ABSTRACT: The observation that inherited demyelinating neuropathies have uniform conduction slowing and that acquired disorders have nonuniform or multifocal slowing was made prior to the identification of mutations in myelin-specific genes which cause many of the inherited disorders involving peripheral nerve myelin. It is now clear that the electrophysiological aspects of these disorders are more complex than previously realized. Specifically, certain mutations appear to induce nonuniform slowing of conduction which resemble the findings in acquired demyelinating neuropathies. It is clinically important to recognize the different electrodiagnostic patterns of the various inherited demyelinating neuropathies. In addition, an understanding of the relationship between mutations of specific genes and their associated neurophysiological findings is likely to facilitate understanding of the role of these myelin proteins in peripheral nerve function and of how abnormalities in myelin proteins lead to neuropathy. We therefore review the current information on the electrophysiological features of the inherited demyelinating neuropathies in hopes of clarifying their electrodiagnostic features and to shed light on the physiological consequences of the different genetic mutations.

ELECTROPHYSIOLOGICAL FEATURES OF INHERITED DEMYELINATING NEUROPATHIES: A REAPPRAISAL IN THE ERA OF MOLECULAR DIAGNOSIS

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It has been over 15 years since the publication of our study comparing the electrodiagnostic features of inherited demyelinating neuropathies with those of acquired demyelinating neuropathies. 63 This study demonstrated that patients with Charcot–Marie–Tooth disease (CMT) with slow conduction velocities (hereditary motor sensory neuropathy 1 or CMT-1 [the hypertrophic form of CMT]) had uniformly slow conduction velocities. In contrast, chronic acquired demyelinating neuropathies, particularly chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), typically had multifocal conduction changes with nonuniform conduction slowing. Similar findings had been presented previously by Wilbourn. 114 At the time of these reports, the diagnostic criteria for CIDP were just being considered, and the genetic causes of CMT were unknown. The distinction between familial and acquired disorders had some practical clinical value and allowed the clinician to utilize electrodiagnostic testing to assist in making diagnostic and therapeutic decisions. These observations were followed by a report that extended the observation of uniform con-
duction slowing to include not only CMT but also other disorders of central and peripheral myelin, metachromatic leukodystrophy, Cockayne’s syndrome, and Krabbe’s disease.

The term “uniform conduction slowing” has been used to describe disorders in which the physiological changes suggest that all myelinated nerve fibers are affected along the entire length of the nerve, from the nerve root to the distal nerve segment. In contrast to disorders that have multifocal or segmental changes, the electrodiagnostic studies in patients with uniform conduction slowing have similar velocity changes when different nerves are compared and when different segments of nerves are compared. This includes distal latencies, forelimb velocities, proximal velocities, and F-wave latencies. Some authors have utilized the terminal latency index to compare the distal motor latency with forearm conduction. Conduction block and excessive temporal dispersion are characteristic of multifocal disorders and are not noted in disorders with uniform conduction slowing. Temporal dispersion, in which the duration of the compound motor action potential (CMAP) becomes prolonged on proximal stimulation compared with distal stimulation, is indicative of excessive conduction slowing of intermediate nerve fibers and points to nonuniform conduction changes. Although some temporal dispersion occurs on proximal stimulation in normal subjects and patients with uniform conduction slowing, excessive temporal dispersion (usually defined as greater than 20% increase in duration for the median, peroneal, and ulnar nerves and greater than 30% for the tibial nerve) is indicative of non-uniform disorders.

Although Lewis and Sumner were able to differentiate patients with CMT-1 from those with CIDP, other studies did not come to similar conclusions. Oh and Chang reported conduction block in over 60% of 22 patients with CMT-1, and Hoogendijk et al. suggested possible block in some CMT patients. Meer and Gilliatt found greater slowing of distal than proximal velocities in CMT-1 patients than in controls. Despite these reports, the concept that inherited disorders had more uniform slowing than acquired disorders, which were characterized by multifocal changes, remained clinically useful.

At the time of these reports, there was still some question as to whether the hypertrophic form of CMT (CMT-1) was primarily axonal or demyelinating. The extensive pathologic study of Dyck et al. suggested that axonal atrophy, which had a proximal to distal gradient, along with secondary demyelination, might be responsible for the conduction slowing. However, the studies of Aguayo et al. showed that Schwann cells from a CMT patient, when grafted into nerves of immune-suppressed mice, failed to myelinate the normal mouse axons. This strongly implicated the Schwann cell in the pathogenesis of the disease. Because all myelinating Schwann cells are presumably affected in the disease, these findings were in keeping with the uniform slowing of nerve conduction described above.

