CMT Type 1: Causes and Symptoms

[The following information about the various forms of type 1 CMT was compiled by CMTA Scientific Advisory Board Member Steven Scherer, MD, PhD, from the University of Pennsylvania. You can read the brief comments about the gene flaw which causes each type and the medical problems associated uniquely with that type.]

CMT1A

CMT1A is a dominantly inherited disease. The clinical onset is often said to occur in the first or second decade, but neuropathy can be detected clinically by age 5, and nerve conduction velocities are abnormally slowed even earlier. Affected patients have weakness, atrophy, and sensory loss in the distal legs followed by the distal arms; foot deformities and areflexia (absence of neurological reflexes such as knee jerk reaction) are sometimes present. There is considerable variability in the degree of neurological deficits within families, and even between identical twins, indicating that other factors modulate disease severity Examinations of sensory and motor function worsen gradually. Atypical presentations are reported, including cranial nerve involvement, proximal weakness, diaphragmatic weakness, calf hypertrophy, and cramps.

Sensory responses are typically absent. Forearm motor conduction velocities are abnormally slowed, from 5-35 m/s; most average around 20 m/s.. Velocities are slow in children, even before the clinical onset of disease. In individual patients, the motor nerve conduction velocities remain constant over many years, whereas the motor amplitudes decrease, albeit slowly. Nerve biopsies evolve during the disease: demyelination is more prevalent in children, and "hypomyelinated" axons (remyelinated axons with myelin sheaths that are inappropriately thin) become relatively more numerous with age. Biopsies also show age-related loss of myelinated axons; disability correlates with axonal loss.

Although duplication of PMP22 is by far the commonest cause of CMT1A, a few PMP22 mutations produce a similar clinical picture (that has been referred to as CMT1E). Most missense PMP22 mutations, however, produce more severe neuropathy than CMT1A.

CMT1B

Dominant mutations in MPZ cause CMT1B. MPZ encodes P0, the major protein of peripheral nerve myelin.

More than 100 different MPZ mutations have been identified, A few mutations likely cause haplotype insufficiency from a simple loss-of-function; these are associated with an exceptionally mild phenotype. For most mutations, the clinical phenotype can be related to the degree of dys/demyelination as judged by conduction slowing and nerve biopsies. About 25 mutations, however, have a peculiar clinical presentation – sometimes termed CMT2I, CMT2J, or CMT2-P0.. Most MPZ mutations cause an early onset, demyelinating neuropathy (that could often be labeled CMT3/Déjérine-Sottas neuropathy, although some patients have a favorable clinical course) or a late-onset phenotype; few patients have a CMT1-like phenotype.

CMT1C

Dominant mutations in LITAF cause CMT1C. LITAF has been found to have several functional roles; how dominant LITAF mutations cause demyelination is unknown.
The clinical onset varies from 6-30 years. Affected patients have weakness and sensory loss in a distal distribution. Motor nerve conductions are slowed (16-33 m/s) and nerve biopsies show remyelinated axons.

CMT1D

Dominant mutations in EGR2 cause CMT1D. EGR2 encodes a transcription factor, EGR2/Krox20, which, along with Sox10, increases the expression of many myelin-related genes. Dominant Krox20 mutants probably cause demyelinating neuropathy because they reduce the activity of wildtype Krox20 on myelin gene expression.

EGR2 mutations are rare, and most cause a severe, demyelinating neuropathy - Déjérine-Sottas Neuropathy or Congenital Hypomyelinating Neuropathy. A few mutations, however, are associated with a milder/CMT1 phenotype. Affected individuals have weakness and sensory loss in their distal extremities; these findings worsen with age.

CMT1E

Experts consider CMT1E to be CMT1 and deafness, caused by a subset of dominant PMP22 mutations, to be a distinct entity. Dr. Thomas Bird, has offered a more reasonable definition - that CMT1E is caused by a subset of PMP22 mutations (besides the more common PMP22 duplication) that result in a similar clinical picture to CMT1A.

CMT1F

CMT1F is CMT1 caused by autosomal dominant NEFL mutations. This subset of NEFL mutations causes a severe, early-onset neuropathy with demyelinating features that are likely the result of a severe axonal pathology.

CMT1X

CMT1X is so-named because it was linked to the X chromosome. Because female carriers are often affected, it is considered to be an X-linked dominant trait Mutations in GJB1, the gene that encodes connexin32 (Cx32), cause CMT1X; hundreds of different mutations have been identified. Cx32 forms gap junctions, which are channels on apposed cell membranes that permit the diffusion of ions and small molecules. Cx32 is localized to incisures and paranodal loops of myelinating Schwann cells, and likely forms gap junctions between adjacent layers of the myelin sheath. The loss of these gap junctions is thought to lead to demyelination and axonal loss - the chief pathological findings in humans and mice with GJB1/Gjb1 mutations.

For affected males, the clinical onset is between 5 and 20 years of age. The initial symptoms include difficulty running and frequently sprained ankles, progressing to involve the gastrocnemius and soleus muscles to the point where assistive devices are required for ambulation. Weakness, atrophy, and sensory loss also develop in the hands, particularly in the thenar muscles. These clinical manifestations are the result of a chronic, length-dependent axonal loss, and are nearly indistinguishable from those seen in patients with CMT1A or CMT1B. However, muscle atrophy, particularly of intrinsic hand muscles, positive sensory phenomena, and sensory loss may be more prominent in CMT1X patients. Forearm median or ulnar motor velocities are typical in the range of 30-40 m/s ("intermediate"); sensory responses are typically absent except in young children.

Affected women usually have a later onset than men, after the end of the second decade, and a milder version of the same phenotype at every age, because only a fraction of their myelinating Schwann cells express the mutant GJB1 allele owing to the randomness of X-inactivation. Women may even be asymptomatic, and a few kindreds have been reported to have "recessive" CMT1X. Even in these kindreds, however, at least some carriers have electrophysiological evidence of peripheral neuropathy.

Many GJB1 mutations appear to be associated with electrophysiological, clinical, and/or MRI findings of Central Nervous System(CNS) involvement. Subclinical involvement is common: many patients have delayed brainstem auditory evoked responses (BAER), and central visual and motor pathways may also be affected. Clinical manifestations (spasticity, extensor plantar responses, and hyperactive reflexes)

have been reported in patients with the same mutations; the degree of these findings may be masked by the peripheral neuropathy. More striking CNS findings have been reported in individual patients with duplication of amino acids 55-61 (cerebellar ataxia and dysarthria) or the Val63Ile mutation (mental retardation), but the relationship of these abnormalities to GJB1 mutations is unproven. Acute, transient encephalopathy associated with MRI changes, suggesting CNS myelin dysfunction, have been described. The acute deficits appear to have been triggered by travel to high altitudes, fever, or strenuous physical activity.