

## REVIEW ARTICLE

# Charcot-Marie-Tooth disease and related inherited peripheral neuropathies

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### **Abstract**

The classification of Charcot-Marie-Tooth disease and related hereditary motor and sensory neuropathies has evolved to incorporate clinical, electrophysiological and burgeoning molecular genetic information that characterize the many disorders. For several inherited neuropathies, the gene product abnormality is known and for others, candidate genes have been identified. Genetic testing can pinpoint a specific inherited neuropathy for many patients. However, clinical and electrophysiological assessments continue to be essential tools for diagnosis and management of this disease group. This article reviews clinical, electrophysiological, pathological and molecular aspects of hereditary motor and sensory neuropathies.

Inherited peripheral neuropathy as a diagnostic group encompasses a broad range of conditions with many presenting symptoms and signs. Major subtypes include hereditary motor and sensory neuropathies, hereditary sensory and autonomic neuropathies, hereditary motor neuronopathies, and neuropathies related to specific metabolic disorders. This review will focus on the inherited motor and sensory neuropathy subgroup usually referred to as Charcot-Marie-Tooth disease (CMT), for which there has been an explosion of new molecular genetic information over the past decade. Advances in our understanding of the molecular basis of CMT have revealed an enormous diversity in genetic mechanisms that lead to a clinical entity that is relatively uniform in presentation. Clinicians experienced in the diagnosis of neuromuscular diseases can readily identify a patient with CMT by a group of symptoms and signs that fits a classical pattern. Yet, that clinical pattern may be the result of vastly different genetic defects. Accurate diagnostic characterization has evolved from simple pattern recognition to a more complex series of diagnostic steps. Understanding the basis for these steps will be essential for clinicians to participate fully in the management of patients with CMT. This review will summarize the current understanding of clinical, electrophysiological, pathological and molecular aspects of the various subtypes of CMT.

### **CMT: GENERAL CLINICAL FEATURES**

CMT is a common genetic disorder, estimated to be present in 1 in 2500-5000 people.<sup>1-4</sup> Patients with CMT can present with a broad range of symptoms and signs. Disease expression varies between and within kindreds. However, certain common features are usually seen. CMT produces a distal greater than proximal, lower extremity greater than upper, motor and sensory deficit, in a typical diffuse peripheral neuropathy pattern. Significant asymmetry of symptoms or signs should not be seen, except in hereditary neuropathy with liability to pressure palsies (HNPP). Hereditary neuropathy with liability to pressure palsies, which is discussed in detail later, is not usually considered a form of CMT but it is aligned with this group of disorders by virtue of the abnormality of peripheral myelin, which is the basis of its pathogenesis. Weakness in CMT is usually present in foot and lower leg muscles but is uncommon in upper leg or hip girdle muscles in all but the most severely affected

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individuals. This means that even patients with marked weakness are still usually able to walk with the aid of ankle splints, due to preserved proximal leg strength. Upper extremity weakness is usually restricted to hand and forearm muscles, which may impair hand function for fine motor and heavy tasks. The sensory loss is glove and stocking in distribution and usually affects all modalities. However, patients are usually less symptomatic from sensory disturbance than motor problems; the early age of onset and slow progression of the sensory deficit likely make sensory loss less apparent to the CMT patient than to a patient with acquired neuropathy. Some patients will deny any sensory symptoms, despite evidence of marked loss of sensation on examination. Paresthesias and neuropathic pain are less common than in acquired sensory motor neuropathies.

Patients usually have foot deformities, most often pes cavus. Pes cavus is recognized by high plantar arches. There is usually wasting of foot muscles and pes cavus is often associated with curled up or "hammer" toes (Figure 1). It is present in the majority of patients with CMT, though it may only be evident as high arches. In a few patients, normal arches or even flat feet may be found.<sup>5</sup> Pes cavus and hammer toes are characteristic of CMT but are not specific. It can also develop with other forms of chronic inherited neurologic dysfunction beginning during childhood, when bone growth is still active.<sup>6,7</sup> Occasionally, in longstanding acquired neuropathies developing in adult life, the

appearance of the feet can mimic mild pes cavus. Pes cavus will sometimes be seen in patients without neuropathy or other neurologic deficit. Nevertheless, pes cavus remains a very important clinical clue that a neuropathy may be due to an inherited process. Wasting of foot and distal lower extremity muscles develops over time and may produce the classical "inverted champagne bottle" appearance. Some severely affected patients will develop scoliosis, but this is less common in CMT than in inherited muscle disease, where weakness of trunk muscles is a greater problem. In the demyelinating forms of CMT, nerve hypertrophy may be visible and palpable in nerves that are superficially located, such as the greater auricular nerve.

### CMT CLASSIFICATION

Early diagnostic characterization of CMT relied on clinical, electrophysiological and inheritance patterns to divide this disorder into logical subgroups.<sup>5,8-10</sup> Dyck and Lambert's<sup>5</sup> classification divided the hereditary motor and sensory neuropathies (HMSN) into HMSN I, II, III, IV, V, VI, VII and X (Table 1).

By the early 1980s, it was clear that multiple genetic abnormalities lead to similar neuropathy phenotypes, such as HMSN I. The earlier HMSN classification was modified to include linkage to chromosome 17 (HMSN IA), chromosome 1 (HMSN IB), the X chromosome (HMSN X) and unlinked kinships (HMSN IC, etc.). As it became clear that the typical HMSN I and II clinical and



Figure 1: Pes cavus. Twenty-year-old male with CMT 1A. This patient has high plantar arches with hammer toes and atrophy of foot muscles

**Table 1: Dyck and Lambert classification of hereditary motor and sensory neuropathy (HMSN)<sup>5</sup>**

| Neuropathy Type | Key Neuropathy Features   |
|-----------------|---|
| HMSN I          | Autosomal dominant inheritance with low NCV*  |
| HMSN II         | Autosomal dominant inheritance with normal or low normal NCV                        |
| HMSN III        | Probable autosomal recessive with very low NCV and very severe clinical abnormality |
| HMSN IV         | Refsum's syndrome   |
| HMSN V          | Neuropathy with spastic paraplegia  |
| HMSN VI         | Neuropathy with optic atrophy   |
| HMSN VII        | Neuropathy with retinitis pigmentosa  |

\*Nerve conduction velocity

electrophysiological features may be seen in patients without autosomal dominant inheritance, the classification scheme was used by some to include patients with nondominant inheritance patterns.<sup>11</sup> Recessive and sporadic inheritance can be difficult to ascertain, depending on how intensively families are studied and the certainty of parentage. Dyck<sup>12</sup> demonstrated that intensive evaluation of families could demonstrate unexpected inherited neuropathy in asymptomatic or minimally symptomatic family members. Nevertheless, recessive inheritance in patients with features of HMSN I and II, from thoroughly assessed kindreds, were well described in the premolecular genetic era.<sup>13</sup>

## MOLECULAR CONTRIBUTIONS TO CMT CLASSIFICATION

The first significant advance toward the current understanding of the molecular basis for CMT came with linkage of families to the Duffy locus on chromosome 1.<sup>14,15</sup> Linkage to the Duffy locus

was designated HMSN IB. Several other families were found to link to chromosome 17p,<sup>16</sup> designated HMSN IA; some families showed linkage to neither loci.<sup>17</sup> The families unlinked to chromosome 1 or 17 were given the designation HMSN IC, though how many additional loci will be discovered for the type I phenotype is not known. Subsequently there has been an explosion of molecular information about the various CMT subtypes. It has become apparent that the classification of CMT needs to incorporate clinical, electrophysiological and molecular features. The current diagnostic classification scheme has evolved using a hybrid of earlier eponyms and Dyck and Lambert's scheme (Table 2).

The molecular abnormalities associated with CMT subgroups exhibiting presumed primary myelin dysfunction, suggested by low nerve conduction velocity (NCV), revolve around abnormalities of four key gene products (Table 3). Abnormalities of chromosome 17p11.2-12 encoding peripheral myelin protein 22 (PMP22), 1q22 encoding myelin P<sub>0</sub> protein, Xq13-22 encoding connexin-32 (Cx32) and 10q21.1-22.1 encoding early growth response 2 (EGR2) produce variable phenotypic presentations of neuropathy predominantly with demyelinating features. These proteins are associated with myelin development and function but it is clear that in severely affected myelinated fibres, axonal degeneration will also occur.<sup>18,19</sup> As noted below, neuropathies associated with Cx32 mutations may have the electrophysiologic features of an axonal or demyelinating neuropathy and the primary process leading to nerve pathology is less certain.