In the subsequent 15 years, there has been a dramatic increase in knowledge of the specific genetic abnormalities that underlie the different forms of inherited demyelinating neuropathy. In many, specific mutations in myelin genes have been shown to cause the disease. However, the mechanisms by which these mutations cause the electrophysiological and pathologic features of demyelination are not understood. In addition, new disorders of peripheral myelin have been discovered in which slowing of nerve conduction velocities is nonuniform and similar to that found in the acquired demyelinating neuropathies. Thus, patterns and features of demyelination in inherited neuropathies appear to be more complex than previously recognized. It therefore seems prudent to review the current state of knowledge of the electrodiagnostic findings in inherited demyelinating neuropathies. Table 1 outlines the inherited disorders of myelin that have uniform conduction slowing, those that appear to be multifocal, and those in which the physiological characteristics remain to be determined. This discussion is re-

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stricted to the disorders of myelin proteins, peripheral myelin protein 22 kDa (PMP22), protein zero (P0), connexin 32 (Cx32), and proteolipid protein (PLP). In addition, the recently recognized mutations of early growth response 2 gene (EGR 2) will be included. Pareyson recently reviewed the molecular distinctions between disorders of these genes.

**MYELIN PROTEINS IN THE PERIPHERAL NERVOUS SYSTEM**

Myelin in the peripheral nervous system (PNS) is a multilamellar structure, composed of a spiral of specialized membrane that surrounds axons. The PNS myelin internode, or segment of myelin generated by an individual myelinating Schwann cell, can be divided into a domain of compact myelin and a domain of noncompact myelin. Compact myelin, which constitutes the bulk of the internode, consists of successive wraps of the Schwann cell plasma membrane around the axon in which the ensheathing membranes adhere to each other at both their extracellular (intraperiod line) and cytoplasmic (major dense line) surfaces. In noncompact myelin, the cytoplasmic membranes of the myelin wraps are not tightly apposed. These noncompacted regions include the inner and outer mesaxon, the paranodal loops adjacent to nodes of Ranvier, as well as the Schmidt–Lanterman incisures (the continuous channels of cytoplasm extending from the periaxonal surface of myelin to the cell soma).

Although myelin is chiefly composed of lipids, PNS myelin contains a unique set of proteins that are thought to play key roles in the myelin sheath. The main proteins in PNS myelin, including P0, PMP22, and myelin basic protein, are localized to compact myelin. Other proteins, including myelin-associated glycoprotein (MAG) and Cx32, are restricted to regions of noncompact myelin (Fig. 1). Proteolipid protein, the main protein in central nervous system (CNS) myelin, is also expressed by myelinating Schwann cells although at much lower levels than in the CNS. Whether PLP in the PNS is localized in compact myelin, noncompact myelin, or the perinuclear Schwann cell cytoplasm is, at present, unclear.

**PMP22 DISORDERS**

**CMT-1A with PMP22 Duplication.** The genetic defect causing CMT-1A has been shown to be a duplication on chromosome 17p11.2 which includes the gene for the myelin protein, PMP22. Peripheral myelin protein 22 is a small integral membrane protein contained in compact myelin of the PNS but not CNS myelin. Although some studies have suggested that PMP22 can function in cell proliferation, its function in PNS myelin remains unknown. Recent studies have demonstrated that PMP22 and P0 may form complexes together in PNS myelin, suggesting that their functions are interrelated. Although patients with point mutations in PMP22 have also been classified as having CMT-1A, clinical descriptions of CMT-1A patients are usually limited to patients with the duplication. The duplication accounts for over 60% of patients with inherited sensory and motor neuropathy, probably over 80% of CMT-1 patients, and is the most extensively studied.

The information that is currently available clearly demonstrates uniform conduction slowing in patients with CMT-1A. The conduction changes in CMT-1A were first reported by Kaku and colleagues. Studying 82 patients with CMT-1A as well as 47 other patients with CMT-1 without genetic identification, the authors showed uniform conduction slowing of ulnar, median, and peroneal nerves, including proximal and distal conduction velocities and F-wave latencies. The F-wave findings were consistent with previous reports in CMT-1 but the authors did not find the differential slowing noted by Meer and Gilliatt. In contrast to the reports of others, the authors did not find evidence of conduction block. The discrepancy between these reports is probably accounted for by different definitions of conduction block as well as by important technical considerations. The threshold for stimulation in patients with CMT-1A can be exceptionally high, and supramaximal stimulation cannot always be certain. In addition, in those nerves with low
CMAP amplitude or severe chronic denervation/reinnervation, amplitude reductions may be more affected by excessive phase cancellation and temporal dispersion.\textsuperscript{21,82} The available data suggest that if conduction block occurs, it is most unusual, may at times reflect superimposed entrapment, and is unlikely to be related to the underlying pathophysiology of this disorder.

The range of median and ulnar conduction velocities in the CMT-1A patients studied by Kaku et al.\textsuperscript{49} was between 10 and 42 m/s. Other studies\textsuperscript{49,55,56,60,103} have shown ranges between 10 and 38 m/s, with most patients having conduction velocities between 15 and 30 m/s. However, an occasional patient may have conduction velocities greater than 40 m/s.\textsuperscript{55,59} The lack of marked conduction slowing does not preclude the diagnosis of CMT-1A, and genetic testing should be considered in the appropriate clinical situation. Although the electrodiagnostic studies may provide valuable diagnostic clues, they are not, in and of themselves, diagnostic.

