described by Mersiyanova et al. [84].

In the patient with Silver Syndrome mutation analysis of BSCL2 was performed according to methods described previously [100]. PCR products were cleaned up before cycle sequencing. Then automated DNA sequencing was performed.

2.4 Statistical analysis

Statistical analysis was done with SPSS 15.0. Electrophysiological data for the various neuropathies were compared using parametric Student`s T-Test for comparison between CMT1A and HNPP-patients and nonparametric Mann-Whitney-U Test for other neuropathies. Differences were considered significantly with a probability of $p < 0.05$. If any responses were unrecordable, they were excluded from statistical analysis. Subanalysis by nerve group was done with Kruskal-Wallis test.

3 Results

The seven diagnostic groups had the following demographic characteristics: The group of 28 CMT1A-patients consisted of 21 females (75%) and 7 males, in the group of 6 CMT2-patients were 2 females (33,3%) and 4 males, the group of 8 CMTX consisted of 2 females (25%) and 6 males, the 14 HNPP-patients consisted of 4 females (28,6%) and 10 males, under the 8 MPZ-patients were 5 females (62,5%) and 3 males, 2 male patients had mutations in the NEFL-gene and one male patient was diagnosed with Silver Syndrome (SS). Descriptive statistics for the several diagnostic groups are shown in table 1 as means ± standard deviation.

Table 1: Measured and calculated electrophysiological parameters as means ± standard deviation (SD) for median, ulnar, peroneal, tibial and sural nerves in the eight diagnostic groups.

Diagnosis	CMT1A	CMT2	CMTX female	CMTX male	HNPP	MPZ	NEFL	Silver Syndrome
Median nerve								
MNCV (m/s)	22.74 ± 8.44	57.52 ± 4.83	31	36.33 ± 7.57	44.1 ± 10.43	33.66 ± 17.8	38	32.2
DML (ms)	11.4 ± 3.03	3.73 ± 0.27	7.6 ± 2.26	5.72 ± 0.46	7.34 ± 2.05	5.4 ± 1.3	4.9 ± 0.71	7.7
CMAP (mV)	3.6 ± 3.25	8.87 ± 5.38	0.5	12.03 ± 20	8.18 ± 5.15	5.18 ± 4.94	3.95 ± 1.48	0.3
RL	7.9 ± 2.92	2.51 ± 0.25	6.94	3.59 ± 0.63	5.64 ± 1.86	3.05 ± 0.58	3.06 ± 0.71	5.63
TLI	0.32 ± 0.11	0.33 ± 0.03	0.25	0.36 ± 0.08	0.24 ± 0.08	0.41 ± 0.14	0.38 ± 0.05	0.28
SNCV (m/s)	37	48.1 ± 13.95	31	41.5 ± 9.19	32.99 ± 5.43	39.73 ± 14.65		59
SNAP (µV)	1.28 ± 0.95	14.84 ± 9.26	2	6 ± 4.24	9.31 ± 3.5	10.4 ± 6.41		21.5
Ulnar nerve								
MNCV (m/s)	23.34 ± 10.1	60.76 ± 6.81	34	38.66 ± 6.66	42.09 ± 11.4	40.95 ± 15.58	40	52.4
DML (ms)	8.27 ± 2.79	2.98 ± 0.6	3.95 ± 0.21	4.33 ± 0.63	4.56 ± 1.24	4.55 ± 1.42	4.1 ± 1	2.5
CMAP (mV)	4.45 ± 3.25	13.19 ± 2.8	0.35 ± 0.07	1.66 ± 1.63	9.11 ± 4.61	6.3 ± 4.39	2.85 ± 0.64	16.8
RL	4.88 ± 2.12	1.82 ± 0.55	1.89 ± 0.21	2.49 ± 0.72	2.71 ± 1.05	2.61 ± 0.66	2.35 ± 1	1.16
TLI	0.42 ± 0.11	0.4 ± 0.08	0.52 ± 0.03	0.43 ± 0.08	0.41 ± 0.13	0.42 ± 0.05	0.44 ± 0.11	0.53
SNCV (m/s)	23 ± 20	57.23 ± 10.9	35	38	35.19 ± 4.1	41.15 ± 11.53	44	56.5
SNAP (µV)	7.4 ± 6.5	17.1 ± 13.48	3	5	10.52 ± 5.43	13 ± 7.07	6	31.4
Peroneal nerve								
MNCV (m/s)	18.83 ± 2.79	47.46 ± 6.29			37.74 ± 5.71	25.01 ± 13.67		31
DML (ms)	9.29 ± 1.83	3.34 ± 1.5			8.26 ± 2.25	8.31 ± 2.61		10.8
CMAP (mV)	1.22 ± 1.34	6.59 ± 5.17			3.44 ± 2.72	2.32 ± 3.02		0.4
Tibial nerve								
MNCV (m/s)	22.34 ± 8	35.36 ± 12.92		32 ± 4.24	37.89 ± 8.15	28.65 ± 12.84	37	42.2
DML (ms)	12.19 ± 6.74	5.3 ± 1.83		6.8 ± 0.57	5.32 ± 1.04	7.07 ± 3.44	3.8	6.4
CMAP (mV)	2 ± 3.1	7.45 ± 8.95		0.37 ± 0.47	7.56 ± 4.62	5.83 ± 7.41	0.7	4.9
Sural nerve								
SNCV (m/s)	30.45 ± 9.26	42.86 ± 12.8			33.98 ± 2.47	38		35.7
SNAP (µV)	1.28 ± 0.95	6.17 ± 5.83			3.56 ± 2.26	7		0.8

3.1 Analysis of motor nerve conduction velocities (MNCVs)

The following section refers to the several values of motor nerve conduction velocities (MNCVs) in the eight diagnostic groups of the study subjects. Distributions of MNCVs are shown in figure 1 as boxplots.

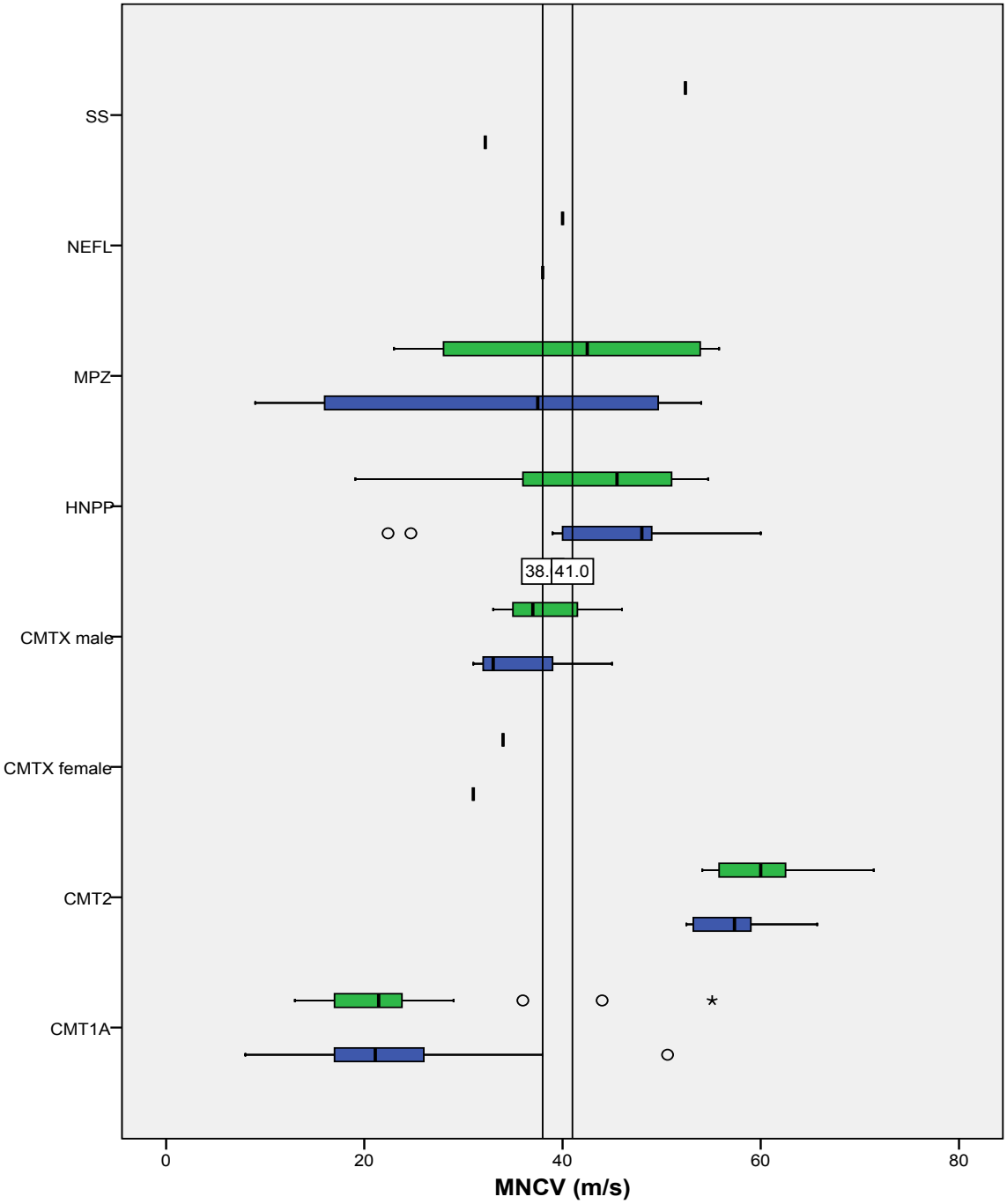


Figure 1: Distribution of motor nerve conduction velocity (MNCV) in the upper limbs in the median (blue) and ulnar (green) nerves among the eight groups of the study subjects. Dashed vertical lines represent cut-off values for median nerve MNCV with 38 m/s and for the ulnar nerve MNCV with 41 m/s. Open dots indicate mild outliers and stars extreme outliers.

3.1.1 CMT1A

The MNCV could not be measured in two cases (7.14%) for the median nerve, in 6 cases (21.4%) for the ulnar nerve, in 20 cases (71.4%) for the peroneal nerve and in 17 cases (60.7%) for the tibial nerve. Unrecorded MNCVs were excluded from statistical analysis.

24 of the 26 measured patients (92.3%) had marked slowing of median motor nerve conduction velocity below 38 m/s, as shown in figure 1. In case 28 a median MNCV at the cut-off value of 38 m/s was observed and in case 20 median nerve MNCV was > 38 m/s. Ulnar MNCV was reduced below the cut-off value of 41 m/s in 21 cases (95.5%). In case 20 (4.5%) ulnar MNCV was 55.1 m/s and in case 28 (4.5%) an ulnar nerve MNCV of 44 m/s was observed. Peroneal MNCV showed a marked slowing below 30 m/s in all eight tested cases (100%) but was not recorded in case 20 and 28. Tibial MNCV was reduced in all cases, including case 20 and 28, below 35 m/s.