PMP22 is present in peripheral nervous system compact myelin and constitutes up to 5% of the total myelin protein content. Its role in myelin function and stability are not completely understood but it contributes to the initial steps of myelin production and maintenance of myelin in

**Table 2: Current classification of Charcot-Marie-Tooth disease and related neuropathies**

| Neuropathy Type            | Key Neuropathy Features   |
|----------------------------|---|
| CMT 1                      | Dominantly inherited with low NCV*  |
| CMT 2                      | Dominantly inherited with normal or low normal NCV                          |
| CMT X                      | X-linked inherited  |
| HNPP**                     | Dominantly inherited with focal nerve lesions                               |
| Dejerine-Sottas syndrome   | Variable inheritance with very low NCV and severe disability                |
| Congenital Hypomyelination | Sporadic inheritance with extremely low NCV and extremely severe disability |
| CMT 4                      | Recessively inherited CMT   |

\*Nerve conduction velocity, \*\*Hereditary Neuropathy with Liability to Pressure Palsies

**Table 3: Neuropathies associated with inherited myelin gene defects**

| Myelin Gene Defect                   | Neuropathy          |
|--------------------------------------|---------------------|
| PMP22                                |                     |
| duplication                          | CMT 1A              |
| homozygous duplication               | DSS                 |
| deletion                             | HNPP                |
| point mutation                       | DSS                 |
| Myelin P <sub>0</sub> point mutation | CMT 1B<br>DSS<br>CH |
| Connexin-32 point mutation           | MT X                |
| EGR2 point mutation                  | CMT 1<br>DSS<br>CH  |

Abbreviations used: Charcot-Marie-Tooth (CMT), Dejerine-Sottas syndrome (DSS), congenital hypomyelination (CH), peripheral myelin protein 22 (PMP22), hereditary neuropathy with liability to pressure palsies (HNPP), early growth response 2 (EGR2)

peripheral nerves.<sup>20</sup> P<sub>0</sub> protein is the major protein component in peripheral myelin and is responsible for adhesion of compact myelin.<sup>21</sup> Cx32 is a membrane spanning gap-junction protein that is present in paranodal loops and Schmidt-Lanterman incisures of central and peripheral nervous system myelin.<sup>22</sup> Connexins form channels that allow diffusion of ions and other molecules between joined cells. Cx32 is likely important for cell-cell interactions between axons and Schwann cells.<sup>23</sup> The most recent gene product found to be associated with demyelinating neuropathies is EGR2.<sup>24</sup> EGR2 is a transcription factor involved in gene expression. It contributes to the maturation of Schwann cells leading to peripheral axonal myelination.<sup>25</sup> EGR2 mutations are uncommon but already it has become clear that different missense mutations will lead to variable demyelinating neuropathy patterns, including CMT 1,<sup>24,26</sup> Dejerine-Sottas syndrome (DSS),<sup>27</sup> and congenital hypomyelination (CH) neuropathy.<sup>24</sup> Most EGR2 mutations have been dominant or sporadic mutations, though recessive inheritance has been described.<sup>24</sup>

There are likely several factors that determine the severity of neuropathy in these demyelinating disorders. For some phenotypes associated with molecular abnormalities of the same gene, gene dosage appears to be important. The neuropathies

associated with PMP22 gene abnormalities provide a good example of this gene dosage effect. The level of expression of the PMP22 gene in a patient will dictate the pattern of neuropathy. With one copy of the gene, as occurs with PMP22 deletion, the patient develops HNPP, usually the mildest phenotype of PMP22-related neuropathies. HNPP patients with the deletion have reduced expression of PMP22 in peripheral nerves.<sup>28</sup> In some HNPP families a frame shift point mutation in the PMP22 gene results in loss of function equivalent to the common deletion, indicating that a reduction in PMP22 dosage is necessary and sufficient for this phenotype.<sup>29-31</sup> Possessing two copies of the gene is normal. With three copies, resulting from PMP22 duplication, the patient develops CMT 1A. Immunohistochemical and immunoelectron microscopic studies have demonstrated increased PMP22 expression in CMT 1A due to the chromosome 17p11.2-12 duplication;<sup>32,33</sup> and increased PMP22 messenger RNA has been found in nerve biopsy specimens.<sup>34</sup> These findings provide clues to the gene dosage effect, whereby increased expression of PMP22 (due to the extra functioning gene copy) leads to an excess of PMP22 in the Schwann cell. It seems clear that the balance of PMP22 expression, reduced in HNPP and increased in CMT 1A, is important in the pathogenesis of these disorders. In CMT 1A, hypermyelination may be an important early stage in the development of eventual demyelination and axon loss,<sup>35</sup> though the precise mechanisms are not understood. Even greater overexpression of the PMP22 gene, as would be expected with homozygous inheritance of the PMP22 duplication from two CMT 1A parents, leads to a more severe phenotype, suggestive of DSS.<sup>36</sup>

Point mutations of the PMP22 and P<sub>0</sub> genes will produce a variety of neuropathy patterns and some will be due to gene underexpression, as in the case of HNPP associated with PMP22 mutation. However, toxic gain of function changes in the gene product have the potential to produce more severe phenotypes, such as DSS and CH.<sup>37</sup> Other unidentified factors presumably play a role, as family members with identical genotype may have markedly variable phenotype.

## CMT 1A

### A) Clinical

The commonest sub-group of CMT is type 1. In a large group of unrelated CMT patients, 84% had electrophysiologic features of CMT 1 and, of

these, 68% had the PMP22 duplication of CMT 1A.<sup>38</sup> The CMT 1A duplication produces a variable clinical presentation with a broad range of clinical severity, evident even within individual families.<sup>5,39</sup> Despite the existence of severely disabled patients with CMT 1A, the majority of patients with the trait are only mildly to moderately disabled. Many patients will be asymptomatic, though careful examination usually demonstrates signs such as loss of ankle reflexes and foot deformity. Birouk<sup>39</sup> found that in a group of 119 patients with the 17p11.2-12 duplication, about 25% were asymptomatic and that a very small percentage had severe disability. The onset of patient awareness of symptoms was in the first decade in 50% and in the first two decades in 70% of the patients. However, some patients did not experience symptoms until their seventh and eighth decades. In children, difficulty running is often the first symptom.<sup>5,39</sup> The age of onset of symptoms does correlate with eventual severity and the disease is slowly progressive.<sup>39</sup> The chromosome 17p11.2-12 duplication will produce atypical presentation in some. In a group of 61 patients with the duplication, eight had the Roussy-Lévy syndrome (CMT plus essential tremor), three had pyramidal signs, one had muscle cramps and calf hypertrophy and one had a predominantly sensory disorder.<sup>40</sup> The new mutation rate of the PMP22 duplication is about 10%,<sup>41</sup> which will account for the lack of family history in some patients. Some patients will develop CMT 1A from a PMP22 point mutation.<sup>42</sup>

## **B) Electrophysiology**

Marked slowing of motor nerve conduction velocities is a hallmark of CMT 1, historically serving as a basis for differentiation of the demyelinating CMT 1 and axonal CMT 2 subtypes.<sup>9,43</sup> In individuals with CMT 1, Harding and Thomas<sup>11</sup> found mean median and peroneal motor velocities of 21.1 and 16.6 m/s respectively. Comparing median motor conduction velocities in patients with CMT 1 and 2, they found that 38 m/s was a useful value in separating these groups. More recent studies in families with documented CMT 1A due to 17p11.2-12 duplications have shown a similar degree of slowing.<sup>19,39,44-46</sup> Occasional outliers with documented duplications have median velocities above 40 m/s.<sup>47</sup> Motor conduction velocities may be quite variable within individual kindreds, with a range of greater than 20 m/s in some families.<sup>47</sup> Demyelination is also manifested by prolonged distal motor latencies<sup>39</sup> and prolonged F-wave latencies.<sup>47,48</sup>

Conduction slowing appears very early in life. Penetrance with respect to slowing is complete and may be evident as early as two years of age.<sup>48,49</sup> The electrophysiologic changes are present in patients with the PMP22 duplication, regardless of the presence or severity of symptoms. In a longitudinal study, Garcia<sup>48</sup> followed 12 children with CMT 1A, performing clinical and electrophysiologic assessments prior to age five and again approximately seven years thereafter. Children as young as one month of age were included. All children with the duplication displayed nerve conduction abnormalities by age two. Changes were usually present even earlier, with prolonged distal motor latencies preceding conduction slowing in two infants less than 12 months of age. Motor and sensory NCV progressively dropped over time, stabilizing by age five; a finding noted by others.<sup>47,49</sup> A reduction in compound muscle action potential amplitude was also an early finding, present in recordings from the foot in 50% of children by age five.