Longitudinal studies have shown that conduction velocity remains relatively stable for at least 20 years. Killian et al.\textsuperscript{56} showed only 2–3 m/s greater slowing in eight patients with CMT-1A when studied in 1989 compared with values when previously studied in 1967. This confirmed, in patients with known duplications, what had previously been shown in the less specific group of CMT-1 patients.\textsuperscript{22,40,85} The conduction slowing has been shown to evolve over the first 3–5 years of age\textsuperscript{34,40,74} and does not appreciably change after the age of 5 years. Garcia et al.\textsuperscript{34} noted conduction changes with slowing of motor conduction velocity and distal motor latencies (DML) before the age of 3 years. Two infants studied serially before the age of 12 months both demonstrated prolonged DML, and one exhibited a slow motor conduction velocity. One had a prolonged DML at birth.

The longitudinal studies of CMT-1 are less clear as to the degree of clinical progression after childhood. Most studies\textsuperscript{7,22,34,45,85} have noted mild progression over years, but Killian et al.\textsuperscript{56} found only one of eight patients had evidence of worsening on examination over 22 years, although half the patients complained of increased weakness. In CMT-1A, Garcia et al.\textsuperscript{34} suggested that clinical signs are seen in 42% by the age of 5 years. Although the neurologic deficits increased in all age groups, the progression was greatest in the second decade of life.

In earlier studies of CMT-1, there had been relatively poor correlation of severity of weakness with conduction velocity.\textsuperscript{7,22,29,45} although some had noted that patients with slower velocities develop more weakness.\textsuperscript{27} However, longitudinal studies in CMT-1 have shown velocities to remain unchanged over decades, whereas CMAP amplitudes decrease.\textsuperscript{85} Dyck et al.\textsuperscript{27} noted that peroneal (but not ulnar) CMAP amplitudes declined when patients were re-studied over an average of 31 years. The authors suspected that the severity of conduction slowing is useful in predicting clinical severity but that CMAP amplitude reduction, as a marker of axonal loss, is more closely linked with disability. Hoogendijk et al.,\textsuperscript{49} in their study of patients with the 17p11.2 duplication, suggested that an inverse correlation exists between the strength component of the neurological disability score and median conduction slowing. Birouk et al.\textsuperscript{12} noted an inverse correlation of “high functional disability” (the more severely affected patients) with conduction velocity but not with CMAP amplitude. The correlation of velocity and disability, however, has not been found in other studies.\textsuperscript{60,103}

Part of the problem with attempts at correlating CMAP amplitude with strength and disability is that the muscles examined electrophysiologically, the extensor digitorum brevis in the foot and the abductor digiti minimi and abductor pollicis brevis in the hand, have only limited influence on strength and disability. Reductions in the CMAP amplitude of these muscles may not indicate changes in other muscles that are more directly related to function. Moreover, functional assessment scales may not be the optimal way of comparing disability with electrophysiological parameters. In addition, CMAP amplitudes may remain high despite severe axonal loss due to collateral sprouting and motor unit reconfiguration. Other electrophysiological correlates of axonal loss, such as motor unit number estimates, may need to be utilized before a full appreciation of the true physiological aspects of the clinical condition is obtained.

There is good reason to suspect that disability in CMT-1A would correlate better with axonal degeneration than with slow nerve conduction, because weak muscles are typically atrophied and pathologically analysis of nerve biopsies of patients demonstrate axonal degeneration.\textsuperscript{7,13,19,22,26} Consistent with this hypothesis, Sahenk and colleagues\textsuperscript{89} have shown that xenograft transplants of CMT-1A Schwann cells into sciatic nerve of nude mice reduced the caliber of regenerating axons. In a series of 42 patients with CMT-1A, we have found that neurological disability correlates with reductions in CMAP and sensory nerve action potential (SNAP) amplitudes but not with slowing of nerve conduction velocities.\textsuperscript{66} How the primary Schwann cell disorder relates to the apparent progressive axonal loss, whether axonal atrophy\textsuperscript{28} is important in this process, and what the im-
portant axon–Schwann cell interactions are that may be altered in CMT-1A are crucial issues that need to be understood. Although affected members of a family all have conduction slowing, the slowing is variable even within families, without relationship to age, sex, severity of the disease, or length of time with symptomatic disease. A study of two sets of identical twins revealed concordance of electrodiagnostic findings within each pair of twins, despite significant discordance of clinical dysfunction. There appear to be modifying factors that influence the severity of the clinical disorder.

The changes in sensory conduction have not been emphasized. Distal sensory responses are frequently absent. However, when obtained, sensory conduction slowing is present to the same extent as motor conduction slowing. Sensory potentials may be difficult to obtain, in part due to the phase cancellation, which has a more profound effect on sensory studies than on motor conduction. However, there is also significant clinical distal sensory involvement in CMT-1A, and the inability to obtain sensory potentials seems to correspond to the clinical disease.