Subanalysis by nerve group revealed that MNCV was not significantly different among the four motor nerves in CMT1A-patients (Kruskal–Wallis test, $P > 0.05$), indicating uniform conduction slowing among all motor nerves. All MNCVs were compared to those of HNPP-patients and we found that median, ulnar, peroneal and tibial MNCVs were significantly lower in CMT1A-patients (Student`s T-Test, Mann Whitney U test, $P < 0.001$). In comparison to MPZ-patients only the ulnar nerve MNCV was significantly lower in CMT1A patients (Mann Whitney U test, $P < 0.05$). However, this was not shown for the median, peroneal and tibial nerves (Mann Whitney U test, $P > 0.05$).

As expected, median, ulnar and peroneal nerve MNCVs were significantly lower in CMT1A-patients in comparison to CMT2A and CMT2B-patients (Mann Whitney U test, $P < 0.001$ for median and ulnar nerve MNCVs, $P < 0.01$ for peroneal nerve MNCV). Interestingly, tibial MNCV was not significantly higher in CMT2-patients (Mann Whitney U test, $P > 0.05$).

3.1.2 CMT2A and CMT2B

Ulnar, peroneal and tibial MNCVs were not recorded in one of six CMT2 cases (16.6%).

Median MNCV was recorded in all 6 cases (100%) and was > 50 m/s in all cases. In 5 cases ulnar MNCV was > 50 m/s and the peroneal MNCV was > 40 m/s. In one case (case 6) tibial MNCV was below 20 m/s, in two cases (case 4 and 5) below 38 m/s and in two cases > 40 m/s.

Subanalysis by nerve group revealed that MNCV was significantly different among the median, ulnar, peroneal and tibial nerve (Kruskal-Wallis-Test, $P < 0.01$). The median and ulnar MNCVs were significantly higher than peroneal and tibial MNCVs.
We compared MNCVs of the CMT2A and CMT2B patients to those of MPZ- and NEFL-patients. The CMT2-group had significantly higher median, ulnar and peroneal MNCVs than MPZ-patients (Mann Whitney U test, $P < 0.01$ for median and peroneal MNCVs, $P < 0.05$ for ulnar MNCVs). This was not shown for the tibial nerve (Mann Whitney U test, $P > 0.05$).
In comparison to NEFL-patients median, ulnar and tibial MNCVs of CMT2A and 2B-patients did not differ significantly (Mann Whitney U test, $P > 0.05$).

3.1.3 CMTX

3.1.3.1 CMTX females

Median MNCV was not recordable in one case (50%), in the other case a reduced median nerve MNCV of 31 m/s was observed. Ulnar MNCV was reduced to 34 m/s in the two cases (100%). Peroneal and tibial MNCVs were not recorded in the two cases.
Subanalysis by nerve group revealed that MNCV was not significantly different among the median and ulnar nerve (Mann-Whitney-U Test, $P > 0.05$).

3.1.3.2 CMTX males

Median and ulnar MNCVs were not recorded in three of six cases (50%). In two cases (66.6%) median MNCV was reduced to 33 m/s (case 3) and 31 m/s (case 6) below the cut-off value with 38 m/s. In one case (33.3%) median MNCV was with 43 m/s higher than this cut-off value. In two cases (66.6%) ulnar MNCV was reduced to 37 m/s (case 4) and 33 m/s (case 3). In one case (33.3%) an ulnar MNCV of 46 m/s was observed. Peroneal MNCV was not recorded. A reduced tibial MNCV was recorded in 33.3% (case 5 and 6).
Subanalysis by nerve group revealed that MNCV was not significantly different among the median, ulnar and tibial nerves (Kruskal-Wallis-Test, $P > 0.05$)
Median and ulnar MNCVs did not differ significantly between CMTX-males and females (Mann-Whitney-U-Test, $P > 0.05$).

3.1.4 HNPP

Median MNCV was recorded in all 14 cases (100%). 2 cases (case 4 and 7) showed a reduction of the median nerve MNCV below 38 m/s, the other 12 cases were higher than this cut-off value. Ulnar MNCV was also recorded in all 14 cases. 35.7% (case 1, 4, 7, 8 and 9) were below the cut-off value of 41 m/s; In 9 cases ulnar MNCV was higher than the cut-off value. Peroneal MNCV was not recorded or recordable in 6 cases (42.9%). 50% of the remaining 8 cases showed a slowing of the peroneal MNCV under 38 m/s, the other 50% were higher than 38 m/s. Tibial MNCV was not recorded in 2 cases (14.3%). 3 cases of the remaining 12 cases (25%) were below 38 m/s (case 7 and 11), in 9 cases tibial MNCV was higher than 38 m/s.

Subanalysis by nerve group revealed that MNCV was not significantly different among the four motor nerves in HNPP-patients (Kruskal–Wallis test, $P > 0.05$)

3.1.5 MPZ-mutations

Median nerve MNCV was recorded in all eight cases. In 50% (case 3, 6, 7 and 8) median nerve MNCV was slowed below the cut-off value with 38 m/s. The ulnar nerve MNCV was not recordable in 4 cases (50%). In 50% (case 7 and 8) ulnar MNCV was slightly reduced below 41 m/s, the other 2 cases (50%) were higher than the cut-off value. The peroneal nerve MNCV was not recordable in 1 case (12.5%). In 71.4% (case 3, 4, 6, 7 and 8) the peroneal MNCV showed a marked slowing below 38 m/s. Two cases were in the normal range with 40 m/s and 43 m/s. Tibial MNCV was not recordable or recorded in 2 cases (25%). 66,6% (case 4, 6, 7 and 8) showed a reduced MNCV below 38 m/s. Case 1 and 2 were in the normal range with 42 and 44 m/s.

Subanalysis by nerve group revealed that MNCV was not significantly different among the four motor nerves (Kruskal-Wallis test, $P > 0.05$).

We compared the MNCVs of the MPZ-patients to those of NEFL-patients. Median, ulnar and tibial MNCVs did not differ significantly between these clinically and electrophysiologically similar neuropathies (Mann-Whitney-U-Test, $P > 0.05$).

3.1.6 Patients with NEFL-mutations

Median MNCV was slightly reduced to the cut-off value of 38 m/s in the two cases. Ulnar MNCV was 40 m/s in both patients. Peroneal MNCVs were not recorded in the two cases. Tibial MNCV was 37 m/s in one case and the other case was not recorded.

Subanalysis by nerve group revealed that MNCV was not significantly different among the median, ulnar and tibial nerve (Kruskal-Wallis-Test, $P > 0.05$).

3.1.7 Silver Syndrome

Median MNCV was reduced below 38 m/s. Ulnar MNCV was with 52.4 m/s in the normal range. Peroneal MNCV was slightly reduced to 30.9 m/s and tibial MNCV was with 42.2 m/s in the normal range.

3.2 Analysis of distal motor latencies (DMLs)

In this section the results of distal motor latencies (DMLs) of the eight diagnostic groups will be reported. The distributions of DMLs of the motor nerves in the upper limbs are shown in figure 2 as boxplots.

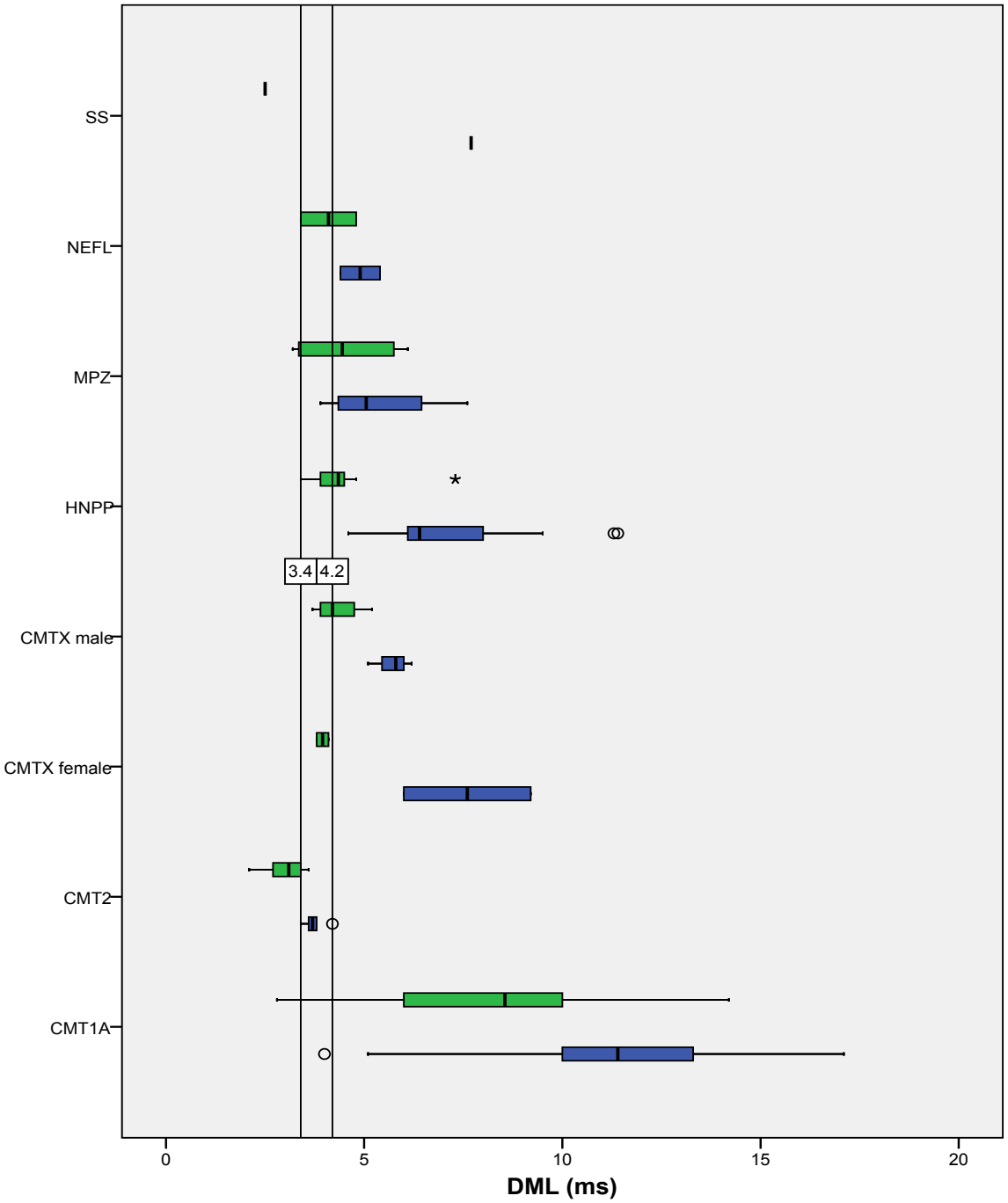


Figure 2: Distribution of distal motor latencies (DMLs) in the median (blue) and ulnar (green) nerves among the eight diagnostic groups of the study subjects. Dashed vertical lines represent cut-off values for median nerve DML with 4.2 ms and for the ulnar nerve DML with 3.4 ms. Open dots and stars indicate outliers.