Uniformity of motor conduction slowing has been emphasized as characteristic of CMT 1.<sup>19,50-52</sup> The underlying demyelinating process affects all myelinated fibres to a similar degree along the entire length of the nerve. Therefore, nerve conduction studies show similar conduction slowing in proximal and distal nerve segments, and among different nerves. Temporal dispersion and conduction blocks are absent. These findings are diagnostically useful in differentiating CMT 1 from acquired (and some inherited) demyelinating neuropathies in which nonuniform slowing is prominent (Figure 2).<sup>51,53</sup> Although a few older series reported block in CMT 1 patients,<sup>54,55</sup> recent large series generally have not confirmed this, instead emphasizing uniformity of slowing. Kaku<sup>52</sup> studied 129 patients with CMT 1, including 82 with a confirmed chromosome 17p11.2-12 duplication. A similar reduction in motor NCV was found comparing adjacent upper limb nerves, contralateral nerves and proximal and distal segments of individual nerves. Dispersion and conduction blocks were rare. Using relatively conservative criteria (50% amplitude difference with proximal versus distal stimulation) dispersion or block was found in only 5.3% of nerve segments studied. In most instances, this was found in the setting of markedly reduced compound muscle action potential amplitude, suggesting that the observed amplitude change reflected phase cancellation rather than true block. Where block occurred with normal motor amplitudes, the affected site was usually

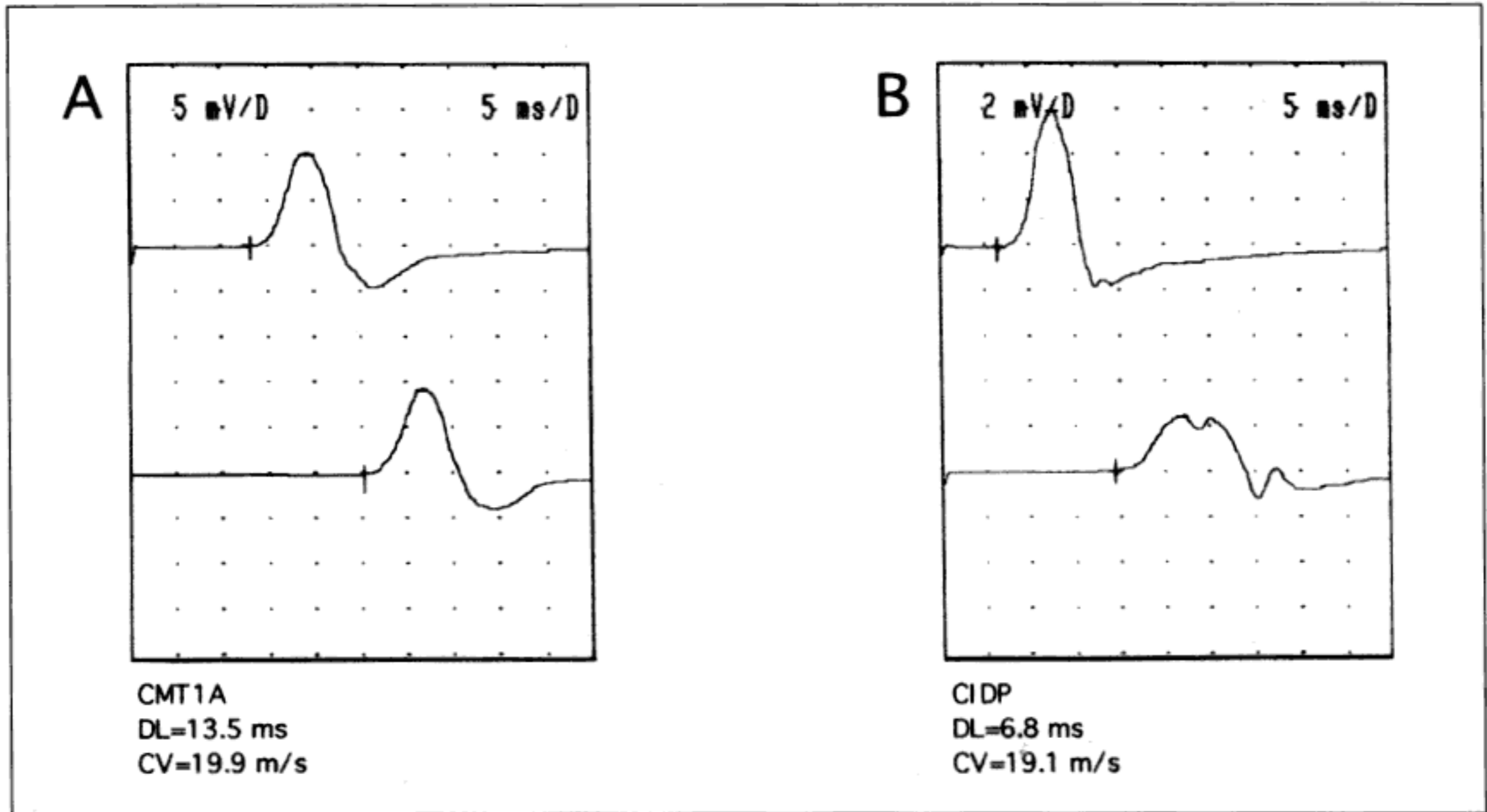


Figure 2: Uniform versus nonuniform conduction slowing of median motor nerve conduction in demyelinating neuropathies. Compound muscle action potentials were recorded from abductor pollicis brevis with stimulation at the wrist (top traces) and elbow (bottom traces). Panel A shows uniform slowing along the forearm segment in a patient with CMT 1A. Panel B shows nonuniform slowing with temporal dispersion in a patient with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). CV=conduction velocity; DL=distal latency.

one of common nerve compression (such as the fibular neck). The authors interpreted these findings as indicative of a high degree of uniformity of slowing. Although sensory NCV are less well-studied, they are also reduced in a uniform fashion.<sup>19</sup>

Sensory, and to a lesser degree, motor responses may be absent. Commonly, no sensory potentials can be recorded from the lower limbs and, in advanced cases, from the upper limbs as well. Motor responses are also often absent recording from foot muscles.

Weakness and clinical disability do not appear to correlate well with NCV,<sup>19,46</sup> although a few studies have noted a correlation.<sup>44,56</sup> Conduction velocities change little over many years despite progressive neurologic disability.<sup>19,46</sup> Among eight members of a family studied at a 22-year interval, Killian<sup>45</sup> noticed a modest mean reduction in motor NCV of 2.2 m/s in the median nerve and 3 m/s in the peroneal nerve. These findings are consistent with the pathological observation that demyelination is most active in the first five years of life but relatively quiescent thereafter.<sup>57</sup> Disability correlates better with compound muscle action potential amplitude.<sup>19,44,46,56</sup> Motor amplitudes gradually decrease over time, in keeping with ongoing axon loss. Median nerve

motor unit number estimates also correlate with thenar weakness.<sup>19</sup> Sensory deficits have been correlated with sensory nerve action potential amplitudes but not sensory NCV.<sup>19</sup> These findings support the notion that clinical severity relates to underlying axon loss rather than to conduction slowing.

### C) Pathology

Until recently, most information was derived from undifferentiated CMT 1 cases. More recently, pathologic findings in patients with 17p11.2-12 duplications have been reported. Endoneurial area is increased.<sup>43,58</sup> Onion bulbs, concentric collections of Schwann cell processes surrounding a myelinated or nonmyelinated axon or a regenerating cluster of axons, are characteristic (Figure 3). Overlapping lamellae are separated by collagen bundles. Onion bulbs are poorly developed in childhood, becoming more prominent over time.<sup>59,60</sup> In advanced cases with severe axon loss, onion bulbs are less prominent, with progressive replacement of the endoneurial space by collagen.<sup>40</sup>

Morphometric studies reveal a reduction in myelinated fibre density.<sup>43,58,61</sup> This reduction correlates with clinical severity.<sup>40</sup> The size