**Hereditary Neuropathy with Liability to Pressure Palsies with PMP22 Deletion.** Hereditary neuropathy with liability to pressure palsies (HNPP) is defined clinically as an autosomal dominantly inherited disorder characterized by nonuniform slowing of nerve conduction velocities and a predisposition to the development of pressure palsies. The electrophysiological findings in HNPP are therefore in striking contrast to the uniform conduction slowing seen in CMT-1A, with duplication of 17p11.2. Most cases of HNPP are associated with a deletion of the same 17p11.2 region that is duplicated in CMT-1A, thus leaving patients with only a single allele expressing PMP22. The underexpression of PMP22 has been correlated with the severity of clinical disease, or length of time with symptomatology. Functional deletions of PMP22 have been emphasized. Distal sensory responses or degree of tomacula formation. Heterozygous PMP22 knockout mice, in which one of the two PMP22 alleles has been deleted, also develop a similar neuropathy. These studies suggest that it is the absence of PMP22 that causes the neuropathy, that axonal diameter may be affected by the underexpression of PMP22, and that the traditional hallmarks of HNPP, tomacula formation and conduction changes at sites of compression, may be related to other factors. Although the deletion of 17p11.2 is found in most cases, there are families with HNPP who do not have this deletion. Some of these cases are caused by PMP22 point mutations resulting in truncated proteins and functional deletions of PMP22. At least one PMP22 missense mutation has been reported to cause HNPP. Sahenk et al. reported an asymptomatic woman with a Val30Met missense mutation (Fig. 2). The electrodiagnostic studies (not reported in detail) were suggestive of multiple entrapments, and the sural nerve biopsy had tomacular changes which they considered to be an HNPP phenotype. Nerve xenograft studies showed a delay in myelination and axonal neurofilament density increase.

Nerve conduction velocities in patients with HNPP associated with the 17p deletion have been characterized by nonuniform slowing, with segmental slowing of the peroneal and ulnar nerves at sites of compression, but only mild slowing in forearm segments of median and ulnar nerves. Distal motor latency prolongation is characteristic and is frequently prolonged out of proportion to forelimb conduction slowing. Terminal latency indexes are abnormal even if the median nerve is excluded from analysis. This has raised the speculation that there may be a distally accentuated myelopathy. Focal slowing and distal latency prolongation can be seen in asymptomatic patients, including 5- and 6-year-olds. Median, ulnar, and peroneal conduction velocities are otherwise only mildly affected. Prolonged F-wave latencies are common. Thus, it appears that there are electrodiagnostic changes consistent with an underlying multifocal demyelinating neuropathy independent of superimposed compression. The conduction slowing is disproportionately distal and involves both sensory and motor fibers.

Conduction block, when defined as amplitude and/or area reduction of >50%, was uncommon in most series ranging from 6 to 22% of nerves studied. However, when smaller amplitude decrements were used as criteria, conduction block was considered more common. Magistris and Roth found a much higher incidence of conduction block than did others, noting 29 focal blocks in 12 patients (the total number of nerves studied is not mentioned). Eleven of these blocks (excluding 2 from a sporadic case) were with amplitude reductions of over 70%, and 10 were of 40 to 70%. Six of the blocks were of the ulnar nerve at the elbow, two were peroneal at the knee, and three were determined to be of the median nerve at the wrist. Uncini et al. compared the incidence of block in HNPP and CMT-1A using two different criteria of block, one with a 20% drop in amplitude and area and the other with 50% drop. Using the less stringent crite-
ria, there was a 21% incidence of block in the CMT-1A patients and 25% in the HNPP. With the more stringent criteria of 50% drop, none of the CMT-1A patients had block and only 6% of the HNPP patients had block. They concluded that the more stringent criteria provided more specific evidence of conduction block and that lesser degrees of amplitude reduction may overestimate the incidence of block.

Thus, there is no consensus regarding the incidence of conduction block. Clearly, the lack of block does not preclude the possibility of HNPP. Even in symptomatic nerves, focal conduction slowing at sites of compression may be the predominant electrodiagnostic feature rather than conduction block. Whether conduction block is the cause of the focal weakness in HNPP is unclear. Magistris and Roth, in a well-documented case, showed persistent block for up to 10 years. Ulnar nerve transposition resulted in partial improvement of the block in 3 days and complete reversal of the block in 1 month, coinciding with symptomatic improvement. Sellman and Mayer noted appropriate neurologic findings associated with the block and relatively normal function when only conduction slowing was present. However, Gouider et al. described a patient who was studied 3 days after partial peroneal nerve palsy and documented focal slowing across the fibula head but no amplitude reduction while the patient had a foot drop. Thus, it appears that, in many patients, focal weakness may correspond to conduction block, but in some, weakness may occur without demonstrated block.

