CMT disease usually manifests during the first to second decades with symptoms related to insidious footdrop: frequent tripping and inability to jump well or run as fast as other children. Over time, distal upper extremity weakness develops, resulting in difficulty with buttoning, handling keys, and opening jars. Examination reveals distal weakness and wasting of the intrinsic muscles of the feet, the peroneal muscles, the anterior tibial muscles, and the calves (inverted champagne bottle legs). A variable degree of impaired large-fiber sensory function is reflected in reduced vibratory sensation at the toes. Muscle stretch reflexes are lost, first at the ankles. Typically, a foot deformity exists, with high arches (pes cavus) and hammer toes, reflecting long-standing muscle imbalance in the feet. Most patients with CMT disease have nearly normal occupational and daily activities, and they have a normal life span. Although no specific treatment has been developed, the foot drop can be treated by appropriate bracing of the ankle with ankle-foot orthoses. Genetic counseling and education of affected patients and their families are important, both for reassurance and to preclude unnecessary diagnostic evaluation of affected members in future generations.

Demyelinating forms of CMT are classified as CMT1 and axonal forms as CMT2. CMT is usually transmitted as an autosomal dominant trait; however, X-linked dominant transmission is responsible for approximately 10% of cases. Rare autosomal recessive forms are designated CMT4, and these patients tend to have an earlier onset and more severe phenotype. CMT1A is the most common form and accounts for 90% of CMT1 and 50% of all CMT cases. CMT1A is associated with the 17p11.2-p12 duplication in the *PMP22* gene expressed by Schwann cells. A deletion or a point mutation of the *PMP22* gene produces a different phenotype: HNPP, which is characterized by recurrent episodes of focal entrapment with attacks of weakness and numbness in the peroneal, ulnar, radial, and median nerves (in descending order of frequency) or in a brachial plexus distribution.

FAMILIAL AMYLOID NEUROPATHIES

Amyloid neuropathy is an autosomal dominant disorder caused by extracellular deposition of the fibrillary protein amyloid in peripheral nerve and sensory and autonomic ganglia, as well as around blood vessels in nerves and other tissues. The age of onset varies from 18 to 83 years. In all forms of amyloidosis, the initial and major abnormalities affect the small sensory and autonomic fibers. Involvement of small fibers responsible for pain and temperature sensibilities leads to loss of the ability to perceive mechanical and thermal injuries and to an increased risk of tissue damage. As a result, painless injuries present a major hazard of this disorder; in advanced stages, they can lead to chronic infections or osteomyelitis of the feet or hands and the necessity for amputation. Amyloid deposition in the heart can lead to cardiomyopathy. Mutations in transthyretin, apolipoprotein A1, or gelsolin are responsible. Early recognition is essential, as liver transplantation has been shown to halt disease progression.

For a deeper discussion on this topic, please see Chapter 420, "Peripheral Neuropathies," in Goldman-Cecil Medicine, *25th Edition.*

SUGGESTED READINGS

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