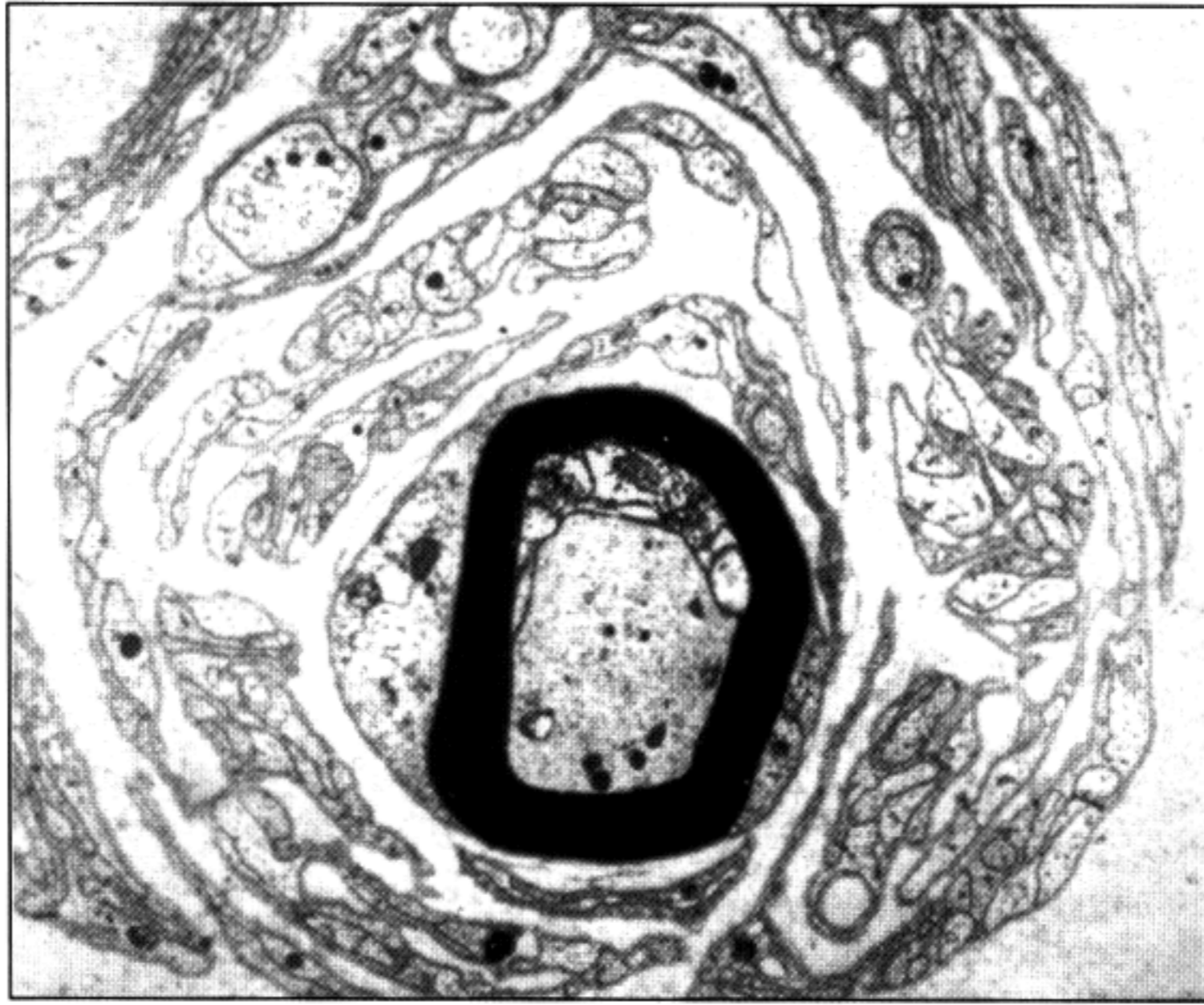


Figure 3: Onion bulb formation. Electron micrograph of sural nerve from an individual with CMT 1A showing characteristic concentric Schwann cell cytoplasmic processes surrounding a myelinated axon.

distribution of myelinated fibres is altered. Early in life there is a modest loss of small fibres<sup>57</sup> with a more prominent reduction in large fibres occurring later.<sup>43,58</sup> Unmyelinated fibres are normal in number.<sup>58,62</sup>

Transverse sections and teased fibre studies reveal demyelination and remyelination involving some fibres, and areas of thin myelin are frequently observed.<sup>43,58</sup> Segmental demyelination is most active before age five, slowing thereafter.<sup>63</sup> Despite frequent areas of myelin remodeling, the mean G ratio (axon diameter:total fibre diameter) is decreased in young patients with CMT 1A,<sup>60</sup> becoming increased later in life.<sup>40</sup> Although axonal atrophy has been suggested as a basis for the initial changes,<sup>64,65</sup> it now seems likely that these abnormalities of myelin thickness reflect a state of hypermyelination.<sup>35,60</sup>

## CMT 1B

### A) Clinical

The less common  $P_0$  protein related neuropathies vary from the severe DSS and CH phenotypes to CMT 1B, which clinically is often indistinguishable from CMT 1A. Multiple  $P_0$  protein mutations have been detected and the site of the mutation and its consequent effect on  $P_0$  function does correlate with disease severity.<sup>37</sup> CMT 1B will vary from a mild neuropathy, as is

often seen in CMT 1A, to a condition that approaches the severity of DSS.<sup>66</sup>

### B) Electrophysiology

The electrophysiologic findings in CMT 1B are less well-documented as large groups of patients are not available for study. Limited information suggests that conduction abnormalities may be more severe than in CMT 1A. Bird<sup>67</sup> described the findings in the original CMT 1B family followed over a 20-year period. Mean motor NCV was in the 9-11 m/s range and lower limb motor responses were frequently unobtainable. Similarly low velocities were described in the original family with Roussy-Lévy syndrome, shown to possess a  $P_0$  mutation. All upper limb motor NCVs in this family were under 16 m/s.<sup>68</sup> Interpretation of reported electrophysiologic abnormalities in patients with  $P_0$  mutations is complicated by the variable clinical phenotype, which includes individuals with DSS and CH; very slow NCV in patients reported as having CMT 1B may reflect overlap with the DSS and CH phenotypes.

### C) Pathology

Similar to electrophysiology, the pathology of CMT 1B has not been described in as much detail as CMT 1A. Bird<sup>67</sup> reported the pathologic

findings in CMT 1B patients with the C270A P<sub>0</sub> transversion. Sural nerve biopsy changes were similar to those described for CMT 1A. A few fibres with focal myelin reduplication (tomaculae) were found in one patient. Myelin thickness was variably increased or decreased. One patient underwent autopsy, revealing degeneration of the dorsal columns (fasciculus gracilis) and chromatolysis and loss of some anterior horn cells. Plante-Bordeneuve<sup>68</sup> described sural nerve biopsy findings in three patients with the Roussy-Lévy syndrome due to a P<sub>0</sub> Asn131Lys (substitution of lysine for asparagine at the 131 position) point mutation. Focal myelin reduplication was present in all patients to some degree. Also in contrast to CMT 1A, onion bulbs were absent in two patients. Gabreels-Festen<sup>69</sup> identified two contrasting patterns of pathology in patients with P<sub>0</sub> mutations. Among seven patients with varying mutations, four demonstrated uncompacted myelin, typically involving the innermost layers of the myelin sheath, and widening of the major dense line. Onion bulbs were prominent in this group. In contrast, three patients showed normal compact myelin but frequent focal myelin reduplication. The mechanism of reduplication is unclear; however, the changes in compact myelin are of interest, given the known role of P<sub>0</sub> as a homophilic myelin adhesion molecule.<sup>70</sup>

### Roussy-Lévy syndrome

The original description by Roussy and Lévy was a large kindred with typical clinical features of CMT, autosomal dominant inheritance and associated essential tremor.<sup>71</sup> Later descriptions of HMSN I included Roussy-Lévy syndrome patients under that general classification, as the clinical and electrophysiologic features of the neuropathy component resembled HMSN I.<sup>5</sup> It has been hypothesized that the genes for the neuropathy and essential tremor are closely linked and in some kindreds may be concurrently abnormal. Modern molecular information has improved our understanding of the tremor component of CMT. Roussy-Lévy syndrome is not due to a single genetic defect. A subset of CMT 1A patients with the chromosome 17p11.2-12 duplication will have a Roussy-Lévy syndrome pattern,<sup>40</sup> but the original Roussy and Lévy family has a missense point mutation in the P<sub>0</sub> protein gene.<sup>68</sup> Tremor has also been reported with CMT X.<sup>72</sup> The coincidental expression of essential tremor and CMT may not have anything to do

with a specific gene abnormality, though a separate genetic defect producing essential tremor may be present in some kindreds. In many patients, the tremor may be merely a clinical manifestation of the neuropathy, as in chronic inflammatory demyelinating polyradiculoneuropathy and other acquired demyelinating neuropathies an essential-like tremor may develop.<sup>73,74</sup> The presence of tremor is not currently a helpful sign in distinguishing CMT genotype.