**PMP Point Mutations.** There have been a number of point mutations of the PMP22 gene, as shown in Figure 2. Gabreels-Festen and colleagues have suggested that patients with PMP22 point mutations develop more severe neuropathies with slower nerve conduction velocities than do those with the 17p duplication. However, a review of the literature suggests that different PMP22 mutations may affect nerve conduction velocities to different degrees. Nicholson et al. reported a patient with a point mutation that caused a frame shift mutation and a premature termination resulting in essentially a null mutation. As expected, the phenotype was consistent with HNPP (the transmembrane mutation with the black square in Fig. 2). Other mutations have had...
clinical and electrophysiological changes consistent with CMT-1A (black circles, Fig. 2)\textsuperscript{71,83} or CMT-III (Dejerine–Sottas disease [D-S]) (gray circles, Fig. 2)\textsuperscript{50,52,66,83,106,109} as described in other sections. The reason that some mutations cause a more severe phenotype than others is not known. Interestingly, virtually all PMP22 point mutations causing neuropathy are located in putative transmembrane domains (Fig. 2). Detailed electrophysiological data on most patients with PMP22 point mutations are not available. When described, nerve conduction velocities in patients with milder, or CMT-1A, phenotypes range from 10 m/s to 25 m/s within the same family (Ser79Cyst [serine at amino acid 79 mutated to a cysteine] Fig. 2).\textsuperscript{80} For patients with D-S phenotypes, routine nerve conduction velocities are either unobtainable (Ser72Trp, Leu80Pro [Fig. 2])\textsuperscript{106} or less than 5 m/s (Ser76Ile,\textsuperscript{98} Ser72Leu,\textsuperscript{66} Met69Lys\textsuperscript{83} [Fig. 2]). However, median motor conduction velocities as high as 21 m/s have been described in some patients with D-S (Ser27Leu)\textsuperscript{83} (Fig. 2).

**DISORDERS**

**CMT-1B with P0 Point Mutations.** Charcot–Marie–Tooth 1B was the first CMT disorder to have an identified gene locus, when it was linked to the Duffy locus.\textsuperscript{10} However, this is a much less common disorder than CMT-1A. The CMT-1B locus has been mapped to the centromeric region of chromosome 1q21–23 and involves the gene encoding the major PNS myelin protein, P0. Figure 3 schematically shows the P0 protein and the point mutations that have currently been demonstrated to cause neuropathy. The numbering system for P0 mutations is confusing, because in some reports a 29 amino acid leader peptide—which is cleaved prior to insertion in the myelin sheath—is included in the numbering, and in some reports it is not. Thus, the same mutation may be characterized as Asp(61)Glu\textsuperscript{111} or Asp(90)Glu.\textsuperscript{9} Figure 3 does not include the leader peptide, so that the previously cited AspGlu mutation is at amino acid 61.

Myelin protein zero is a single transmembrane protein with a highly basic 69-residue intracellular domain and a 124-residue extracellular domain that shows sequence similarity to immunoglobulins. It comprises 60% of all PNS myelin proteins. An essential function of P0 is to mediate adhesion between adjacent wraps of myelin, forming the intraperiod line. Myelin protein zero–mediated adhesion appears to require both the extracellular and intracellular portion of the molecule.\textsuperscript{98} Thus, mutations in each of these portions, as well as in the transmembrane domain, have been shown to cause the various clinical presentations of CMT-1B, including a classic CMT phenotype (black circles, Fig. 3), a D-S phenotype (gray circles, Fig. 3) a congenital hypomyelination phenotype (black rectangle, Fig. 3), and possibly a CMT-2 phenotype (open rectangles, Fig. 3). Preliminary evaluations suggest that certain mutations may cause more severe clinical phenotypes than others\textsuperscript{79,111} although this needs to be evaluated in greater detail. Similarly, preliminary results suggest that certain mutations disrupt nerve conduction velocities much more severely than others.

Bird and colleagues\textsuperscript{89} reported a 20-year study of the original CMT-1B family that was demonstrated to have linkage to the Duffy blood group locus on chromosome 1.\textsuperscript{10} The mutation has subsequently been mapped to Asp61Glu. Conduction velocities were uniformly very slow (5–15 m/s), significantly slower than patients with CMT-1A. Children were affected at an early age, with slow conduction velocities noted in 4- and 6-year-olds. There was significant clinical variation, and although the clinical severity was greater than most patients with CMT-1A, the authors believed the disorder overlapped with CMT-1A and was not as severe as most cases of D-S. Sindou et al.\textsuperscript{89} described two patients with different autosomal dominant mutations, also involving the extracellular domain of P0. The nerve conduction changes were uniformly slow (15–17 m/s for one patient and 21–30 m/s for the other) with sensory and motor conduction slowing consistent with each other. However, Marrosu and colleagues\textsuperscript{67} described a Sardinian family with an autosomal dominant P0 mutation with electrophysiological findings suggestive of a primary axonal disorder as seen in CMT-2 (Ser15Phe, Fig. 3). Distal latencies were normal and velocities were normal or near normal despite distal denervation on electromyography. However, nerve biopsies were not obtained, and electrophysiological variability existed between patients. Heterozygous patients with Phe35 deletion\textsuperscript{111} and Thr95Met mutations were also characterized as CMT-2 phenotypes based on normal or near-normal conduction velocities \textsuperscript{18,24} (Fig. 3). However, physiological and pathological analyses remain inconclusive, and whether any P0 mutation causes a true axonal neuropathy, independent of demyelination, remains to be convincingly demonstrated.

Part of the confusion is based on the attempts to classify patients based on nerve conduction velocities alone. DeJonghe et al.\textsuperscript{24} classified their CMT-2 patients based on at least one patient in each family having a motor conduction velocity of >38 m/s. In the patients with the Thr95Met mutation, a number of patients had motor conduction velocities of <35
m/s and those with normal velocities had normal amplitudes. The slower conduction velocities suggest a demyelinating disorder. The normal velocities may be due to minimal disease. The classification of CMT-2 or any axonal disorder should be based on normal or near-normal conduction velocities despite significant denervation and/or low CMAP amplitudes in the corresponding muscles.