3.2.1 CMT1A

Median nerve DML (norm value: < 3.6 ms, cut-off: < 4.2 ms) could not be measured in 7.15% (case 14 and 23). In 25 cases (95%) median nerve DML was severely prolonged > 4.2 ms, including case 28 with median MNCV of 38 m/s, as shown in figure 2. Case 20 with median nerve MNCV of 51 m/s was below this cut-off value with a slightly prolonged median DML of 4 ms. Ulnar nerve DML (norm value: < 3 ms; cut-off: < 3.4 ms) could not be measured in 6 cases (2, 4, 15, 17, 21, 23). In 21 cases (95.5%), including case 28 ulnar DML was prolonged > 3.4 ms. Case 20 had an ulnar DML of 2.8 ms in the normal range. Peroneal nerve DML (norm value: 5.8 ms) was not measured in 20 cases (71.4%). In the remaining 8 cases a prolonged peroneal DML was observed, except in case 14 with a peroneal nerve DML of 5.2 ms. Tibial nerve DML (norm value: < 6.5 ms) was prolonged in all cases, except in case 23 with a tibial DML of 5.5 ms and in case 28 with 5.3 ms.

Subanalysis by nerve group revealed that DML was significantly different among the four nerve groups (Kruskal–Wallis test, $P < 0.05$). Median nerve DML was significantly greater than ulnar and peroneal nerve DML.

DMLs of the four motor nerves in CMT1A-patients were compared to those of MPZ-patients. Median and ulnar nerve DMLs were significantly greater in CMT 1A-patients (t-Test, Mann Whitney U test, $P < 0.001$ for the median nerve DML and $P < 0.05$ for the ulnar nerve DML). This was not shown for the peroneal and tibial nerves (t-Test, $P > 0.05$).

We compared DMLs of CMT1A-patients to those of HNPP-patients. Median, ulnar and tibial DMLs were significantly greater in CMT1A-patients (t-Test, $P < 0.001$). No significant difference was found in the peroneal nerve DML (t-Test, $P > 0.05$).

DMLs of the four motor nerves in CMT1A-patients were significantly greater in comparison to CMT2A and CMT2B-patients (Mann Whitney U test, $P < 0.001$ for median and ulnar nerve DMLs, $P < 0.01$ for peroneal nerve DML and $P < 0.05$ for the tibial nerve DML).

3.2.2 CMT2A and CMT2B

Median DML was recorded in all cases. In 5 cases median nerve DML was in the normal range below 4.2 ms. In the fifth case a slightly prolonged DML of 4.2 ms was observed. Ulnar nerve DML was not recorded in one case. Case 4 showed a slightly prolonged ulnar DML > 3.4 ms. In one case (case 6) ulnar DML was 3.4 ms. The other cases were in the normal range below 3.4 ms. Peroneal DML was not recorded in one case. In the remaining five cases a normal peroneal DML below 5.8 ms was observed. Tibial DML was not recorded in one case.

Two of the five remaining cases showed a slightly prolonged tibial DML > 6.5 ms. The other three cases were below this value.

We compared DMLs of the CMT2A and CMT2B-patients to those of MPZ-patients. Median and peroneal nerve DMLs were significantly greater in MPZ patients (Mann Whitney U Test, $P < 0.01$ for median nerve DML, $P < 0.05$ for peroneal nerve DML). No significant difference was found in the ulnar and tibial nerve DMLs (Mann Whitney U test, $P > 0.05$).

Furthermore we compared DMLs of CMT2A and CMT2B-patients to those of NEFL-patients. No difference was found in the median, ulnar and tibial nerve DMLs between those groups (Mann Whitney U test, $P > 0.05$).

3.2.3 CMTX

3.2.3.1 CMTX females

Median nerve DMLs were prolonged > 4.2 ms in the examined two cases. Ulnar nerve DMLs were also prolonged to the cut-off value with 3.4 ms in both cases. Peroneal and tibial nerve DMLs were not recorded.

3.2.3.2 CMTX males

Median nerve DML was not recorded in 2 cases (case 1 and 2). In the other four cases median nerve DML was prolonged > 4.2 ms. Ulnar DML was not recorded in 2 cases (case 1 and 6); in the other 4 patients a prolonged ulnar DML was observed (cut-off: 3.4 ms).

We compared the DMLs of the four motor nerves of the CMTX-females to those of CMTX-males. No significant difference of median and ulnar nerve DML was observed between males and females (Mann Whitney U Test, $P > 0.05$).

In comparison to CMT1A-patients median and ulnar nerve DMLs were significantly lower in CMTX males and females (Mann Whitney U test, $P < 0.01$). Tibial nerve DMLs did not differ significantly (Mann Whitney U test, $P > 0.05$).

3.2.4 HNPP

Median nerve DMLs were recorded and prolonged over the cut-off value of 4.2 ms in all 14 cases (100%). Ulnar nerve DML was also recorded in all cases. In 2 cases (case 1 and 5) an ulnar DML at the cut-off value of 3.4 ms was observed, the other 12 cases showed a

prolonged DML for the ulnar nerve. Peroneal DML was not recorded in 6 cases (42.9%). In one case (case 3) peroneal nerve DML was below 5.8 ms, in the other seven cases peroneal nerve DML was prolonged. Tibial DML was not measured in 2 cases (14.3%). In 10 of the remaining 12 cases tibial nerve DML was in the normal range below 6.5 ms, the other 2 cases (case 7 and 8) showed prolonged tibial DMLs over 6.5 ms.

Subanalysis by nerve group revealed that DMLs were significantly different among the four nerves (Kruskal-Wallis test, $P < 0.05$). Median and peroneal nerve DMLs were significantly greater than ulnar and tibial nerve DMLs.

3.2.5 MPZ

Median nerve DML was recorded in all eight cases. In 7 cases (87.5%) median DML was prolonged over the cut-off value with 4.2 ms. Case 1 (12.5%) with a median MNCV > 50 m/s had a slightly prolonged DML of 3.9 ms. Ulnar nerve DMLs were recordable in 4 cases (50%). In 3 cases a prolonged ulnar DML was observed. One patient with an ulnar MNCV > 38 m/s had a normal ulnar DML with 3 ms. Peroneal DML was not recorded in 1 case (16.6%). 5 of the seven remaining cases showed a prolonged peroneal DML over the norm value of 5.5 ms and 2 cases were below 5.5 ms. Tibial DML was not recordable in 2 cases. In 3 cases tibial DML was prolonged over the norm value of 5.5 ms. The 3 other patients were below this value in the normal range.

The DMLs of the four nerves in MPZ-patients were compared to those of NEFL-patients. The DMLs of the various nerves did not differ significantly between these patients (Mann Whitney U Test, $P > 0.05$).

3.2.6 NEFL

Median nerve DMLs were slightly prolonged > 4.2 ms in the two cases. Ulnar DML was prolonged to 4.8 ms in one case and in the other case a slightly prolonged ulnar DML at the cut off value of 3.4 ms was observed. Tibial DML was only recorded in one case and was in the normal range < 6.5 ms.

3.2.7 Silver Syndrome

Median DML was prolonged up to 7.7 ms. Ulnar DML was in the normal range below 3.4 ms. Peroneal DML was prolonged with 10.8 ms and tibial DML was in the normal range below 6.5 ms.

3.3 Analysis of compound muscle action potentials (CMAPs)

This section refers to the values of compound muscle action potentials (CMAPs). The distributions of CMAPs in nerves of the upper limbs are shown as boxplots in figure 3.

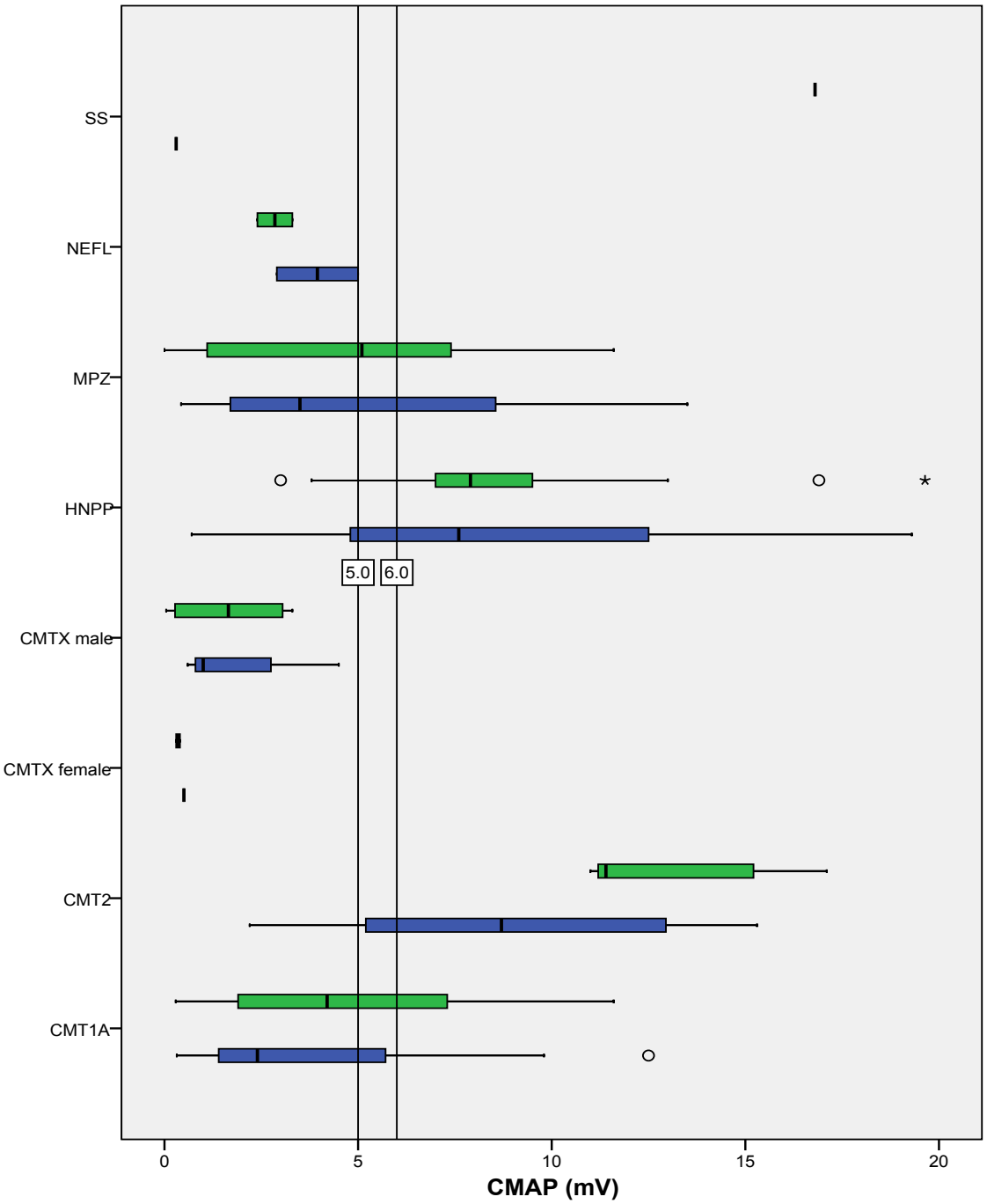


Figure 3: Distribution of compound muscle action potentials (CMAPs) in the median (blue) and ulnar (green) nerves among the eight groups of the study subjects. Dashed vertical lines represent cut-off values for median nerve CMAP with 5 mV and for the ulnar nerve CMAP with 6 mV. Open dots and stars indicate mild and extreme outliers, respectively.