## CMT 2

### A) Clinical

Patients with a typical dominantly inherited CMT phenotype who have electrophysiologic features of a primarily axonal disorder have CMT 2. Typical patients with CMT 2 have a similar clinical appearance to patients with CMT 1, though some differences have been detected. The CMT 2 patients tend to present with symptoms later in life than CMT 1 and the degree of atrophy and weakness in distal lower extremity muscles may be greater with relatively less weakness of intrinsic hand muscles.<sup>8</sup> Nerve hypertrophy is absent. Similar to CMT 1, multiple genetic abnormalities have been described producing the CMT 2 phenotype but less is known about the gene products of loci identified to date. Families with CMT 2 have been linked to chromosome 1p35-p36 (CMT 2A),<sup>75,76</sup> 3q13-q22 (CMT 2B),<sup>77,78</sup> 7p14 (CMT 2D)<sup>79</sup> and 8p21 (CMT 2E).<sup>80</sup> The CMT 2C kindred has not yet been linked to a chromosomal region. The CMT 2E trait has been associated with a mutation in the neurofilament-light gene (NF-L), which likely leads to impairment of axonal transport and axonal diameter. Some CMT 2 families have special features, such as mutilating ulcers (CMT 2B),<sup>78</sup> diaphragm and vocal cord paralysis which can lead to early death (CMT 2C)<sup>81</sup> and greater weakness of hands than legs (CMT 2D).<sup>79</sup> However, most CMT 2 families have typical CMT features and would be difficult to distinguish from CMT 1 based on clinical assessment alone without electrophysiologic information.

Myelin protein gene abnormalities can occasionally lead to a disorder that appears primarily axonal. In CMT 1 axonal neurofilament numbers are reduced out of proportion to myelin sheath thickness<sup>65</sup> and Schwann cells may influence axonal repair through nerve growth factor support<sup>82</sup> and other influences on cytoskeletal elements.<sup>23</sup> The CMT 2 phenotype

has been associated with mutations of myelin proteins such as  $P_0$  gene mutations.<sup>83-85</sup> A Thr124Met mutation on myelin  $P_0$  may be particularly important as multiple families with this mutation have shown features of CMT 2.<sup>85</sup> As well, CMT X electrophysiology and nerve pathology can have the appearance of an axonal process.

## B) Electrophysiology

The EMG findings in CMT 2 are not distinctive and reflect an axonal sensorimotor polyneuropathy. CMT 2 is differentiated from distal spinal muscular atrophy (which it may resemble clinically) by the presence of sensory conduction abnormalities.<sup>86</sup> Compound muscle action potentials are reduced in amplitude or unobtainable but conduction velocities are normal or only mildly reduced.<sup>8</sup> In Dyck's<sup>8</sup> series, motor NCV were within normal limits in most affected subjects, although slightly reduced as a group when compared to unaffected family members. Harding and Thomas<sup>11</sup> noted that CMT 2 motor NCV exceeded 38 m/s. Sensory nerve action potentials are reduced or unobtainable.<sup>8</sup> It should be noted that these changes are nonspecific, and may also be seen in patients with CMT X and CMT 4. Electrodiagnostic studies are thus mainly useful in excluding CMT 1.

CMT 2 kindreds may include individuals with rather low NCV, despite most affected subjects having velocities in the normal range. Timmerman<sup>75</sup> reported one individual in an otherwise typical CMT 2 family with motor conduction velocities in the 25 m/s range. Patients with "intermediate" conduction velocities (i.e. 30-40 m/s) may be identified, in whom assignment to CMT 1 versus CMT 2 would be difficult in isolation. Possibilities include CMT X<sup>87-90</sup> and CMT 2. Electrodiagnostic study of family members will usually clarify this.

Needle examination demonstrates evidence of chronic de- and reinnervation. Motor unit recruitment is reduced, with increased motor unit duration and amplitude. Motor units may appear polyphasic but are often of simple configuration and high amplitude given the indolent nature of the process. Fibrillations are often present in distal muscles.

## C) Pathology

These disorders are less well-characterized than CMT 1 and the pathology is less distinctive. Myelinated fibre density is reduced, especially

distally.<sup>62</sup> The size distribution may be altered, with a relative reduction in large fibres.<sup>58,62</sup> Small myelinated fibres are normal or increased in number relative to controls, particularly in proximal nerve segments, due in part to the presence of regenerating axons.<sup>58,62</sup> Axonal atrophy is present.<sup>91</sup> Morphometric studies have shown a shift in the small fibre peak to smaller diameters than controls, in keeping with axonal atrophy, regeneration or both. Endoneurial area is normal or slightly increased.<sup>58</sup> Occasional small onion bulbs are present. Teased fibres may show evidence of myelin re-modeling.

With the sub-classification of CMT 2 based on genetic markers, more distinctive pathologic changes may eventually be identified. In a German kindred with CMT 2 associated with cardiomyopathy, sural nerve biopsy demonstrated focal axonal swellings containing accumulations of neurofilaments.<sup>92</sup> This family appeared clinically and genetically distinct from giant axonal neuropathy, in which similar pathology is seen.

## CMT X

### A) Clinical

Typical CMT with more severe expression in males than females characterizes CMT X. The age of onset of symptoms is usually younger in affected males than in female heterozygous expressors. At least half of affected males have recognized symptoms in the first two decades, whereas less than a third of females note symptoms by this age.<sup>89</sup> Males have significantly greater muscle wasting, loss of reflexes and disability. However, there is overlap in the severity of manifestations between males and females of different kindreds. The intra-family comparison is an important yardstick, which may raise consideration of X-linked inheritance. Variable expression of CMT within families is common in CMT 1 and 2 and without large kindreds it may not always be obvious that the inheritance is X-linked. Absence of male-to-male transmission of a dominantly inherited CMT trait should always raise the consideration of CMT X.<sup>93</sup> The pedigree in Figure 4 demonstrates the inheritance of a maternal mutant Cx32 allele by a son and daughter.

CMT X is associated with point mutations in the gap-junction protein Cx32 located at Xq13-22.<sup>94</sup> The disorder is almost always inherited dominantly. A *de novo* Cx32 mutation has been

described and this should be considered in seemingly sporadic CMT cases.<sup>95</sup> Recessive inheritance has been reported,<sup>96</sup> though recessive inheritance should not be assumed without careful clinical and electrophysiological assessment of female carriers, due to the often-mild expression. Currently, around 160 mutations have been reported with some phenotypic variability between families represented by different mutations. There is some correlation between the location of the mutation on the Cx32 gene and the character of the neuropathy. Missense mutations within regions of the protein less critical to Cx32 function lead to a milder neuropathy. Nonsense mutations are associated with earlier onset of disease expression and more severe neuropathy.<sup>89,90</sup> About 10% of CMT patients have X-linked inheritance, making CMT X the second most common form of CMT<sup>97</sup> after CMT 1A.

The Cx32 defect has produced clinical manifestations restricted to the peripheral nervous system in the majority of patients reported to date, despite the presence of Cx32 in oligodendrocytes. Mice without the Cx32 gene develop a peripheral neuropathy but central myelinated fibres are unaffected.<sup>98</sup> Asymptomatic electrophysiological abnormalities within the central nervous system have been reported in some patients<sup>99,100</sup> but a comprehensive assessment of CNS function is not available for the majority of reported CMT X patients. It seems unlikely that the CNS consequences of this gene defect will be significant given the experience with the disorder to date.

### B) Electrophysiology

Motor conduction slowing is typical of CMT X but this entity has caused confusion in part due to the common occurrence of intermediate velocities falling between the ranges typical for CMT 1 and CMT 2.<sup>87,89,90,101</sup> Men generally show slower velocities than women.<sup>87,89,90</sup> Interestingly, there is some disagreement about which group displays the "intermediate" velocities. For example, Nicholson<sup>87</sup> described marked slowing in affected males and intermediate velocities in females, while Hahn<sup>90</sup> described intermediate velocities in males with borderline normal values in women. Distal motor latencies are typically prolonged. Compound muscle action potential amplitudes are often reduced. Sensory potentials are small or unobtainable; sensory conduction changes probably show less difference between affected males and females than do motor changes.<sup>90</sup> Needle examination shows evidence of chronic

denervation and reinnervation, most marked in distal muscles.