**Dejerine-Sottas and Congenital Hypomyelination Neuropathy.** Prior to the identification of specific myelin gene disorders, D-S was considered an autosomal recessive disorder having a severe phenotype, manifesting in young children with delayed motor milestones, leading to an inability to walk. Studies by Benstead et al. prior to identification of specific gene defects demonstrated uniform conduction slowing below 10 m/s in all nerves tested. Proximal nerves, including the musculocutaneous nerve, revealed slowing that was similar to that of more distal nerves. Nerves were difficult to stimulate, and supramaximal stimulation was not always possible. Marked temporal dispersion was noted, but conduction slowing was consistent between different nerves.
It was recognized that because of the severe slowing, the reduced amplitudes, and the difficulty in obtaining supramaximal stimulation, the usual criteria for temporal dispersion and conduction block were not valid for D-S. The authors believed that both the temporal dispersion and amplitude drop did not necessarily indicate multifocal demyelination and that the disorder was most likely uniform but very severe.

Congenital hypomyelination neuropathy is a term used for children who present in the neonatal period with hypotonia, weakness, and dysphagia. Some have arthrogryposis. The children either die in infancy or are severely disabled. The pathology of the nerves is remarkable for hypomyelination and onion-bulb formation. Whether congenital hypomyelinating neuropathy is one end of the spectrum of D-S or represents different genetic mutations is not clear.

It is now apparent that the D-S phenotype can be caused by both autosomal dominant and autosomal recessive mutations. Tyson et al. described nine patients with hereditary demyelinating neuropathy of infancy with D-S phenotype. Four patients (two were mother and son) demonstrated novel missense mutations of PMP22, all in exon 3, whereas two patients had novel P0 mutations and three had no demonstrable abnormality of P0 or PMP22. There was consanguinity in these three cases, and they were suspected to be autosomal recessive disorders of an unidentified locus. At least three cases had neonatal symptoms. Two of these three had PMP22 mutations and one had an unidentified mutation. The electrophysiological features of the nine patients were remarkable for markedly slow motor conduction velocities which were less than 10 m/s in one of four with the PMP mutation, both patients with the P0 mutations, and one of the recessive cases. The other two recessive cases had velocities of 15–17 m/s. The other three PMP22 cases had inexorable nerves.

The available data suggest that the electrodiagnostic features of D-S include severe conduction slowing, usually below 10 m/s, which is consistent in all nerves from which responses can be obtained. Nerves are difficult to stimulate, and there may be marked temporal dispersion and amplitude reduction on proximal stimulation. However, these latter findings are not due to nonuniform conduction but represent changes due to severe slowing and axonal loss.

**CMT-X with Connexin 32 Disorders.** Although reports of X-linked CMT date back to 1889, it was considered a rare disorder until the identification of genetic defects on the proximal long arm of the X chromosome and localized to Xq13.1. It has now been established that this is the localization of the Cx32 protein which is expressed by myelinating Schwann cells. Connexin32 belongs to a family of proteins, all of which have a similar structure. When connexins meet at opposed cell membranes, channels (called gap junctions) through which ions and small molecules are able to pass can form. Each connexin protein has four-membrane–spanning domains connected by two extracellular and one intracellular loops. Six connexin molecules assemble to form a connexon, with the third transmembrane domain lining the central pore. The six cysteine residues in the Cx32 are necessary to maintain the structure of the extracellular loops. It has been suggested that mutations located within the second transmembrane domain, and/or cytoplasmic loop (Fig. 4), are associated with a milder clinical phenotype. However, detailed, individual descriptions of genotype/phenotype correlations are not available on many of the patients with CMT-X mutations (Fig. 4). As a result, it is not currently possible to correlate specific mutations with severity of disease.

Over 150 different genetic mutations of the gene for Cx32 have been identified. It now appears that CMT-X is the second most common form of CMT and may account for some families considered to have CMT-2. The characteristics of the electrodiagnostic findings of patients with CMT-X remain somewhat confused. In part, this is because females with the mutation may manifest symptoms, but the clinical and electrophysiological features are not consistent with males. The conduction velocities in men are usually between 30 and 40 m/s, values that would be considered an intermediate range between CMT-1 and CMT-2. Prior to gene localization, some authors recognized a group of CMT patients with intermediate conduction velocities, but because of frequent female involvement, this intermediate form was considered autosomal dominant rather than X-linked. It is increasingly apparent that CMT-X accounts for the majority of CMT patients with intermediate conduction slowing. Birouk and colleagues noted that 90% of the 21 males with CMT-X who they studied had median motor nerve conduction velocities in the intermediate range, whereas only 40% of the 27 females had intermediate slowing. Of the women, 24% had mild slowing (in a range considered typical of CMT-2) and 36% were normal. This variability in females, noted by others, which is also apparent clinically, partially explains why some female patients classified as CMT-2 may have CMT-X. It is
likely that the lack of conduction slowing in some women may be related to the expression of normal Cx32 from the other normal X chromosome. Thus, females with relatively normal conduction studies may have CMT-X, whereas both males and females with slow or intermediate velocities may have Cx32 mutations. The clinician should be suspicious of CMT-X in any familial neuropathy without male-to-male transmission.