In CMT1A-patients CMAP amplitudes were frequently reduced (70% of cases for the median nerve, in 72% of cases for the ulnar nerve, in 83% for the peroneal and tibial nerves).

In CMT2A and CMT2B-patients median nerve CMAPs were reduced in 66.6%, ulnar CMAPs in 80%, peroneal and tibial CMAPs in 60%. Interestingly, median and ulnar CMAPs were significantly lower in CMT1A-patients in comparison to CMT2A and CMT2B-patients (Mann Whitney U Test, $P < 0.05$), as shown in figure 3. This was not shown for the peroneal and tibial CMAPs.

In the two CMTX females severely reduced median and ulnar CMAPs were observed. Also CMTX males showed reduced median, ulnar and tibial CMAPs in all cases.

In HNPP-patients median and ulnar CMAPs were reduced in 21%, peroneal CMAPs in 33% and tibial CMAPs were reduced in 18%. Sometimes conduction block and chronodispersion of the CMAPs were observed. We compared CMAPs of the four motor nerves to those of CMT1A-patients. Median, ulnar and tibial nerve CMAPs were significantly lower in CMT1A-patients (Mann Whitney U Test, $P < 0.01$). No significant difference was observed in peroneal CMAPs between CMT1A and HNPP-patients.

The MPZ-patients showed reduced median CMAPs in 62.5% < 5 mV, ulnar CMAPs were reduced in 50% < 6 mV, peroneal CMAPs in 57% < 2 mV and tibial CMAPs were reduced below 3 mV in 50%. We compared the CMAPs of the MPZ-patients to the CMAPs of CMT1A-patients and we did not observe a significant difference between them.

In NEFL-patients median nerve CMAPs were reduced in one case below the cut-off value of 4.4 mV. The other case was in the normal range. Ulnar nerve CMAPs were reduced below 6 mV in both cases. Peroneal CMAPs were not recorded. Tibial CMAP was severely reduced in one case. The other case was not recorded.

In comparison to MPZ-patients median, ulnar and tibial CMAPs of NEFL-patients did not differ significantly.

The Silver Syndrome patient had the following characteristics: median nerve CMAP was severely reduced to 0.3 mV. Ulnar nerve CMAP was > 6 mV. Peroneal CMAP was severely reduced to 0.8 mV. Tibial nerve CMAP was > 3 mV.

3.4 Analysis of residual latency index (RL)

The following section refers to the values of residual latency index (RL) of the eight diagnostic groups. Distributions of RL are shown as boxplots in figure 4.

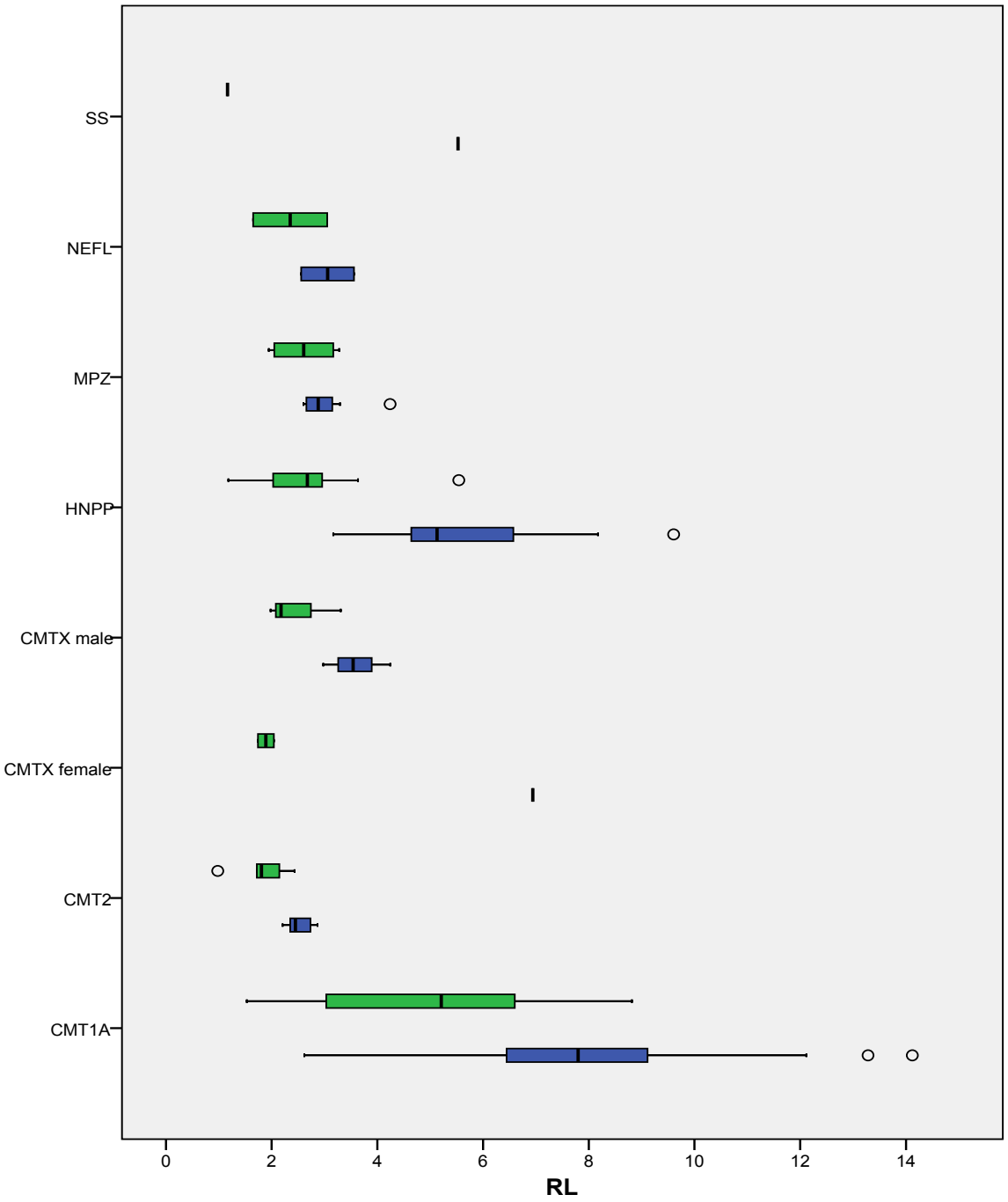


Figure 4: Distribution of residual latency index (RL) in the median (blue) and ulnar (green) nerves among the eight groups of the study subjects. Open dots indicate outliers. We see in distribution of RL a similar picture to that of distribution of DML, as shown in figure 2.

In CMT1A-patients mean median nerve RL was 7.9 ± 2.92 with a wide range from 2.62 to 14.12, as shown in figure 4. Mean ulnar RL was 4.88 ± 2.12 (Range: 1.53 to 8.82). Median and ulnar nerve RL of CMT1A-patients were significantly higher than median and ulnar nerve RL in HNPP-patients (T-Test, $P < 0.01$ for median nerve RL, $P < 0.001$ for ulnar nerve RL). Furthermore we compared RLs of CMT1A-patients to those of MPZ-patients. Median nerve RL was significantly higher in CMT1A-patients than in MPZ-patients (Mann-Whitney U test, $P < 0.001$). However, this was not shown for ulnar nerve RL (Mann Whitney U test, $P > 0.05$).

In CMT2-patients mean median RL was 2.51 ± 0.25 (Range: 2.21 to 2.87) and mean ulnar nerve RL was 1.82 ± 0.55 (Range: 0.98 to 2.43). Median and ulnar RL was significantly lower in the CMT2-patients in comparison to CMT1A-patients (Mann-Whitney U test, $P < 0.001$ for the median nerve RL, $P < 0.01$ for the ulnar nerve RL).

In CMTX-females median RL was high with 6.94 (one case), whereas mean ulnar RL was 1.89 ± 0.21 (Range: 1.74 to 2.04), shown in figure 4. Mean median RL in CMTX-males was 3.59 ± 0.63 (Range: 2.98 to 4.24) and mean ulnar RL was 2.49 ± 0.72 (Range: 1.98 to 3.31). We compared median and ulnar RLs between males and females with CMTX and to CMT1A-patients, respectively. There was not a significant difference (Mann Whitney U test, $P > 0.05$).

Mean median nerve RL in HNPP-patients was 5.64 ± 1.86 (Range: 3.17 to 9.61) and mean ulnar nerve RL was 2.71 ± 1.05 (range: 1.18 to 5.54).

In MPZ-patients mean median RL was 3.05 ± 0.58 (Range: 2.6 to 4.24) and mean ulnar RL was 2.61 ± 0.66 (Range: 1.95 to 3.28). The median nerve RL of MPZ-patients was significantly higher than the median RL in CMT2-patients with MFN2 and RAB7 mutations (Mann Whitney U test, $P < 0.05$). However, this was not shown for the ulnar nerve RL (Mann Whitney U test, $P > 0.05$). Furthermore, median and ulnar nerve RL did not differ significantly between MPZ and NEFL patients (Mann Whitney U test, $P > 0.05$).

Mean median nerve RL of NEFL patients was 3.06 ± 0.71 (Range: 2.56 to 3.56) and mean ulnar nerve RL was 2.35 ± 1 (Range: 1.65 to 3.05).

The patient with Silver Syndrome had a median RL of 5.53 and the ulnar nerve RL was 1.16.

3.5 Analysis of terminal latency index (TLI)

This section refers to values of TLI in the motor nerves of the upper limbs. Distributions of TLI of the eight diagnostic groups are shown in figure 5 as boxplots.

