CHAPTER 42

Pathogenesis And Clinical Presentation Of Charcot-Marie-Tooth Disease

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Charcot-Marie-Tooth disease (CMT) is a hereditary sensory-motor neuropathy (HSMN) which is generally credited as being described simultaneously in 1886 by Charcot and Marie[1] of France, and Tooth[2] of England. In a study at a cavus foot clinic, Brewerton et al.[3] found that two-thirds of the patients who seek treatment for a painful high-arch foot will have an underlying neurologic problem, and half of these will have CMT disease. Thus, the clinician treating problems of the lower extremity must have a working knowledge of this unique disease process.

PATHOLOGY

CMT disease is a hereditary, demyelinating, hypertrophic neuropathy involving peripheral nerves, which causes gross slowing of sensory and motor nerve conduction velocities. Because the name of Charcot is in the eponymic name for the disease, CMT disease is often confused with Charcot's neurogenic osteoarthropathy by the inexperienced clinician or student. CMT disease typically results in bilateral, symmetrical, neurogenic weakness and atrophy. This often results in joint contractures with a cavus foot deformity, clawed or hammered toes, and frequently a drop foot. Rarely, and usually only late in the disease process, joint destruction and osteoarthropathy are seen[4].

In the past, CMT disease has been incorrectly termed peroneal muscular atrophy, progressive peroneal atrophy, or peroneal palsy. Indeed, the most recent editions of *Stedman's Medical Dictionary*[5] and *The Merck Manual*[6] define CMT disease as peroneal muscular atrophy. These misnomers became popular as the CMT patient commonly presented with a cavus foot deformity and an apparent weakness of the peroneal musculature. Years ago, many clinicians falsely believed that both the peroneus longus and peroneus brevis muscles were equally strong evertors of the foot. Thus, when the CMT patient had weakness upon attempted eversion combined with distal leg wasting, both muscles were felt to be atrophied by the disease process. It is now established, but still not widely known, that the primary function of the peroneus longus muscle is to plantarflex and stabilize the first ray against the ground, and it is not typically weakened early in CMT disease. Thus, although the peroneus brevis may weaken early in the disease process, it would be inaccurate to conclude that the "peroneal muscle group is the first to weaken" or that "CMT disease is characterized primarily by peroneal muscle weakness."

In CMT disease, it is most common to see intrinsic muscle atrophy first, followed by wasting of the extrinsic muscles. Recognizing this pattern of weakness, Sabir and Lyttle[7] suggested a logical pattern for CMT muscular atrophy. This pattern is based upon two primary assumptions: (1) the muscles supplied by the longest axons of the sciatic nerve are affected first, and (2) the muscles with the smallest muscle bulk are the first to show wasting and atrophy. In this fashion, a typical pattern of atrophy might start with the intrinsic muscles of the foot, followed by the peroneus tertius, flexor longus muscles, extensor longus muscles, tibialis anterior, and peroneus brevis. The peroneus longus, tibialis posterior, and triceps surae are usually the last to weaken due primarily to their increased relative muscle mass. More proximal muscles above the knee are generally not affected.

Similar to the foot, the musculature of the hand may also be affected. Wasting of the thenar, hypothenar, and the first dorsal interosseous muscles in the hand is common in CMT disease. In more advanced cases, an intrinsic muscle deformity of the fingers develops. This can result in numerous concavities between the metacarpals, and has been termed a "monkey fist" or "skeleton hand."[4]

INCIDENCE/GENETIC FACTORS

The incidence of CMT disease has not been clearly established. However, the disease does appear to be more common in males than in females, and is very rare in black persons.[4] Further, unilateral involvement of an extremity is rare.[8]

The genetic factors of CMT disease have been extensively studied, but are also not well understood. In one of the more thorough studies, Skre[9] studied a population of 725,000 in western Norway. He found three hereditary modes of transmission: (a) autosomal dominant CMT disease, with an estimated prevalence of 36.0/100,000; (b) X-linked recessive CMT disease with an estimated prevalence of 3.6/100,000; and, (c) autosomal recessive CMT disease with an estimated prevalence of 1.4/100,000. Thus, CMT disease is most commonly inherited in an autosomal dominant fashion.