Recent attention has focused on the occurrence of nonuniform conduction slowing in CMT X. This is manifested as heterogeneous slowing comparing multiple nerves and by the presence of dispersion.<sup>102,103</sup> Sural nerve biopsy in these cases has shown thin myelin and onion bulbs, in keeping with a chronic demyelinating process. However, nonuniform conduction slowing is not invariably found.<sup>90</sup>

The electrophysiologic features of CMT X are more likely to suggest an axonal disorder than one characterized by primary demyelination. However, some patients will have strong indicators of demyelination, such as slow conduction velocities and prolonged distal latencies. Differences in electrophysiologic findings of various studies have made it difficult to categorize CMT X based on usual parameters. The primary process leading to neuropathy in CMT X will be difficult to define using electrophysiologic criteria alone.

### C) Pathology

Typical nerve biopsy findings include a reduction in myelinated fibre density,<sup>89,90</sup> thinly myelinated fibres, many regenerating clusters, and low-grade axonal degeneration.<sup>90,104</sup> In the largest series, Hahn<sup>90</sup> described sural, superficial peroneal or deep peroneal (motor) biopsy changes in seven unrelated male patients with a variety of Cx32 mutations. There was mild to moderate loss of myelinated fibres, which appeared age-related. Frequent regenerating clusters and myelin remodeling were present. Onion bulbs were absent. Teased fibre studies revealed prominent paranodal demyelination with little segmental demyelination or active axonal degeneration. Electron microscopy revealed widening of the periaxonal space, Schmidt-Lanterman incisures and adaxonal Schwann cell cytoplasm. Axonal cytoskeletal changes were present with increased neurofilament content.

There has been disagreement as to whether CMT X is a primary demyelinating or axonal neuropathy. Previous reports have emphasized the axonal changes,<sup>75,89</sup> while others have described demyelination.<sup>102,103</sup> This issue has not been completely resolved. However, currently available evidence suggests that while the most prominent, consistent changes are axonal, some degree of demyelination is also present. Increasing evidence, including that from animal models<sup>105</sup> suggests that Cx32 is important in Schwann cell-

axon interactions and it may be most accurate to categorize this disorder as a disease of Schwann cells that leads to axonal loss and demyelination. The variability in reported findings may relate to the large number of Cx32 mutations described and to varying disease expression according to the specific mutation and resulting alteration in protein function.

## **Hereditary neuropathy with liability to pressure palsies**

### **A) Clinical**

Hereditary neuropathy with liability to pressure palsies is a familial disorder with a predisposition to develop compression and entrapment neuropathies. The condition has been recognized for almost 50 years<sup>106</sup> with clear descriptions, in the premolecular era of the clinical, electrophysiological and morphological features.<sup>107</sup> The disorder is dominantly inherited and most kindreds demonstrate a deletion of the 17p11.2-12 region containing the PMP22 gene.<sup>108</sup> In one group of HNPP families the prevalence of the 17p11.2-12 deletion was 68%. Affected family members of symptomatic patients are often asymptomatic or minimally symptomatic. Determining the inheritance of patients with suspected HNPP often requires detailed assessment of family members, as presence of the disorder may not be appreciated by affected family members.<sup>107</sup> The family history may also be truly negative due to rare sporadic cases from new mutations.<sup>109</sup> In some nondeletion families a loss of function point mutation in the PMP22 gene will produce the HNPP phenotype.<sup>29-31</sup>

Symptomatic HNPP patients may only become aware of their problem after developing a focal neuropathy from an episode of nerve compression or traction. From the history, the compressive insult is often seemingly minor. Common sites for traumatic or compressive nerve lesions are the median nerve at the wrist, ulnar nerve at the elbow, radial nerve at the humeral groove and peroneal nerve at the knee. However, HNPP patients will also develop lesions at less common sites of compression if the provocative factor is appropriate. The lesions usually recover in a few weeks to months, similar to most sporadic mild compression neuropathies. Without a provoking episode the patient is often not aware of the problem. An exception is carpal tunnel syndrome, which will often become symptomatic without any definite provoking event. Family members of patients with HNPP may have a history of carpal

tunnel syndrome as the only clue of their involvement.

The prevalence of HNPP was 16/100,000 in one population<sup>110</sup> but epidemiological data are sparse in this disorder. In the population studied, it was felt that the prevalence might have been underestimated due to HNPP's insidious nature and the failure of many patients to seek attention for typical symptoms. Variability in the phenotypic expression may also contribute to under-recognition, as patients without typical syndromes may not be tested appropriately. In a group of patients with multifocal neuropathies, a PMP22 deletion was found in patients with a typical presentation and in some with atypical features.<sup>111</sup> Atypical presentation of HNPP includes episodes of acute brachial neuropathy<sup>107,111-113</sup> and polyneuropathy.<sup>112,114</sup> The brachial plexus lesions of HNPP are painless, as opposed to inherited recurrent brachial neuropathy (hereditary neuralgic amyotrophy), which is typically heralded by severe pain and unaccompanied by nonbrachial conduction abnormalities. Patients with hereditary neuralgic amyotrophy do not have a chromosome 17p11.2-12 deletion,<sup>115</sup> but a locus has been identified in the chromosome 17q24-q25 region.<sup>116,117</sup> HNPP can produce a more diffuse polyneuropathy, sometimes severe and fulminant<sup>118,119</sup> but, in others, without a clear stepwise progression. Patients with polyneuropathy may be older, perhaps due to the coalescence of many focal lesions in distal nerves producing a diffuse symmetrical appearance.<sup>114</sup>

### **B) Electrophysiology**

The electrodiagnostic picture in HNPP reflects single or multiple focal compressive neuropathies at common entrapment sites. Focal conduction abnormalities are no different from those seen in entrapment neuropathies unassociated with HNPP. Nerve conduction studies demonstrate focal slowing, temporal dispersion and conduction block, alone or in combination.<sup>107,120,121</sup> With more severe or chronic focal lesions, axonal degeneration may develop, resulting in a reduced compound muscle action potential amplitude stimulating distal to the site of injury and evidence of denervation on needle examination. When axon loss is the major finding, localization of the site of nerve injury may not be possible.

These focal changes are often multiple and may be asymptomatic.<sup>122</sup> The disorder is often suspected through detection of multiple asymptomatic abnormalities at sites of common

