unmyelinated fibers. The density of these nerve fibers is reduced in patients with small-fiber neuropathies in whom NCS and routine nerve biopsies are often normal. This technique may allow for an objective measurement in patients with mainly subjective symptoms. However, it adds little to what one already knows from the clinical examination and EDx.

SPECIFIC DISORDERS

HEREDITARY NEUROPATHIES

Charcot-Marie-Tooth (CMT) disease is the most common type of hereditary neuropathy. Rather than one disease, CMT is a syndrome of several genetically distinct disorders (Table 459-4). The various subtypes of CMT are classified according to the nerve conduction velocities and predominant pathology (e.g., demyelination or axonal degeneration), inheritance pattern (autosomal dominant, recessive, or X-linked), and the specific mutated genes. Type 1 CMT (or CMT1) refers to inherited demyelinating sensorimotor neuropathies, whereas the axonal sensory neuropathies are classified as CMT2. By definition, motor conduction velocities in the arms are slowed to less than 38 m/s in CMT1 and are greater than 38 m/s in CMT2. However, most cases of CMT1 actually have motor nerve conduction velocities (NCVs) between 20 and 25 m/s. CMT1 and CMT2 usually begin in childhood or early adult life; however, onset later in life can occur, particularly in CMT2. Both are associated with autosomal dominant inheritance, with a few exceptions. CMT3 is an autosomal dominant neuropathy that appears in infancy and is associated with severe demyelination or hypomyelination. CMT4 is an autosomal recessive neuropathy that typically begins in childhood or early adult life. There are no medical therapies for any of the CMTs, but physical and occupational therapy can be beneficial, as can bracing (e.g., ankle-foot orthotics for footdrop) and other orthotic devices.

CMT1 CMT1 is the most common form of hereditary neuropathy, with the ratio of CMT1:CMT2 being approximately 2:1. Affected individuals usually present in the first to third decade of life with distal leg weakness (e.g., footdrop), although patients may remain asymptomatic even late in life. People with CMT generally do not complain of numbness or tingling, which can be helpful in distinguishing CMT from acquired forms of neuropathy in which sensory symptoms usually predominate. Although usually asymptomatic in this regard, reduced sensation to all modalities is apparent on examination. Muscle stretch reflexes are unobtainable or reduced throughout. There is often atrophy of the muscles below the knee (particularly the anterior compartment), leading to so-called inverted champagne bottle legs.

Motor NCVs are usually in the 20–25 m/s range. Nerve biopsies usually are not performed on patients suspected of having CMT1, because the diagnosis usually can be made by less invasive testing (e.g., NCS and genetic studies). However, when done, the biopsies reveal reduction of myelinated nerve fibers with a predilection for the loss of the large-diameter fibers and Schwann cell proliferation around thinly or demyelinated fibers, forming so-called onion bulbs.

CMT1A is the most common subtype of CMT1, representing 70% of cases, and is caused by a 1.5-megabase (Mb) duplication within chromosome 17p11.2-12 wherein the gene for peripheral myelin protein-22 (PMP-22) lies. This results in patients having three copies of the PMP-22 gene rather than two. This protein accounts for 2–5% of myelin protein and is expressed in compact portions of the peripheral myelin sheath. Approximately 20% of patients with CMT1 have CMT1B, which is caused by mutations in the myelin protein zero (MPZ). CMT1B is for the most part clinically, electrophysiologically, and histologically indistinguishable from CMT1A. MPZ is an integral myelin protein and accounts for more than half of the myelin protein in peripheral nerves. Other forms of CMT1 are much less common and again indistinguishable from one another clinically and electrophysiologically.