The electrophysiological changes have suggested to some investigators that the disorder may be primarily axonal rather than a disorder of myelin. They note that CMAP amplitudes are all reduced in the nerves with intermediate slowing as well as in the patients with relatively normal velocities. This was interpreted as demonstrating a primary axonal disorder. Moreover, xenograft studies have confirmed, in an experimental model, that Cx32 mutations can cause axonal degeneration. Hahn and colleagues initially considered their patients to have electrophysiological changes of an axonal disorder based on peroneal conduction studies of 57

FIGURE 4. Mutations in the open reading frame of Cx32 associated with peripheral neuropathy. Letters indicate respective amino acid. (Figure modified from Scherer et al.)
patients from one family. However, when they evaluated 116 patients from 13 families (including the patients from the previous report), studying the median as well as the peroneal nerve, they recognized changes in conduction velocity, distal motor latencies, and F-wave latencies that were consistent with demyelination.\(^4\)\(^2\) Peroneal conduction studies can be difficult to interpret when comparing conduction slowing to amplitude reduction and may overemphasize the axonal pathology. There are other studies\(^9\)\(^0\)\(^6\)\(^2\)\(^1\)\(^0\)\(^2\) that have reported that the electrodiagnostic findings not only pointed to a primary demyelinating disorder but also suggested nonuniform conduction slowing. Lewis and Shy's patients\(^6\)\(^2\) had distal latencies that were not always prolonged despite moderate forearm slowing. Gutierrez and colleagues\(^9\)\(^0\) reported excessive temporal dispersion, conduction block, and differential slowing of conduction velocities in a three-generation family with CMT-X. Sural nerve biopsy showed loss of large myelinated fibers and onion-bulb formation. Tabaraud et al.\(^1\)\(^0\)\(^2\) reported a female CMT-X patient who was initially thought to have CIDP because of the multifocal conduction changes. These reports of differential slowing in different segments of nerves strongly suggest that segmental demyelination is a significant aspect of the disorder in at least some families.

Whether CMT-X is primarily axonal or demyelinating remains to be determined. Although investigations utilizing electrophysiological criteria can be very helpful, interpretation of the conduction changes in CMT-X based on grouped data should be done with caution. Because the conduction velocities are intermediate between normal and those of CMT-1A, are possibly nonuniform, and are sometimes different between males and females within the same family, analysis of grouped data may be misleading. To best understand the relationship between the electrophysiology and the pathophysiology of CMT-X, it is preferable to examine the conduction studies of individuals, with particular attention to differential slowing.

Some pathological studies\(^1\)\(^1\)\(^,\)\(^4\)\(^3\) have tended to suggest an axonal neuropathy with evidence of loss of myelinated fibers; minimal, if any, onion bulbs; and no evidence on teased-fiber analysis of segmental demyelination or remyelination. Other histopathological studies have revealed thinly myelinated fibers,\(^9\)\(^0\) onion-bulb formations,\(^3\)\(^0\)\(^,\)\(^9\)\(^0\) and marked variation of myelin thickness,\(^9\)\(^0\) suggesting a primary demyelinating process.

The confusion regarding the primary pathophysiology of Cx32 disorders may, in part, be caused by the number of different mutations that have been identified in CMT-X. It is possible that some mutations affect the channel properties of Cx32 and may not affect conduction velocity as much as they influence Schwann cell-axonal interactions. Others may affect conduction to a greater extent. It is anticipated that further genotype, phenotype, electrophysiological, and pathological correlations will shed more light on the true nature of the pathophysiology of Cx32 disorders.

Connexin 32 is also expressed in the CNS, and some patients with CMT-X have been noted to have mild hearing loss.\(^7\)\(^2\)\(^,\)\(^7\)\(^6\) Brainstem auditory evoked potentials have demonstrated prolonged central conduction times in males with CMT-X. Wave 1 was normal, but all central latencies were significantly slow. Females also showed statistically significant central latency prolongation but not as severely or as consistently as did males. This is distinctly different from CMT-1A, in which wave 1 was prolonged but central conduction was normal.\(^7\)\(^2\)\(^,\)\(^7\)\(^6\)

**Pelizaeus–Merzbacher Disease and PLP mutations**

Pelizaeus–Merzbacher disease (PMD) is an X-linked disorder of myelin caused by mutations in the PLP gene.\(^5\) Proteolipid protein is an integral membrane protein constituting approximately 50% of the total protein mass of CNS myelin. Proteolipid protein is thought to comprise the intraperiod line of CNS myelin.\(^3\) It has been proposed to act both as an adhesion molecule and as an ion channel, but its actual function in oligodendrocytes remains unknown.\(^3\)\(^7\)\(^,\)\(^8\) Proteolipid protein is also expressed by myelinating Schwann cells, although its precise location within the myelin sheath remains uncertain.