Fortunately, when inherited in an autosomal dominant fashion, CMT disease usually manifests itself in its mildest form. When dominant, the disease typically presents at about 30 years of age, tends to progress slowly, and leads to steadily progressive muscle impairment. The sex-linked mode of inheritance becomes apparent during the second decade of life and tends to run a more severe course. Patients with autosomal-recessive inheritance have the worst prognosis. These patients typically have clinical manifestations around age 8, and profound weakness by age 20.

Because of the high association between CMT disease and pes cavus deformity, and since CMT disease is hereditary, patients presenting for evaluation of a pes cavus deformity should have a thorough family history taken. If the patient does not relate a history of CMT disease, neurological consultation should be considered if CMT disease is suspected.

CLINICAL PRESENTATION

CMT disease should be considered in any patient presenting with lower leg atrophy, pes cavus deformity, poor balance, or an unsteady gait. Typically, CMT patients will present with specific pedal complaints including pain and/or callouses under the metatarsal heads, corns with clawed or hammered toes, foot fatigue, difficulty in finding properly fitting shoes, lateral ankle instability, or difficulty walking. The deformity is almost always bilateral, although one side may be more affected or symptomatic than the other.

In the CMT patient, wasting of the lower leg musculature is a common finding. Due to the relative sparing of the proximal thigh musculature, the CMT patient usually has an upturned or inverted "champagne bottle" or "stork leg" appearance (Fig. 1). With significant anterior crural muscle weakness, the patient may present with a drop foot deformity. In CMT patients with significant drop foot, the gait has been described as a "marionette" or modified high-steppage gait.[7] In this gait pattern, pelvic elevation and pelvic shift on the swing side compensate for the foot drop present. The loss of balance caused by this pelvic elevation and shift is compensated for by bending of the upper trunk in the contralateral direction. This keeps the center of gravity above the foot in stance. Thus, these patients are very unsteady during gait and can have marked problems walking on uneven surfaces, on inclines, or in turning.

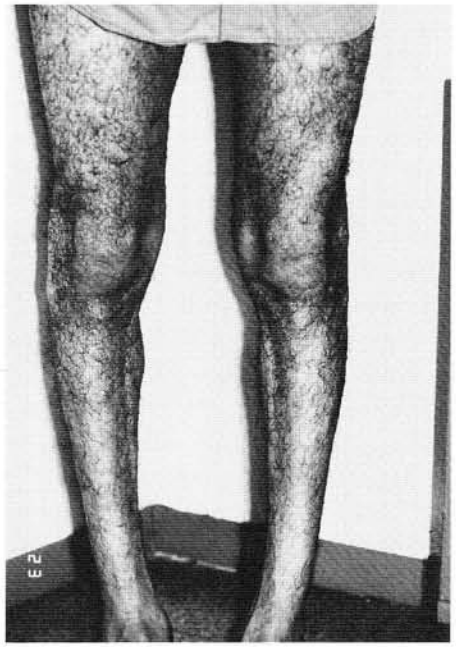

Figure 1. Typical upturned or inverted "champagne bottle" or "stork leg" appearance in CMT patient.

The pes cavus deformity is the most consistent finding in the CMT patient (Fig. 2). The cavus deformity may be flexible or rigid, depending on the length of time the deformity has been present and the degree of muscle imbalance. With time, a rigid pes cavus or cavovarus deformity will certainly develop. Flexible or rigid forefoot valgus

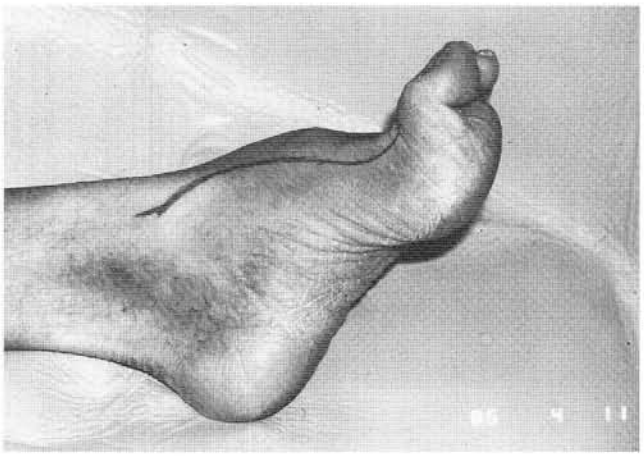

Figure 2. Typical pes cavus deformity in CMT patient.

and rearfoot varus are usually prominent components of the deformity, suggesting continued function of the peroneus longus muscle. In some cases, a pan-metatarsal equinus deformity with a neutral heel position will be seen. Rarely, the CMT patient will present with a pes valgo planus deformity (Fig. 3).

