# Pediatric Charcot-Marie-Tooth Disease

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**KEYWORDS**

• Charcot-Marie-Tooth disease • Pediatric • Electrophysiology • Gait

**KEY POINTS**

- Charcot-Marie-Tooth disease (CMT) is the most prevalent genetic neuromuscular disease in children.
- Dejerine-Sottas syndrome is the infantile form of inherited neuropathy.
- CMT is divided into 2 major groups: demyelinating and axonal neuropathy.
- More than 80 CMT-causing genes have been identified with the aid of new-generation DNA sequencing.
- PMP22 duplication in CMT1A is the most frequent cause of CMT.
- Standardized evaluation tools have been developed, including a pediatric neuropathy scoring system and gait analysis (computerized motion analysis).
- Therapeutic management consists of physical and orthopedic therapies that should be tailored individually in order to maintain the quality of life of children with CMT.

## INTRODUCTION

Charcot-Marie-Tooth disease (CMT), or hereditary motor and sensory neuropathy, has long been recognized as a heterogeneous group of inherited neuropathies.[1,2] These two terms have been used interchangeably, but the scientific literature tends to use the eponym CMT more often.

Perhaps the first description of this neuropathy in medical literature originated from Friedreich[3] or Eichhorst[4] in 1873. Familial length-dependent peripheral neuropathy

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was later described by the French neurologists, Charcot[5] and Marie, and independently by a British neurologist, Tooth,[6] in 1886 referring to the prominent distal muscle wasting of the weak muscles as peroneal muscular atrophy. The infantile form was first reported by Dejerine and Sottas[7] in 1893. Dyck and Lambert[8] in 1968 published their work on the major electrophysiologic characteristics of inherited neuropathies and later initiated the first classification based on the electrophysiologic features of their patients. They identified 2 major groups: 1 as CMT1, with slow nerve conduction velocities (NCVs) along with pathologic finding of hypertrophic demyelination; and CMT2, with normal or mildly reduced NCVs along with pathologic evidence of axonopathy. Most patients with CMT (~70%) belong to the first group and have autosomal dominant inheritance pattern.[9]

According to Ouvrier and Nicholson's[10] estimation, about 30% of pediatric neuromuscular patients have some form of neuropathy, but only about 10% of these are acquired, whereas the rest are likely to have genetic causes. CMT represents the largest group of inherited neuromuscular diseases with an estimated prevalence of 0.5 to 1 in 2500.[11,12] During a 33-year retrospective analysis of data from 260 patients, Wilmshurst and colleagues[13] documented that about 1 in 5 cases had an infantile (less than 1 year of age) presentation. The medical literature has been sparse in pediatric CMT until recently, which can be attributed to an absence of national or international data collection programs, uniform evaluation tools, and long-term natural history studies.[14,15] Another contributing factor is the significant delay in diagnosis for the pediatric CMT population. Based on our own observation of 117 pediatric patients with CMT at the former Wayne State University CMT Clinic (Detroit, MI), the average delay of clinical diagnosis was more than 10 years even in families known to have CMT (Acsadi and Shy, unpublished observation, 2005). In another cohort of 39 patients, we documented that the mean age at CMT diagnosis was 8 $\pm$ 5 years (range, 18 months to 16 years).[16] Most adults with CMT experienced some clinical signs during their childhood; however, these signs, such as motor delay, hip dysplasia, foot abnormalities, scoliosis, pain, or decreased athletic abilities, can be subtle.[17]

## FORMS AND GENETICS OF CHARCOT-MARIE-TOOTH DISEASE

The initial term hereditary sensorimotor neuropathy was based on the pathology and inheritance pattern.[18] Based on the pathology and electrophysiology, there are 2 major types of CMTs: the most frequent is the dysmyelinating form caused by defects in myelin-forming Schwann cells, and the less common is the axonal form caused by primary abnormalities in the nerve axon and/or its interactions with Schwann cells (reviewed by Saporta and Shy[19] in 2013). Motor and sensory or autonomic nerves are variably affected in CMT; however, autonomic symptoms are uncommon.[20] After detailed electrophysiologic characterization of various neuropathies[8] and in the era of molecular genetic association, the CMT eponym has gained popularity in the scientific literature.

CMT is monogenic and the rate of gene discovery has been exponential since the availability of new-generation whole-exome DNA sequencing (WES) techniques. More than 80 genes have been identified as disease-causing genes.[21] Because of space limitation, this article cannot describe all of the CMT-related gene defects. For a comprehensive list of CMT genes, see the recent review by Timmerman and colleagues[21] (2014) and Gene Reviews (http://www.ncbi.nlm.nih.gov/books/NBK1205/). Depending on the molecular techniques used to identify the genetic cause in individual patients, about 20% to 30% of patients with inherited neuropathy have unknown genetic causes; however, this rate is rapidly declining because of new-generation sequencing tools.[22]