Until recently, PMD was considered a disorder confined to the CNS. Classic forms of PMD involve infants and children with spasticity, ataxia, nystagmus, optic atrophy, and delayed psychomotor development with evidence of widespread CNS demyelination.\(^9\)\(^5\)\(^,\)\(^9\)\(^6\) Some forms of hereditary spastic paraparesis have been linked to PLP mutations.\(^1\)\(^6\)

With the discovery of the specific gene for PLP, it has become apparent that most disorders are due to duplications or missense mutations. Recently described\(^9\)\(^3\) was a family with a unique mutation leading to the absence of PLP protein expression in which the affected members of the family had a CNS disorder similar to, but less severe than, other cases of PMD. In addition, the affected family members were noted to have a demyelinating peripheral neuropathy. The electrodiagnostic findings were consistent with a nonuniform disorder, with median and ulnar velocities that varied from 37 to 52 m/s in the forearm segments. A few patients had significant.
conduction slowing across the elbow, and distal latencies were variably slow, more frequently in the median than ulnar nerves. These changes were seen in both the clinically affected males and the relatively asymptomatic females. The abnormalities suggested a multifocal disorder with a possible predilection for changes at sites of compression. Teased-fiber analysis of axillary and sciatic nerves obtained from an autopsy of one of the affected males revealed paranodal and segmental demyelination. Other families with null mutations have had similar phenotype with milder CNS disease but evidence of peripheral nerve involvement.33,81,100

It is of interest that in this genetic disorder of a myelin protein that is a relatively minor constituent of peripheral nerve myelin, missense mutations and duplications appear to have little phenotypic expression in peripheral nerve, whereas null mutations or complete absence of protein expression adversely affect peripheral nerve myelin function. In the CNS, where PLP is the major myelin protein, duplications and missense mutations appear to cause more severe CNS disease than null mutations. If PLP accounts for 50% of CNS myelin protein, how does some of the myelin continue to function when no PLP is made? Are other myelin protein genes upregulated? It will require further investigation of the different mutations of PLP in patients and animal models to better understand the role of PLP in peripheral and central myelin in the normal and diseased state.

EARLY GROWTH RESPONSE 2.

Recent studies have shown that mutations in EGR 2 (also known as Krox 20) cause a novel form of CMT. Early growth response 2 functions as a transcription factor, which means that it binds to specific DNA sequences on the promoter region of genes whose expression it regulates.105 Early growth response 2 is expressed in developing Schwann cells at a time when future myelinating Schwann cells have established a 1:1 ratio with axons and have made the commitment to myelinate. During this same period, the expression of PMP22, P0, and other myelin-specific genes are also upregulated. It is attractive to think that EGR 2 might be directly responsible for binding to the promoters of, and upregulating the expression of, myelin genes such as PMP22 and P0. However, no definite binding of EGR 2 to promoters of myelin-specific genes has been established.

Warner and coworkers have identified two families with clinical signs and symptoms of CMT-1 caused by a point mutation in the EGR 2 gene.112 Both these EGR 2 mutations segregated as an autosomal dominant trait, and both were found in the zinc finger region of the protein, which is the region that directly binds to DNA. Median and ulnar conduction velocities were 25–30 m/s. A third family with a congenital hypomyelinating neuropathy caused by an EGR 2 mutation was also identified. This mutation, however, segregated as an autosomal recessive trait and was located in a region of the protein outside of the DNA-binding domain.101,112

Limited electrophysiological studies of these patients were reported. Nerve conductions, when obtainable, were between 3 and 7 m/s. However, both CMAP and SNAP amplitudes were often absent or significantly reduced.112 At this time, there is not enough information to further characterize the electrophysiological characteristics of these disorders.

CONCLUSION

The identification of specific genetic defects associated with some of the inherited demyelinating neuropathies provides a tremendous opportunity to better understand the pathophysiological processes that determine the clinical disorders. Previous concepts of the electrophysiological nature of inherited demyelinating neuropathies must be reconsidered. Although CMT-1A, the most common form of inherited demyelinating neuropathy, has uniform slowing, there are a number of inherited neuropathies that have multifocal conduction slowing. Some other disorders—such as metachromatic leukodystrophy, Cockayne’s syndrome, and Krabbe’s disease—have been shown to have uniform conduction slowing, but in only a small number of patients. The full spectrum of the peripheral neuropathy in these disorders has not been characterized. There are also a number of other disorders, many just recently recognized, in which there is evidence of peripheral nerve demyelination. Other disorders will likely be identified and characterized over the next few years, adding to the complexity of diagnostic possibilities.

The different patterns of conduction slowing are important to recognize. The identification of a number of inherited disorders with multifocal conduction slowing must be taken into account when attempting to diagnose and treat individual patients. Patients with multifocal slowing may have HNPP or CMT-X rather than an acquired neuropathy such as CIDP and its variants. Careful family history, examination of family members, and appropriate use of genetic testing may be required before a definitive diagnosis can be made.

The different electrophysiological findings are potential clues to the further understanding of the roles that the individual myelin proteins play in peripheral nerve function. It is clear that there are mul-
multiple factors that determine the clinical and electrophysiological phenotype of the different genetic defects. These include the specific myelin protein involved, the type of mutation, and the location of the mutation. Continued investigations of families with different mutations, coupled with research on appropriate animal models, will bring us closer to an understanding of the pathophysiology of the inherited demyelinating neuropathies.

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