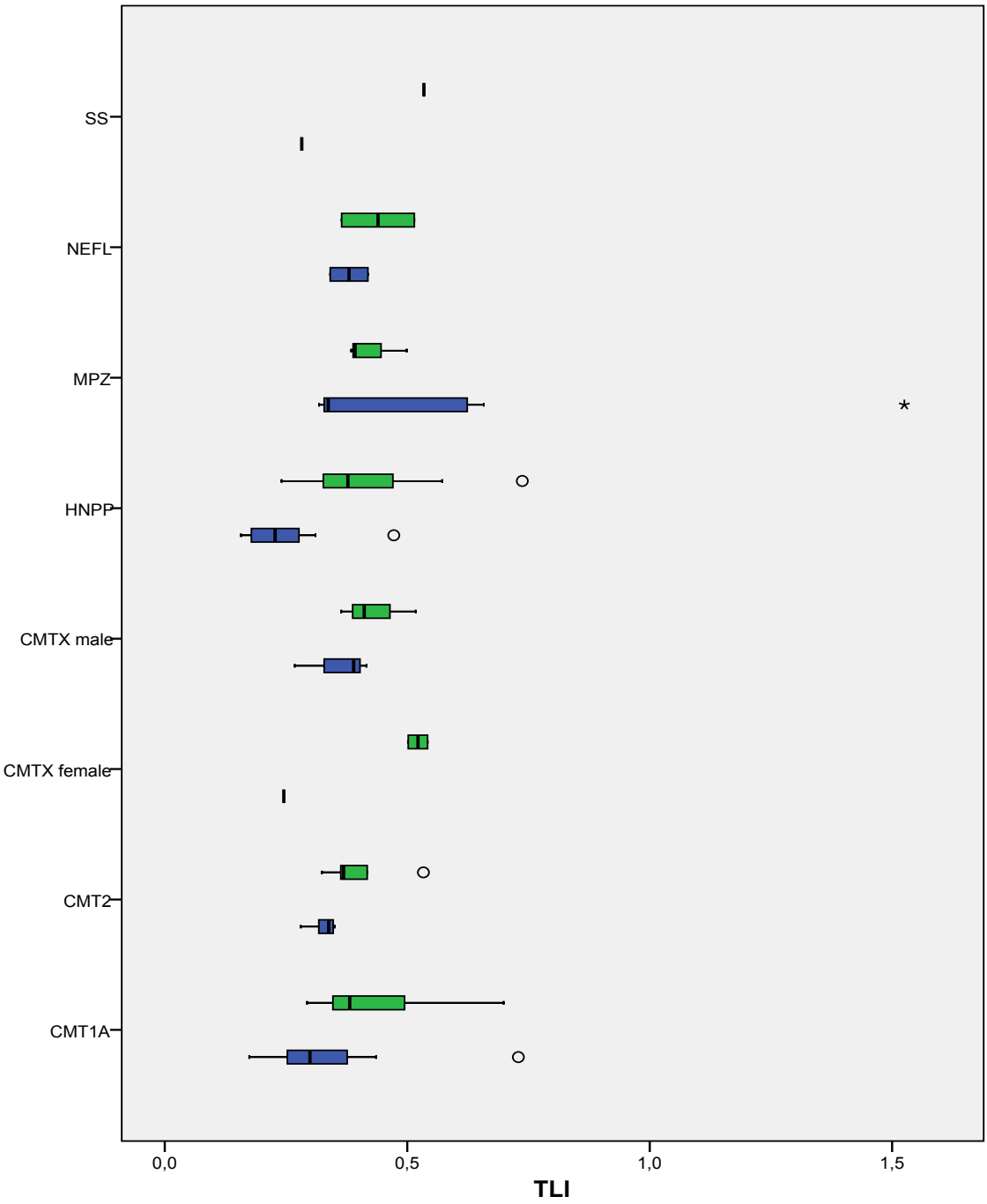


Figure 5: Distribution of terminal latency index (TLI) in the median (blue) and ulnar (green) nerves among the eight groups of the study subjects. Open dots and stars indicate mild and extreme outliers, respectively.

In CMT1A-patients mean median nerve TLI was 0.32 ± 0.11 with a wide range from 0.17 to 0.73, as shown in figure 5. Mean ulnar nerve TLI was 0.42 ± 0.11 (Range: 0.29 to 0.7). We compared median and ulnar nerve TLIs with those of HNPP-patients. Median nerve TLI in CMT1A-patients was significantly higher than median nerve TLI of HNPP patients (T-Test, $P < 0.05$). This was not shown for the ulnar nerve TLI (T-Test, $P > 0.05$). Median nerve TLI of CMT1A-patients was furthermore significantly lower in comparison to the median nerve TLI of MPZ-patients (Mann-Whitney U test, $P < 0.05$). This was not shown for the ulnar nerve TLI (Mann-Whitney U test, $P > 0.05$).

Mean median nerve TLI in CMT2-patients was 0.33 ± 0.03 (Range: 0.28 to 0.35) and mean ulnar nerve TLI was 0.4 ± 0.08 (Range: 0.32 to 0.53) and did not differ significantly to median and ulnar nerve TLIs of CMT1A-patients. The range of median and ulnar TLI of CMT2-patients was considered for homogeneous conduction slowing.

The two CMTX female patients had a low median nerve TLI of 0.25 and the mean ulnar nerve TLI was high with 0.52 ± 0.03 (Range: 0.5 to 0.54). Mean median nerve TLI of the CMTX-males was 0.36 ± 0.08 (Range: 0.27 to 0.42) and mean ulnar nerve TLI was 0.43 ± 0.08 (Range: 0.36 to 0.52).

In HNPP patients mean median nerve TLI was low with 0.24 ± 0.08 (Range: 0.16 to 0.47) and mean ulnar nerve TLI was 0.41 ± 0.13 (Range: 0.24 to 0.74). Median nerve TLI was significantly lower than ulnar nerve TLI in HNPP-patients (Student`s T-Test, $P < 0.001$).

The MPZ-patients had a mean median nerve TLI of 0.55 ± 0.42 with a wide range from 0.32 to 1.53. In contrast, mean ulnar nerve TLI was 0.42 ± 0.05 with a low range from 0.38 to 0.5, as shown in figure 5. The median and ulnar nerve TLI of MPZ patients did not differ significantly to the median and ulnar TLI of NEFL (Mann-Whitney U test, $P > 0.05$) and CMT 2A and CMT 2B-patients (Mann-Whitney U test, $P > 0.05$), respectively.

Mean median nerve TLI in NEFL-patients was 0.38 ± 0.05 (Range: 0.34 to 0.42) and mean ulnar nerve TLI was 0.44 ± 0.11 (Range: 0.36 to 0.51).

Median nerve TLI of the Silver Syndrome patient was 0.28 and ulnar nerve TLI was 0.53.

3.6 Analysis of sensory nerve conduction velocity (SNCV)

The following section refers to the values of sensory nerve conduction velocities (SNCVs) of the eight groups of the study subjects. Distributions of SNCVs are shown in figure 6 as boxplots.

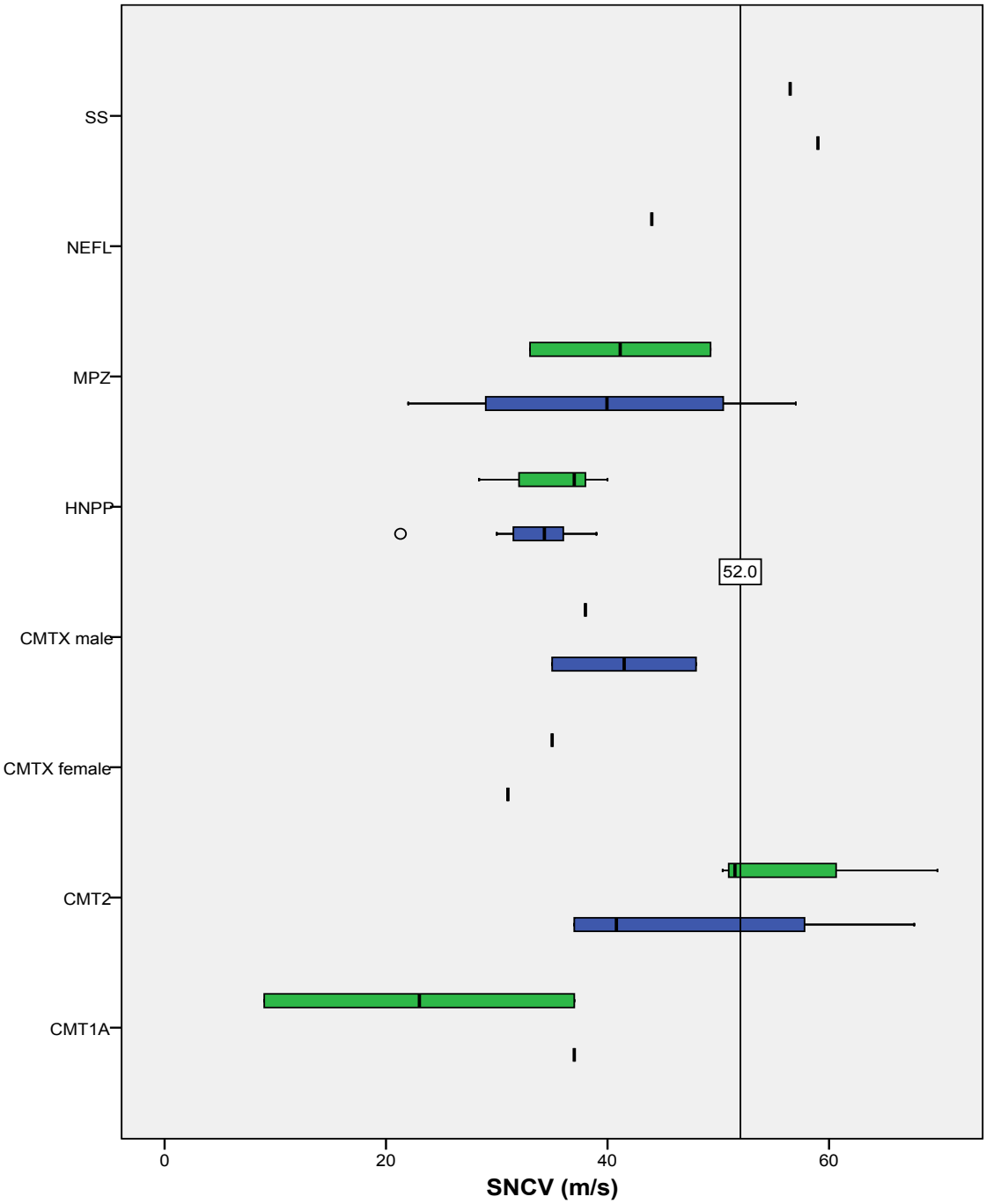


Figure 6: Distribution of sensory nerve conduction velocity (SNCV) in the median (blue) and ulnar (green) nerves among the eight groups of the study subjects. The dashed vertical line represents the cut-off value for median and ulnar nerve SNCV with 52 m/s. Open dots indicate mild outliers.