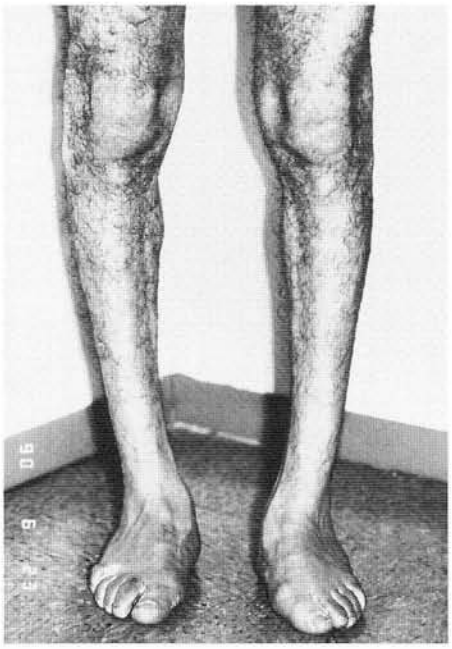

Figure 3. Patient with CMT disease and pes valgo planus deformity. Note the severe wasting of calf musculature typical in CMT disease.

Intrinsic muscle weakness associated with CMT disease often results in dynamic hammertoe or claw toe formation (Fig. 4). Extensor substitution and flexor stabilization deformities are often seen in CMT patients. With loss of the lumbricales and interossei, flexion at the metatarsophalangeal joints is lost, and the long extensors and long flexors overpower the lumbricales and interossei, respectively. Dorsiflexion at the metatarsophalangeal joints may be flexible or rigid, depending primarily on how long the imbalance has been present. Similarly, the muscle imbalance causes plantarflexion at the proximal interphalangeal joints and either dorsiflexion or plantarflexion at the distal interphalangeal joints. With time, the toes become fixed, dorsally subluxed or luxated at the metatarsophalangeal joints, and flexed at the interphalangeal joints. As this occurs, the metatarsal heads become even more prominent plantarly, accentuating the declination of the forefoot.

Another common feature of the CMT patient is the presence of sensory neuropathy. However, it should be noted that most of the patients will be unaware of their lost sensory capacity, and atrophy is a more common finding. All modalities of sensation are affected, including pain, temperature, vibration, touch, and proprioception. Areflexia or hyporeflexia of the Achilles tendon and patellar

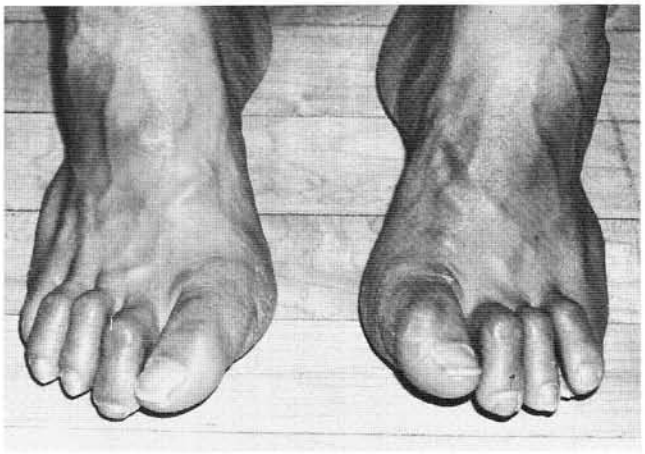

Figure 4. Claw toe deformities in a patient with CMT disease.

tendon reflexes is evident. The diminished pain sensation may decrease the need for narcotic medications in those CMT patients who elect to undergo surgical correction of their deformities. In advanced cases, the lack of sensation and proprioception can lead to neuroarthropathy. Bruckner and Kendall[10] termed the concomitant presence of Charcot-Marie-Tooth disease and Charcot's osteoarthropathy to be "Double Charcot's Disease" (Fig. 5A-C).