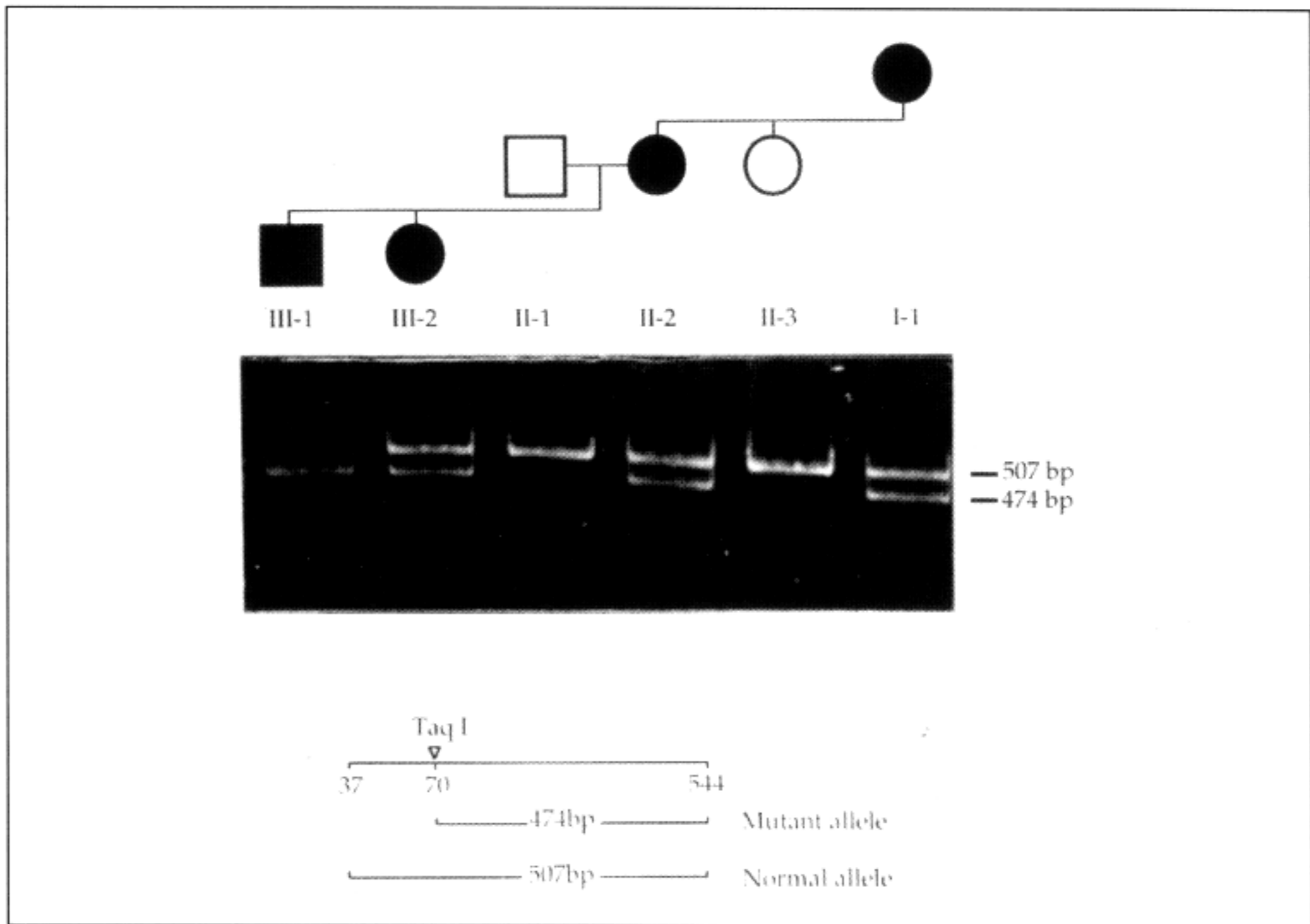


Figure 4: CMTX. The pedigree in the top panel demonstrates maternal transmission of a mutant connexin 32 gene to a son and daughter. This family was shown to have a codon 3 mutation in the connexin 32 gene by polymerase chain reaction amplification followed by TaqI restriction analysis. The G>C mutation in codon 3 creates a novel TaqI restriction site. The mutant allele was detected in patients III-1, III-2, II-2 and I-1 (middle panel) by the presence of a 474 base pair fragment (lower panel). [From Gupta S, Benstead T, Neumann P, Guernsey D. A point mutation in codon 3 of connexin-32 is associated with X-linked Charcot-Marie-Tooth neuropathy. *Hum Mutat* 1996;8(4):375-376. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.]

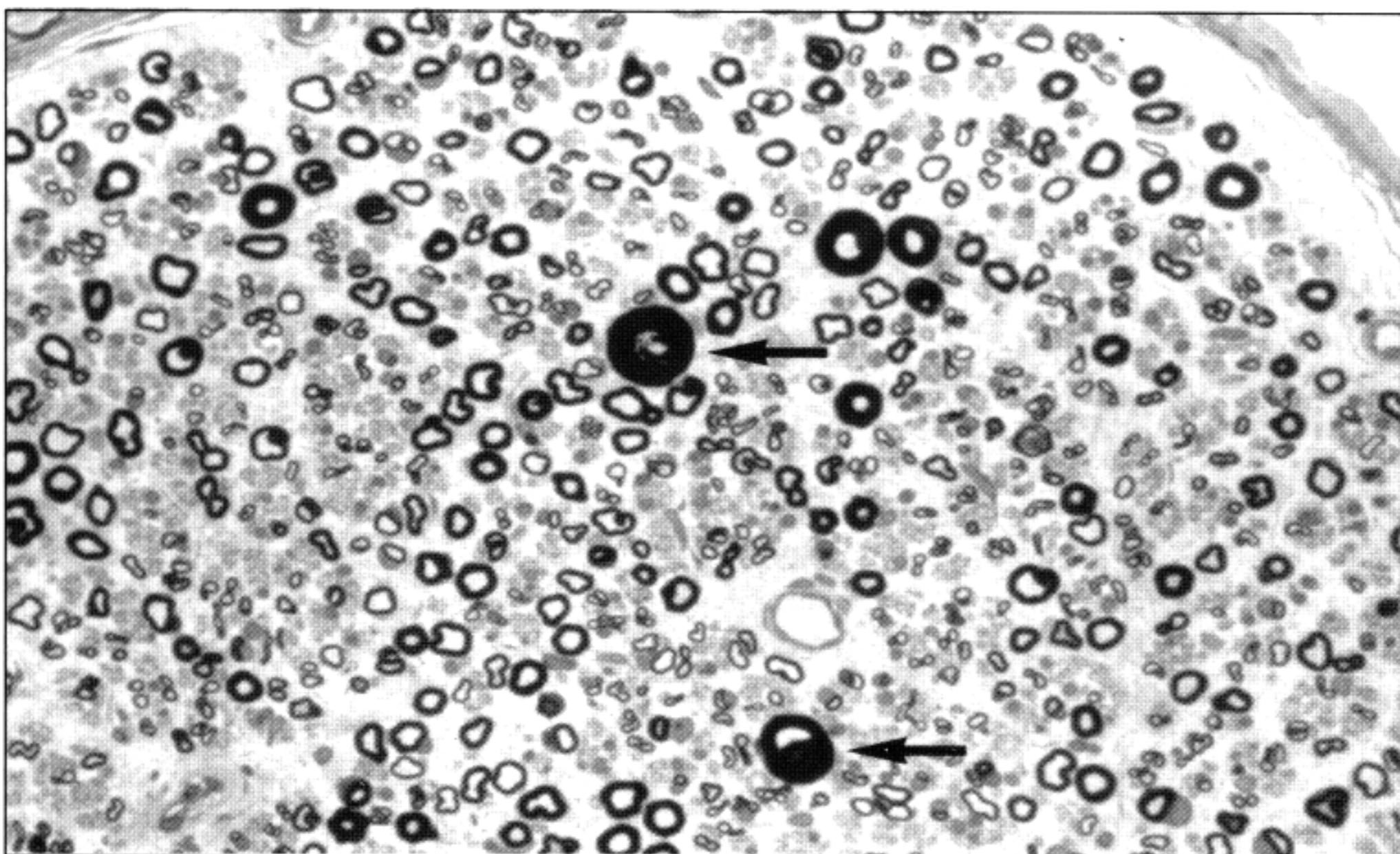


Figure 5: Hereditary neuropathy with liability to pressure palsies. Semithin section of sural nerve demonstrating several fibres within a fascicle surrounded by focal reduplication of the myelin sheath (arrows). (Methylene blue, 400X)

compression, found during evaluation of a single symptomatic lesion. With or without associated symptoms, conduction block may persist over a period of years.<sup>120</sup> The prevalence of conduction block in HNPP is unclear, as the frequency in published reports varies according to the definition of block used.<sup>121</sup>

Typically, focal lesions occur against a background of diffuse polyneuropathy. These generalized changes are characterized by diffuse slowing of sensory NCV,<sup>107,114,123</sup> prolonged distal motor latencies<sup>114,122,123</sup> and prolonged F latencies.<sup>114,123</sup> Evidence of a focal median neuropathy at the wrist is particularly common<sup>114,123</sup> but the characteristic prolongation of distal motor latencies is evident even if the median nerve is excluded.<sup>123</sup> This distal slowing is out of proportion to slowing in proximal segments, as illustrated by a low terminal latency index.<sup>123</sup> Notably, forelimb motor NCV is relatively spared.<sup>114,122,123</sup> Andersson<sup>123</sup> found reduced motor NCV in 31% of HNPP nerves studied but the overall mean motor velocity was normal. This contrasted with control groups with CIDP and diabetes, in whom motor slowing was significantly more frequent.

Given the potential difficulty in recognizing this pattern in patients in whom HNPP is not suspected, diagnostic criteria have been proposed. Verhagen<sup>124</sup> has proposed a formula combining changes in peroneal and ulnar motor NCV with the peroneal distal motor latency. Gouider<sup>125</sup> found that HNPP was likely when the following criteria are met: bilateral prolongation of median distal motor latencies, reduced median sensory NCV in the palm to wrist segment and either a prolonged peroneal distal motor latency or reduced peroneal motor NCV.

In patients with HNPP, diffuse conduction abnormalities are more prominent in cases due to PMP22 point mutations or insertions than in those with the more common 17p11.2-12 deletion. Lenssen<sup>29</sup> described six families with a heterozygous insertion of six nucleotides at nt276-281 of the PMP22 gene, resulting in a frame shift. Motor NCVs were slowed in the CMT 1 range and sural sensory responses were usually absent. The authors suggested these changes reflect not just reduced PMP22 expression but the additional detrimental effect of a truncated protein on Schwann cell function.