In CMT1A-patients sensory nerve conduction velocities (SNCVs) were abnormal in all tested cases. They could not be recorded in 27 cases (96%) for the median and ulnar nerve and in 26 cases (93%) for the sural nerve. We compared median, ulnar and sural nerve SNCV of CMT1A-patients to those of HNPP and there was not a significant difference of SNCVs between CMT1A and HNPP-patients. Furthermore we compared SNCVs of CMT1A-patients to those of MPZ-patients and the SNCVs of the three nerves did not differ significantly between those groups.

In CMT2-patients median SNCV was reduced below 52 m/s in 3 of 5 cases (60%), ulnar SNCV was reduced in 2 of 3 cases (66%) below 52 m/s. Sural nerve SNCV was abnormal in one of three cases below 42 m/s.

The one recorded CMTX-female had a median SNCV of 31 m/s, an ulnar SNCV of 35 m/s and sural SNCVs were not recorded in the two patients.

In male CMTX-patients median SNCV was recorded in two of six cases and was reduced below 52 m/s in both cases. Ulnar SNCV was recorded in only one case and was reduced to 38 m/s.

Median SNCV was recorded in eight of 14 cases in HNPP-patients and was reduced below 40 m/s in all cases. Ulnar SNCV was recorded in 9 of the 14 cases and was reduced below 40 m/s in all cases. Sural nerve SNCV was recorded in six cases and was reduced below 38 m/s in all cases.

In MPZ-patients median SNCV was recorded in four of the eight cases and was reduced in three cases below 52 m/s. In one case median SNCV was 57 m/s. Ulnar SNCV was recorded in only two cases and in both cases a reduced ulnar SNCV below 52 m/s was observed. Sural SNCV was recorded in one case and was reduced to 38 m/s.

Median and sural SNCVs in NEFL-patients were not recorded. Ulnar SNCV was recorded in one case and was reduced to 44 m/s.

The patient with Silver Syndrome had a normal median SNCV of 59 m/s, ulnar SNCV was 56.5 m/s and sural nerve SNCV was slightly reduced to 35.7 m/s.

3.7 Analysis of sensory nerve action potentials (SNAPs)

The last section refers to the results of the sensory nerve action potential (SNAP) study of the eight groups of the study subjects. Distributions of SNAPs are shown in figure 7 as boxplots.

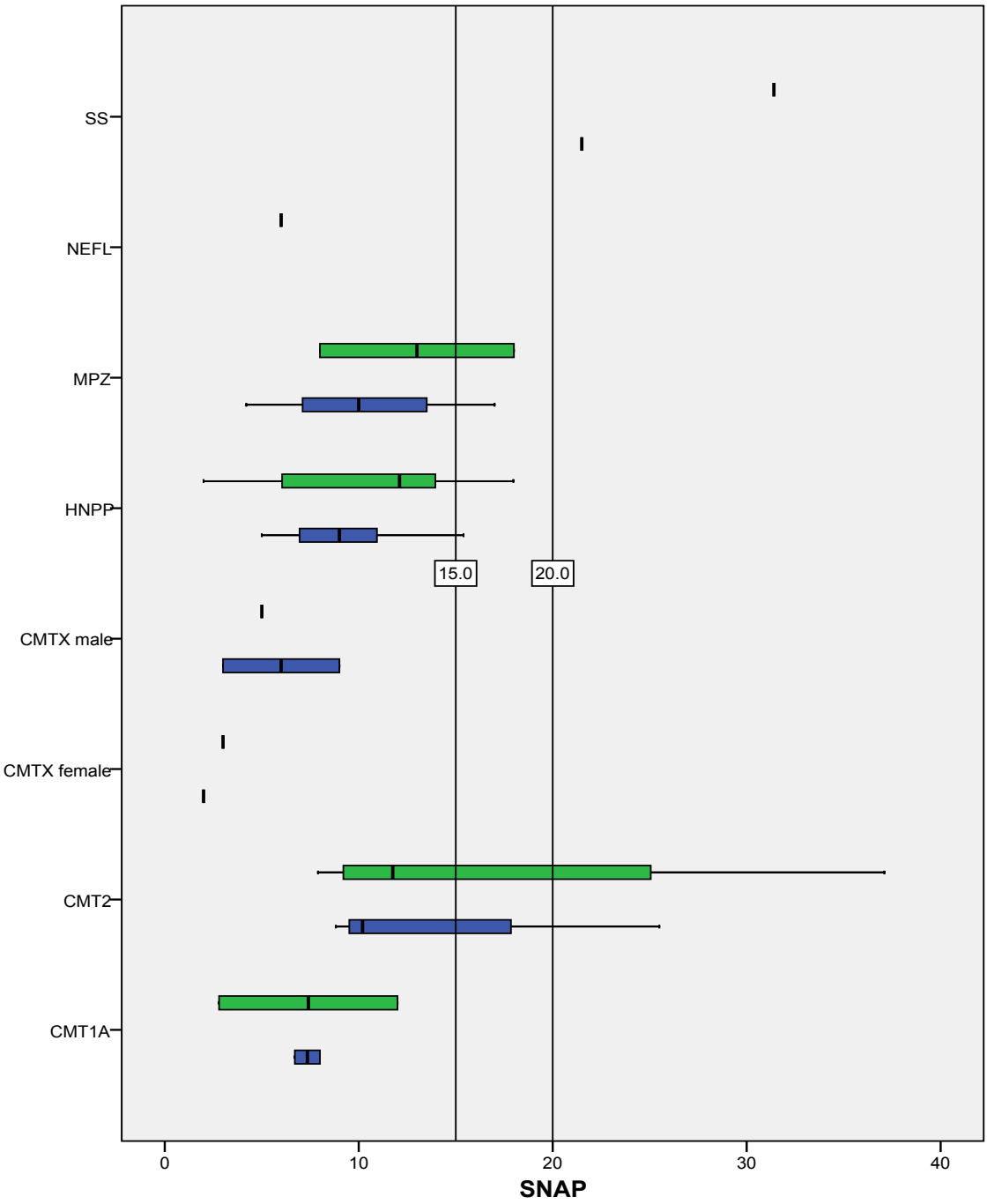


Figure 7: Distribution of sensory nerve action potentials (SNAPs in µV) in the median (blue) and ulnar (green) nerves among the eight groups of the study subjects. Dashed vertical lines represent cut-off values for median nerve SNAP with 20 µV and for the ulnar nerve SNAP with 15µV. Sural SNAPs are not shown as a boxplot because they were abolished in most cases and not examined systematically.

In CMT1A-patients median nerve SNAPs were reduced in two recorded cases below 10 µV, ulnar SNAPs were below 10 µV in two recorded cases and sural SNAPs were severely reduced in the two measured cases below 2 µV. Median, ulnar and sural nerve SNAPs did not differ significantly to those of CMT2A and CMT2B-patients, to those of HNPP-patients and to those of MPZ-patients (Mann-Whitney-U test, $P > 0.05$).

Median nerve SNAPs were recorded in three cases in CMT2A and CMT2B-patients. In two of the three cases median nerve SNAPs were severely reduced below 11 µV. In CMT2A-patients median SNAPs were in the normal range > 20 µV. Ulnar nerve SNAPs were reduced in three cases below 15 µV and in one case ulnar SNAP was > 30 µV. Sural nerve SNAPs were abnormal below 6 µV in two cases and in one case in the normal range > 6 µV.

Median nerve SNAP was measured in only one CMTX female and was reduced to 2µV. Ulnar SNAP was also measured in one case and severely reduced to 3 µV. Sural nerve SNAPs were not recorded.

In CMTX-males median nerve SNAPs were recorded in two cases, they were severely reduced below 10 µV. Ulnar SNAP was recorded in one case and was reduced to 5 µV. Sural nerve SNAPs were not recorded.

Median nerve SNAPs were recorded in seven cases in HNPP-patients, they were all reduced below 20 µV. Ulnar SNAPs were reduced below 15 µV in seven cases. In one case ulnar SNAP was > 15 µV. Sural nerve SNAPs were reduced in four cases. In two cases sural nerve SNAPs were in the normal range at 6 µV.

In MPZ-patients median nerve SNAPs were reduced in all three recorded cases below 20 µV. Ulnar nerve SNAPs were recorded in two cases. In one case it was abnormal with 8 µV and in the other it was in the normal range > 15 µV. Sural nerve SNAP was only recorded in one case and was in the normal range with 7 µV.

In NEFL-patients median and sural nerve SNAPs were not recorded. A reduced ulnar nerve SNAP was recordable in one case with 6 µV.

The median nerve SNAP of the Silver Syndrome patient was 21.5 µV, the ulnar nerve SNAP 31.4 µV and the sural nerve SNAP was reduced to 0.6 µV.

4 Discussion

We performed an electrophysiological study in 67 patients with proven hereditary neuropathies. In the following section the results of the study will be interpreted and related to those of other studies that have been performed up to now.

4.1 Sources of error and inaccuracy of neurography

When we neurologists examine nerves by electroneurography, we should be aware of some sources of error. It was shown that the time elapsing between the moment of stimulation and the onset of the muscle or nerve action potential can be measured electronically to 0.1 ms, but it is not clear whether the onset of the action potential can always be determined with the same degree of accuracy [106].

The intensity of stimulation, as mentioned already above, must be supramaximal to record the fastest conducting fibers, otherwise a falsely long latency may be recorded [106].

Another source of error is that the point of stimulation on the nerve itself may not correspond exactly with the surface position of the stimulating electrode and may vary by 5 to 10 mm at the usual intensities of stimulation. This phenomenon may increase to 25 mm or more at higher intensities of stimulation.

Furthermore, the surface measurement of the nerve trunk may be up to 1 cm different from its real length [106].

It has been shown that testing the same normal subject at different times using an exactly similar technique on each occasion can vary up to 10 m/s. Slowing of nerve conduction should not be regarded as significant until the speed falls to at least 10% below the lower limits of normal for the nerve tested. Because of this, recording of distal motor latencies (DMLs) are said to be more useful in detecting borderline abnormalities than conduction velocities. Variations in speed due to temperature changes are relatively slight and can usually be ignored except in an obviously cold limb [112].