CMT2 CMT2 tends to present later in life compared to CMT1. Affected individuals usually become symptomatic in the second decade of life; some cases present earlier in childhood, whereas others remain asymptomatic into late adult life. Clinically, CMT2 is for the most part indistinguishable from CMT1. NCS are helpful in this regard; in contrast to CMT1, the velocities are normal or only slightly slowed. The most common cause of CMT2 is a mutation in the gene for mitofusin 2 (MFN2), which accounts for one-third of CMT2 cases overall. MFN2 localizes to the outer mitochondrial membrane, where it regulates the mitochondrial network architecture by fusion of mitochondria. The other genes associated with CMT2 are much less common.

CMTDI In dominant-intermediate CMTs (CMTDIs), the NCVs are faster than usually seen in CMT1 (e.g., >38 m/s) but slower than in CMT2.

CMT3 CMT3 was originally described by Dejerine and Sottas as a hereditary demyelinating sensorimotor polyneuropathy presenting in infancy or early childhood. Affected children are severely weak. Motor NCVs are markedly slowed, typically 5–10 m/s or less. Most cases of CMT3 are caused by point mutations in the genes for PMP-22, MPZ, or ERG-2, which are also the genes responsible for CMT1.

CMT4 CMT4 is extremely rare and is characterized by a severe, childhood-onset sensorimotor polyneuropathy that is usually inherited in an autosomal recessive fashion. Electrophysiologic and histologic evaluations can show demyelinating or axonal features. CMT4 is genetically heterogenic (Table 459-4).

CMT1X CMT1X is an X-linked dominant disorder with clinical features similar to CMT1 and CMT2, except that the neuropathy is much more severe in men than in women. CMT1X accounts for approximately 10–15% of CMT overall. Men usually present in the first two decades of life with atrophy and weakness of the distal arms and legs, areflexia, pes cavus, and hammertoes. Obligate women carriers are frequently asymptomatic, but can develop signs and symptoms. Onset in women is usually after the second decade of life, and the neuropathy is milder in severity.

NCS reveal features of both demyelination and axonal degeneration that are more severe in men compared to women. In men, motor NCVs in the arms and legs are moderately slowed (in the low to mid 30-m/s range). About 50% of men with CMT1X have motor NCVs between 15 and 35 m/s with about 80% of these falling between 25 and 35 m/s (intermediate slowing). In contrast, about 80% of women with CMT1X have NCVs in the normal range and 20% have NCVs in the intermediate range. CMT1X is caused by mutations in the connexin 32 gene. Connexins are gap junction structural proteins that are important in cell-to-cell communication.

Hereditary Neuropathy with Liability to Pressure Palsies (HNPP) HNPP is an autosomal dominant disorder related to CMT1A. Although CMT1A is usually associated with a 1.5-Mb duplication in chromosome 17p11.2 that results in an extra copy of PMP-22 gene, HNPP is caused by inheritance of the chromosome with the corresponding 1.5-Mb deletion of this segment, and thus affected individuals have only one copy of the PMP-22 gene. Patients usually manifest in the second or third decade of life with painless numbness and weakness in the distribution of single peripheral nerves, although multiple mononeuropathies can occur. Symptomatic mononeuropathy or multiple mononeuropathies are often precipitated by trivial compression of nerve(s) as can occur with wearing a backpack, leaning on the elbows, or crossing one's legs for even a short period of time. These pressure-related mononeuropathies may take weeks or months to resolve. In addition, some affected individuals manifest with a progressive or relapsing, generalized and symmetric, sensorimotor peripheral neuropathy that resembles CMT.

Hereditary Neuralgic Amyotrophy (HNA) HNA is an autosomal dominant disorder characterized by recurrent attacks of pain, weakness, and sensory loss in the distribution of the brachial plexus often beginning in childhood. These attacks are similar to those seen with idiopathic brachial plexitis (see below). Attacks may occur in the postpartum period, following surgery, or at other times of stress. Most patients recover over several weeks or months. Slightly dysmorphic features, including hypotelorism, epicanthal folds, cleft palate, syndactyly, micrognathia, and facial asymmetry, are evident in some individuals. EDx demonstrate an axonal process. HNA is caused by mutations in septin 9 (*SEPT9*). Septins may be important in formation of the