Overall, the electrophysiologic changes in HNPP are consistent with a background, predominantly sensory demyelinating polyneuropathy, with distal accentuation.<sup>122,123</sup>

## C) Pathology

Most reports describe sural nerve biopsy findings. Focal thickening of the myelin sheath is the most distinctive finding (Figure 5). These were first described by Behse,<sup>107</sup> who called them "sausages". They have also been called "tomaculae".<sup>126</sup> The tomaculae consist of redundant folds or loops of the myelin sheath, resulting in thickened segments best appreciated in semi-thin sections and teased fibre preparations.<sup>107,126,127</sup> The redundant loops are continuous with internodal myelin.<sup>127</sup> Although ultrastructural studies usually demonstrate normal myelin layering, uncompacted lamellae involving the innermost layers of the myelin sheath have been described.<sup>127</sup> Focal myelin reduplication is not specific to HNPP, and has also been described in CMT 1A,<sup>40</sup> CMT 1B, and CMT 4B (see below). HNPP pathologic changes also include segmental demyelination and remyelination.<sup>107,127</sup> Axonal diameter is reduced adjacent to tomaculae.<sup>128</sup>

## Dejerine-Sottas Syndrome

Dejerine-Sottas syndrome is a rare, severe neuropathy with onset very early in life and loss of motor function such as walking at a young age. It is often associated with scoliosis and nerve hypertrophy is usually easily detectable. Early reports suggested recessive inheritance but modern molecular studies have shown most DSS patients have sporadic point mutations in the genes for P<sub>0</sub> protein,<sup>37,129,130</sup> PMP22<sup>131,132</sup> or EGR2.<sup>27</sup> A phenotype more severe than CMT 1, suggestive of DSS, can also occur with homozygous expression of CMT 1A or CMT 1B. This was described prior to linkage studies by Killian<sup>133</sup> in 1979 and later once the gene abnormalities were recognized.<sup>36,134</sup> Homozygous 17p11.2-12 duplication patients have four copies of the PMP22 gene resulting in greater over-expression of the gene than occurs in CMT 1A, where three copies of the gene are present. These patients have more severe neuropathy than their parents and some have NCV less than 10 m/s but the Killian patients did not exhibit the severity of neuropathy typical of the DSS patients reported by Dyck, in whom the ability to walk independently was lost in childhood.

The electrodiagnostic characteristics of DSS were described by Benstead.<sup>135</sup> This study predated identification of the underlying genetic abnormalities outlined above, and diagnosis was based on clinical criteria. Eleven unrelated patients with a mean age of 17 years were reported.

Nerve conduction abnormalities were qualitatively similar but more severe than those of a control group with CMT 1. Upper limb motor amplitudes were severely reduced, typically to 10% of the lower limit of normal. Motor NCV was invariably less than 6 m/s, with uniform slowing comparing multiple nerves. Distal motor latencies were severely increased to 6-7 times normal values. Dispersion was sometimes noted with proximal stimulation, although in association with very low amplitude compound muscle action potentials. Sensory responses were almost always unrecordable. Similar severely reduced NCVs were noted by others.<sup>5,59</sup>

A recent statement of criteria for DSS (or HMSN III) has become very important, as evidence for the genetic heterogeneity for the disorder has appeared. It will not be possible to diagnose the disorder merely on the basis of a characteristic DNA abnormality, as several exist.<sup>136</sup> Gabreels-Festen proposed the HMSN III (DSS) designation be reserved for patients with congenital or early childhood onset, NCV < 7 m/s, virtual absence of myelin on biopsy and basal lamina onion bulbs.

### **Congenital hypomyelination neuropathy**

Lyon<sup>137</sup> and others<sup>138-140</sup> described a congenital hypomyelination neuropathy with features similar to DSS but possibly worse, in that some patients never walked, which is uncommon in descriptions of DSS. Infants with CH have severe hypotonia, weakness, respiratory and swallowing difficulty. Early reports of CH emphasized the virtual absence of myelin sheaths, with only multiple layers of basement membrane surrounding large axons and forming onion bulbs.<sup>140</sup> The disorder was considered to either represent the severest end of the spectrum of patients with HMSN III or DSS or to be a separate genetic entity with complete failure of myelin production by Schwann cells. Mutations of the P<sub>0</sub> protein<sup>37</sup> and EGR2<sup>24</sup> have been described in patients with CH.

## **CMT 4**

### **A) Clinical**

The issue of recessive inheritance has confounded classification schemes in the past. Though usually referring to dominantly inherited neuropathies, the HMSN I and II designations have been used in patients with apparent recessive inheritance.<sup>11</sup> Dejerine-Sottas syndrome was suspected to be usually recessively inherited based on early

kinships.<sup>5</sup> Molecular analysis has demonstrated spontaneous point mutations in disorders previously thought to be predominantly recessively inherited.<sup>131</sup> Nevertheless, genetic loci have been identified through homozygosity mapping in kindreds with autosomal recessive CMT. The first locus mapped was in chromosome 8q13-q21.1 in four Tunisian families.<sup>141</sup> The recessive demyelinating form of CMT has been designated CMT 4, with the 8q13-8q21.1 locus assigned CMT 4A. The CMT 4A patients demonstrated evidence of hypomyelination and basal lamina onion bulbs on nerve biopsy. Additional loci in other pedigrees include chromosome 11q23 (CMT 4B),<sup>142</sup> 5q23-q33 (CMT 4C),<sup>143,144</sup> 8q24 (CMT 4D)<sup>145</sup> and 19q13.1-13.3 (CMT 4F).<sup>146</sup> Two autosomal recessive forms of CMT with axonal features have been mapped to 1q21.2-q21.3<sup>147</sup> and 19q13.3.<sup>148</sup> The autosomal recessive axonal neuropathies are sometimes designated AR-CMT 2. The recessive neuropathies, in general, have been severe and have arisen from a broad range of European and non-European communities. The 8q24 locus has associated deafness.<sup>145</sup>

### **B) Electrophysiology**

Electrophysiological findings reflect the severe nature of these neuropathies. Quattrone<sup>149</sup> described the electrophysiology in 10 patients from a family now considered to have CMT 4B. Affected individuals had a severe demyelinating neuropathy approaching the degree of changes seen in DSS. Motor NCVs in the upper limbs were in the 15-17 m/s range in children, with unrecordable motor responses in older patients. Sensory responses were usually absent. Compound muscle action potentials were low in amplitude and dispersed. Brain stem auditory evoked potentials revealed prolonged peak 1-3 interpeak latencies.

### **C) Pathology**

Nerve biopsy in Quattrone's series demonstrated severe myelinated fibre loss, maximal in older patients.<sup>149</sup> Most fibres showed focal myelin reduplication ("focal folding of the myelin sheath"). Thin myelin was present surrounding fibres without reduplication. Occasional onion bulbs were noted. On teased fibre studies, the areas of focal folding were felt to differ from classic tomaculae by virtue of their marked nodular irregularity. These changes were confirmed on electron microscopy.

Focal myelin reduplication has frequently been reported in association with autosomal recessive CMT.<sup>150-155</sup> Most patients have had a neuropathy of congenital or childhood onset with severe progressive disability and a shortened life span, overlapping with DSS. Some authors have noted a similar morphology to the tomaculae of HNPP<sup>150,152</sup> while others have emphasized morphologic differences.<sup>149,154</sup>

Limited information is available about other CMT 4 subtypes. Ben Othmane<sup>141</sup> described the conduction slowing, severe hypomyelination and basal lamina onion bulbs in patients with CMT 4A. Kessali<sup>156</sup> noted typical onion bulbs in patients with CMT 4C. Characteristic morphologic features of nerve biopsy specimens have been associated with some recessive loci but the morphologic abnormalities are not specific to any single phenotype. For instance, the 11q23 locus (CMT 4B) abnormality produces a severe neuropathy with focally folded myelin.<sup>149</sup> However, focally folded myelin sheaths have also been associated with a heterozygous dominant point mutation on the myelin P<sub>0</sub> gene.<sup>157,158</sup> The gene products associated with several CMT 4 chromosomal loci identified are not known, though some candidate gene products have been identified.<sup>159</sup>

## Conclusion

Advances in understanding the many faces of CMT have been rapid, fueled by the progress in correlating clinical presentation with molecular defect. Some of the CMT phenotypic variability clinicians detect can be explained by abnormalities in different target genes, or differences in gene target dosing. There is more to learn, as there is striking phenotypic variability within and between families with identical gene defects, as seen in CMT 1A. Identification of gene product abnormalities is the first step toward developing therapies that will effectively treat CMT. Already the knowledge available is useful for genetic counseling and aiding prognosis. For the commoner forms of CMT, such as CMT 1, CMT X and HNPP, genetic tests are readily available to the clinician. However, accurate diagnosis and management of this diverse group of peripheral neuropathies continues to demand skill and experience in the clinical and electrophysiological evaluation of neuromuscular disease.

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