4.2 CMT1A

In CMT1A patients with PMP22 duplication, almost all patients showed predominantly demyelinating features through the entire length of nerves and among different nerves in the nerve conduction study, with variable severity among individuals. Median and ulnar nerve MNCVs were < 33 m/s in 93%; these cases also showed marked prolongation of DMLs > 8 ms in the median nerve and prolonged DMLs > 5.4 ms in the ulnar nerve, indicating rather uniform conduction slowing. Only one patient had a median nerve MNCV of 38 m/s and one other patient had a median MNCV of > 50 m/s. CMT1A-patients with MNCVs of 38 m/s to 42 m/s were reported in previous studies [113, 114]. Whereas in other studies the highest value for median nerve MNCV was 33 m/s [23]. The patient with a median MNCV of 38 m/s had a prolonged DML > 5 ms in the median nerve and a prolonged DML with 4 ms in the ulnar nerve. The other patient with the median MNCV of > 50 m/s had only a slightly but prolonged median nerve DML of 4 ms, defending the thesis that DML-prolongation in CMT1A due to PMP22-mutations precedes slowing of MNCV in motor nerves. This was also reported in a previous study where prolonged DMLs were already present in the first months of life and preceded slowing of MNCV [28].

Subanalysis by nerve group revealed that MNCV did not differ significantly between the four motor nerves, whereas median nerve DMLs were significantly greater than DMLs of the ulnar nerve, showing some heterogeneousness among motor nerves in the distal parts, as shown in figure 2. This accentuated prolongation of median nerve DML may also be due to coincidence with idiopathic carpal tunnel syndrome [115]. Carpal tunnel syndrome (CTS) is one of the most common peripheral neuropathies and affects mainly middle aged women. In the majority of the patients with CTS the underlying cause remains unclear [116].

However, features of axonal loss became evident as decrease in CMAP amplitude that was variably present irrespective of marked slowing of nerve conduction. In addition, neither conduction block nor temporal dispersion of the CMAP was observed, confirming the uniform slowing of motor nerve conduction in our patients.

Furthermore mean median and ulnar TLIs did not differ significantly to those of CMT2-patients, further indicating uniform conduction slowing between distal and proximal segments of the motor nerves at group level. In a previous study median nerve TLI was used to distinguish neuropathy with antibodies against myelin-associated glycoproteins from CMT1A. In this study CMT1A-patients were characterized by median nerve TLI > 0.26 [107]. Our results differ a little bit because median nerve TLIs below 0.26 were also observed.

We saw that TLI had a wide range among individuals with CMT1A. So we came up with a simple classification. CMT1A-patients with ulnar TLI < 0.32 can be classified as distal conduction slowing type, patients with ulnar TLI from 0.32 to 0.53 are those with homogeneous conduction slowing along the entire length of the nerve and patients with ulnar TLI > 0.53 are classified as the proximal conduction slowing type with more slowing of MNCV in relation to DML-prolongation. For this classification we took the ulnar nerve TLI because the median nerve TLI may be low due to the above mentioned common carpal tunnel syndrome.

Residual latency index (RL) had like TLI a wide range. Median nerve RLs were compared to those of MPZ-patients and CMT2-patients and RLs of CMT1A-patients were significantly higher, underlining the strongest prolongation of distal motor latencies in CMT1A-patients. In CMT1A-patients median nerve RL was in 96% > 3, whereas CMT2A and CMT2B-patients were < 3 in 100%.

SNCVs and SNAPs were abnormal in the measured patients but in most cases they were abolished. This is in line with previous studies [23, 26, 114].

We conclude that DML-prolongation is a reliable tool in identifying affected individuals. Median nerve DMLs and ulnar DMLs were severely prolonged > 8 ms and > 5.4 ms in 93%, respectively. Nerve conduction velocity is uniformly reduced in all nerves but not always equally along nerve segments, as can be made clear by the wide range of TLI. Problems arise when MNCVs are nearly in the normal range and DMLs are only slightly prolonged because these constellations were also found in patients with NEFL and MPZ-mutations or in carpal tunnel syndrome.

4.3 CMT2A and CMT2B

In CMT2A due to MFN2-mutations and in CMT2B due to RAB7-mutations, all patients showed median and ulnar nerve MNCVs > 50 m/s. In previous studies slightly-to-moderately reduced median MNCVs were observed [82]. In almost all patients peroneal and tibial nerve MNCVs were in the normal range. In five of the six examined cases median and ulnar nerve DMLs were in the normal range < 4.2 ms for the median nerve and < 3.6 ms for ulnar nerve. In one case a slightly prolonged median DML of 4.2 ms was observed and in one case ulnar DML was 3.6 ms. Median and ulnar nerve RLs were < 3 in CMT2A and CMT2B-patients.

Median and ulnar nerve TLIs did not differ significantly to those of CMT1A-patients. We took the range of TLIs in CMT2-patients as the normal range because MNCVs and DMLs were in the normal range. This observation is consistent with previous studies [81, 107]. Surprisingly, in most cases CMAPs in the normal range were observed, as shown in figure 3. This is not in line with other studies showing reduced CMAPs [81].

4.4 CMTX

4.4.1 CMTX females

Electrophysiological findings in CMTX were reported in different studies [30, 61, 65], as already mentioned in the introduction. Extended statistical analysis was not carried out because the number of examined patients was too small. We examined two female patients and six male patients. Median nerve MNCV of the one measured female case was reduced with 31 m/s and the two recorded ulnar MNCVs were also reduced to 34 m/s. Median nerve DMLs were prolonged in the two female cases, in one case severely up to 9 ms and in the other moderately up to 6 ms. Ulnar nerve DMLs were only slightly prolonged > 4 ms.

To estimate whether motor conduction was heterogeneous within and among the different motor nerves, as reported in previous studies [67, 68], we calculated RL and TLI for the median and ulnar nerves. We compared median and ulnar nerve RLs and TLIs to those of CMT2-patients. Previous studies chose for comparison CMT1A-patients, we did not do this because in CMT1A RL and TLI showed a wide range. In the one female case median nerve RL was increased up to 7, whereas in CMT2 mean median RL was 2.51 ± 0.25. Mean ulnar nerve RL of the two recorded females was 1.89 ± 0.21 and did not differ significantly to those of CMT2-patients with a mean ulnar nerve RL of 1.82 ± 0.55. This may also be due to the above mentioned common carpal tunnel syndrome (CTS) where we see median DML-prolongation and normal median MNCVs. Median nerve TLI was 0.25 in the one female case and was reduced in comparison to mean median nerve TLI with 0.33 ± 0.03 of CMT2-patients. Ulnar nerve TLI in the same female patient was 0.55, whereas mean ulnar TLI in CMT2-patients was 0.4 ± 0.08. These data indicate distal accentuation of the demyelinating process in the median nerve and rather homogeneous demyelination in the ulnar nerve, suggesting some heterogeneity of nerve conduction between the median and ulnar nerves as well as in the median nerve itself. But as mentioned above, this distal accentuated conduction

slowing in the median nerve may also be due to carpal tunnel syndrome which is more common in females. However, authors of previous studies postulate internerve heterogeneity but not heterogeneity within a given nerve [60].

The nature of the neuropathy in CMTX-patients due to Cx-32-mutations has been discussed in previous studies. We observed that axonal and demyelinating features were closely related in CMX-females because compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) were moderately or severely reduced in all patients. This is in line with a previous study, defending this thesis [60]. Previous studies reported that temporal dispersion of the CMAPs might be specific to CMTX-patients [67, 68]. However, data concerning conduction block or temporal dispersion of the CMAPs were not available for all patients and not studied systematically. Authors of previous studies reported that axonal loss may differ between median and ulnar nerves in CMTX females because median nerve CMAPs were frequently more reduced than ulnar nerve CMAPs [60]. Our observations were not in line with that because CMAPs were severely reduced in the median and ulnar nerves. SNCVs and SNAPs were moderately reduced.

4.4.2 CMTX males

In CMTX males the lowest value for the median MNCV was 31 m/s. In one case a median MNCV of > 38 m/s was observed. Ulnar MNCV was slightly reduced to 33 m/s, also a value > 41 m/s was observed. Median nerve DMLs were prolonged > 5 ms and ulnar nerve DMLs were slightly prolonged > 3.6 ms. We compared MNCVs and DMLs of the male patients to those of females. Surprisingly, they did not differ significantly, whereas other studies have shown a significant difference between male and female CMTX patients [60, 61, 65]. This might be because the number of recorded cases was too small in our study. The lowest value for median nerve RL was 3 and the highest was 4.2. The range of ulnar nerve RL was from 2 to 3.3. This is in contrast to females, where we observed median RL-values of 7. Mean median TLI was 0.36 ± 0.08 and mean ulnar nerve TLI was 0.43 ± 0.08; they did not differ significantly to those of CMT2-patients. This supports the hypothesis that demyelination in CMTX males is rather homogeneous within a given nerve, but also between different nerves in one patient. This was also postulated by other authors [60, 68]. CMAPs of all motor nerves were severely reduced underlining the axonal nature of male patients with Cx-32-mutations, as proposed by other authors [60, 68].

4.5 HNPP

In this study we elucidated two characteristic aspects of the electrophysiologic profiles of HNPP, namely a generalized sensorimotor neuropathy and superimposed focal conduction abnormalities preferentially located at common entrapment or compression sites, as proposed in previous studies [51]. Our findings are in accordance with previous observations, defending the thesis that DMLs are typically prolonged in almost all motor nerves, which is disproportionate to the relatively infrequent and minor decrease of MNCVs [51, 54].

Median nerve MNCVs were below 38 m/s in only two of the fourteen analyzed cases, whereas median nerve DMLs were prolonged > 4.2 ms in all fourteen cases. In two cases DMLs were severely prolonged up to 11ms. Ulnar MNCVs differed slightly to those of the median nerve. In five cases we observed a reduction of the ulnar MNCV below 41 m/s, in some cases independently to median nerve MNCVs. So, the ulnar nerve showed prominent segmental slowing at the usual proximal compression site, although not significantly. Such a focal conduction slowing has been suggested to be a distinct feature of HNPP, and our study is in line with these previous reports [26, 51, 53].

Ulnar nerve DMLs were slightly prolonged ≥ 3.4 ms in all cases, but not as high as median nerve DMLs. This distal accentuation of nerve conduction abnormalities can be made clear by analyzing RL and TLI. In recent studies median and ulnar nerve TLI were compared to that of CMT1A-patients and were significantly lower in HNPP-patients [51]. In our study the range of RL and TLI in CMT1A was wide and not enough homogeneous to compare. So we also compared RLs and TLIs to those of CMT2-patients. Median and ulnar nerve RLs were significantly lower in HNPP-patients in comparison to CMT1A-patients but significantly higher than median and ulnar nerve RLs of CMT2-patients. As mentioned above, RL assesses the distal proportion of the motor nerve and is more influenced by values of DMLs than by MNCVs. Concerning this data, we would say that the distal proportion of the two measured motor nerves of the upper limbs is more affected in HNPP in comparison to a control group such as CMT2, but less affected in comparison to CMT1A. Median nerve TLI in HNPP-patients was significantly lower than median nerve TLI of CMT1A-patients and CMT2-patients. This was not shown for the ulnar nerve, indicating selective distal abnormality of nerve conduction in the median nerve of HNPP-patients. This might be due to the distal entrapment site in the carpal tunnel. Myelinopathy beginning in the terminal portion of the nerve fibers has been postulated in previous studies [54, 55].

In a previous study was reported that the unique feature of generalized conduction abnormalities in HNPP was not altered after excluding median nerve data from the analysis, which led to the speculation that the background polyneuropathy might be independent of the superimposed focal entrapment neuropathies [55]. In contrast to this observation, other authors suggest that the background polyneuropathy may be difficult to explain without considering the characteristic susceptibility of HNPP nerves to pressure injury because abnormalities of the conduction parameters, such as SNCV and DML were more frequent and severe in the median and ulnar nerve that contain the common entrapment sites at distal segments, such as the carpal tunnel, Guyon's canal, respectively, than in the other motor and sensory nerves [51]. Some of our results are in line with that because prolonged DMLs were more frequently and severely in median and peroneal nerves than in the tibial and ulnar nerves. In the tibial nerve DMLs were in the normal range in most cases. SNCVs were rather homogeneously reduced in the three measured sensory nerves, which may lead to the speculation that the background polyneuropathy might be independent of the superimposed focal entrapment neuropathies, as proposed by Andersson et al. [55].

We conclude that all HNPP patients in our study showed electrophysiological evidence of a generalized background neuropathy, although the widespread electrophysiological abnormality of HNPP patients was not so severe in comparison to that of CMT1A-patients, as shown in figure 1 and 2. The concept of a background neuropathy could be characterized by SNCV slowing, as proposed by other authors [51].

Conduction block was rarely found in the present study and was not examined systematically. In previous reports frequency of conduction block in HNPP was highly variable, ranging from 6 to 22%, which might depend on the criteria used and circumstances of conduction block measurement, when the patients were examined and the presence of technical problems, such as submaximal stimulation at proximal sites, as shown by different authors [52, 53].

4.6 Patients with mutations in the MPZ gene

It has been demonstrated that MPZ-mutations can lead to peripheral neuropathies that are clinically and electrophysiologically distinct, such as CMT1, Dejerine-Sottas syndrome and congenital hypomyelinating neuropathy [40].

We examined eight patients carrying a mutation in the MPZ-gene. 50% of these patients had a median nerve MNCV < 38 m/s and were therefore correctly classified as CMT1B. The other

half was diagnosed with a median MNCV > 38 m/s and should therefore be classified as CMT2I. Several studies in the recent past have shown this heterogeneity of MNCVs among MPZ-patients [40, 43, 44, 117].

Subanalysis by nerve group revealed that there was no significant difference between the different motor nerves, meaning that nerve conduction is rather homogeneous between the different motor nerves.

The values of DMLs in MPZ-patients were not elucidated in previous studies yet.

Median nerve DMLs were slightly prolonged > 4.2 ms in seven of the eight examined cases, independently of median MNCV. Ulnar nerve DMLs were recorded in only four cases and were slightly-to-moderately prolonged in two cases. Peroneal and tibial DMLs showed a marked variability.

Authors of a recent study postulated that two main phenotypes with MPZ-mutations exist, namely an early (childhood) onset neuropathy with very slow NCVs and predominant demyelination on nerve biopsy and a late (adult) onset neuropathy with minimal to moderately slowed NCVs and a predominant axonal neuropathy on nerve biopsy [41]. The patients in our study can be, at least, based on electrophysiological data, subdivided in two groups. In one young female patient we observed a severely reduced median MNCV with 9 m/s, whereas median nerve DML was only slightly prolonged up to 5.1 ms. Median nerve RL in this patient was -2.7 and TLI was 1.53. These extreme values indicate maximal proximal accentuation of nerve conduction slowing in the early onset type and were therefore excluded from statistical analysis.

To assess the distal proportion of the remaining seven patients we calculated median and ulnar nerve RL. In comparison to CMT1A-patients median nerve RL was significantly lower in MPZ-patients, which means that the distal proportion is not as severely affected as in CMT1A-patients. This was not shown for the ulnar nerve.

Median nerve TLI of MPZ-patients was significantly higher in comparison to CMT1A and CMT2 patients, also defending the thesis that the proximal parts of the nerves in the upper limbs are more affected. This was not shown for the ulnar nerve, probably because the number of examined cases was too small for the ulnar nerve.

CMAPs were normal or reduced in the several examined nerves, independently of the MNCVs. Median, ulnar and sural SNCVs and SNAPs were reduced in most of the recorded cases.

In conclusion, we can say that the electrophysiological picture is like the clinical more heterogeneous than in CMT1A-patients. This is true for MNCVs which may range from

severe reduction, such as in Dejerine Sottas syndrome due to MPZ-mutation, to moderately reduced and also normal MNCVs were observed in the adult onset neuropathy secondary to MPZ-mutations. What we saw in median and ulnar nerve DMLs was quite homogeneous. Only slightly prolonged DMLs in the median and ulnar nerves < 8 ms and < 6 ms, respectively, were observed, independently of MNCVs. Even in the female DSS-patient median nerve DML was only slightly prolonged, whereas median MNCV was severely reduced below 10 m/s.

4.7 Patients with mutations in the NEFL gene

We examined two adult male patients with a hereditary neuropathy due to mutations in the NEFL gene.

Median and ulnar nerve MNCVs were slightly reduced to the cut-off value with 38 m/s in the median nerve and slightly reduced to 40 m/s in the ulnar nerve. Median and ulnar nerve DMLs showed a slight prolongation in the two recorded cases. Therefore, these two cases can be classified as intermediate type of CMT.

Recent studies showed several families with NEFL-mutations in which affected members had highly variable MNCVs, ranging from normal to severely reduced.

The electrophysiological data show wide NCV ranges [11]. Recently, authors proposed that in the upper and lower limbs of several patients the DMLs are prolonged disproportionally to the MNCV slowing, indicating distal demyelination [89]. This was also seen in hereditary neuropathy with liability to pressure palsies (HNPP) and neuropathy associated with monoclonal IgM antibodies directed against myelin-associated glycoprotein [32].

Extended statistical analysis was not carried out because the number of examined cases was too small.

To assess the distal proportion we calculated TLI of the median and ulnar nerves. Median nerve TLI was in one case 0.34, indicating homogeneous conduction velocities within the median nerve. In the other case median nerve TLI was 0.42. The same was observed in the ulnar nerve. SNCVs and SNAPs were not recorded systematically.

4.8 Silver Syndrome

The electrophysiological features of Silver Syndrome (SS) and distal hereditary motor neuropathy 5 (dHMN-5) had been elucidated in a study by Auer-Grumbach et al. [95]. Authors of previous studies underlined the enormous heterogeneity of dHMN concerning the distribution of muscle wasting and upper motor neuron involvement [93, 95, 118].

Sensory nerves may become involved only in advanced stages of disease course and show predominant axonal damage, as shown in a previous study [95].

The electrophysiological data of the adult male patient we examined were pretty much in line with previously published facts. The median nerve MNCV was reduced to 32.2 m/s and the peroneal MNCV was also reduced, whereas ulnar and tibial MNCVs remained in the normal range.

Median nerve DML was moderately prolonged up to 7.7 ms, peroneal nerve DML was also slightly prolonged, whereas ulnar and tibial DMLs were normal. CMAPs were severely reduced in the median and peroneal nerves, indicating severe axonal loss.

Median nerve TLI was 0.28, suggesting a slight distal reduction of nerve conduction velocity. Ulnar nerve TLI was slightly increased with 0.53 but ulnar MNCV and DML were in the normal range.

The electrophysiological data of our patient did not suggest sensory involvement. Median and ulnar nerve SNCVs and SNAPs were in the normal range. This was not shown for the sural nerve.

In conclusion we can say that the electrophysiological data of our patient are in line with previous studies. The results of the electrophysiological examination were consistent with a predominant axonal motor neuropathy. In the upper limbs the median nerve was concerning MNCV, DML and CMAPs more severely affected than those of the ulnar nerve, as shown in the study by Auer-Grumbach et al. [95]. In our study sensory nerve involvement was not observed in the upper limbs.

4.9 Conclusion

We conclude that measurement of motor nerve conduction velocity (MNCV) in median and ulnar nerves of the upper limbs is enough to distinguish CMT1 from CMT2-patients by the cut-off values of 38 m/s for the median and 41 m/s for the ulnar nerve MNCV. The results, as shown in figure 1, correspond to that what is known in literature.

In addition measurement of distal motor latencies (DMLs) can give us a more specific picture of the underlying genetic cause. Marked slowing of median and ulnar MNCVs may occur in CMT1A but also in patients with mutations in the MPZ gene. We can distinguish them by median DML, such as median DMLs are severely prolonged > 8 ms in CMT1A, whereas in patients with mutations in the MPZ gene we found only slightly prolonged median and ulnar DMLs < 8 ms and < 6 ms, respectively. Motor nerves of the lower limbs are severely affected early in the disease course and therefore it is not possible to perform longitudinal studies. We should keep in mind that median nerve DML may be prolonged independently of hereditary neuropathies due to idiopathic carpal tunnel syndrome, especially in CMTX females making the ulnar nerve DML a more reliable tool to examine the distal proportion of the nerves. This study revealed that calculation of TLI is not a reliable tool in classification of hereditary neuropathies. The advantage of TLI calculation is that it can clarify the location of conduction slowing, so that we can classify neuropathies further into distal and proximal conduction slowing types with median or ulnar nerve TLI. Further studies are necessary to evaluate whether hereditary neuropathies with low TLI are those with early stages in disease course, which has been postulated by previous authors [28]. Furthermore it should be mentioned that median nerve TLI can be low due to idiopathic carpal tunnel syndrome making the ulnar nerve TLI more reliable. However, extreme high positive outliers of median nerve TLI were only found in CMT1A and MPZ patients, especially in MPZ patients, where we found frequently slight DML-prolongations independently of MNCV-slowing that causes a wide range of median nerve TLI. Interestingly, ulnar nerve TLI was in the normal CMT2-range in MPZ-patients, as shown in figure 5. Residual latency index (RL) is not that influenced by MNCV-slowing as TLI and responses more to changes in the distal motor latencies. We conclude that calculation of RL, shown in figure 4, has the same diagnostic value as the DML alone.

Because of the facts mentioned above, we recommend to consider both, MNCVs and DMLs when we classify hereditary neuropathies. The number of examined cases in CMTX, NEFL and Silver Syndrome was too small to find electrophysiological criteria that are able to

separate these neuropathies from each other. Sensory nerve conduction velocities are shown in figure 6. The results correspond to that what is known from literature. Interestingly, sensory nerve action potentials (SNAPs), shown in figure 7, were lower in CMT1A-patients in comparison to those of CMT2-patients, although not significantly.

5 References

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