

Charcot-Marie-Tooth Disease

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Introduction

Charcot-Marie-Tooth (CMT) disease is the most common hereditary polyneuropathy and is classically associated with an insidious onset of distal predominant motor and sensory loss, muscle wasting, and pes cavus. The disease illustrates a multitude of genetic principles, including diverse mutational mechanisms from point mutations to copy number variation (CNV), allelic heterogeneity, age-dependent penetrance and variable expressivity.¹ Clinical diagnosis is based on family history and characteristic findings on physical examination, EMG/NCV testing, and occasionally sural nerve biopsy. Molecular genetic testing is possible for some types of CMT.²

Case report

A seven years of age female presented with complaints of difficulty in walking for 5 years and hand deformity for 4 years (Figure 1). The walking difficulty was insidious in onset with slow progression and severe disturbance in daily activities associated with frequent falls, inability to hold feet above ground, to climb stairs without support, paresthesia and numbness. The hand deformity was bilateral with slow onset, flexion deformity of fingers and wasting of muscles of hands (progressively increasing for 4 years), difficulty in holding objects and difficulty in writing and combing. There was no history of Fever, joint deformity or swelling, tremors, seizures, loss of consciousness, visual and hearing problems, intellectual impairment and calf muscle hypertrophy. She was born by spontaneous vaginal delivery at hospital with no history of perinatal complications, achieved developmental milestones at appropriate age and was vaccinated according to EPI schedule. Her parents had a consanguineous marriage and two family members were affected with similar complaints. On general physical examination there was obvious claw hand deformity, wrist and foot drop, while rest of the examination was unremarkable. Also there was wasting of distal musculature, flattening of the thenar and hypothenar eminence, power was 3/5 in the distal musculature and 5/5 in the proximal muscles. Brachioradialis reflex was absent but biceps and triceps reflexes were elicited. Tone, however, was normal. In

lower limb there was bilateral foot drop and wasting of the distal muscles of the leg (Figure 2). Tone was normal while power was 3/5 in the distal muscles 4/5 in the proximal muscles but normal in the axial muscles. Ankle jerk was absent, knee reflex was elicitable and plantars were bilaterally nonspecific and there was a characteristic high stepping gait.

On sensory system examination there was loss of proprioception and vibratory sense distally in all four limbs but pain and temperature sensations were intact. The sensory examination of the proximal limbs was unremarkable. Cerebellar examination was unremarkable. On nerve conduction studies lead potential was not recordable in median, ulnar and sural nerve while on EMG there were fibrillations with large polyphasic motor unit action potentials and reduced recruitment of tibialis anterior, gastrocnemius, brachioradialis, first dorsal interossei (bilateral). In short there were absent sensory studies in median, ulnar and sural nerve and absent motor studies in median, ulnar, common peroneal and tibial nerve.

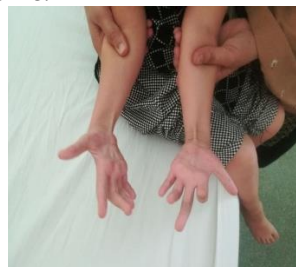


Figure 1. Claw hand deformity.

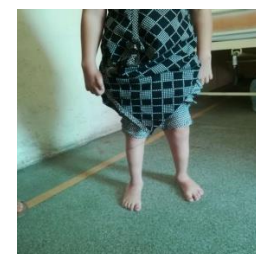


Figure 2. Bilateral foot drop and wasting of the distal muscles of the leg

The electrophysiological studies were suggestive of chronic sensorimotor polyneuropathy. So hereditary motor sensory neuropathy - II was considered. On sural nerve biopsy there were reduced large and medium sized myelinated fibers, collagen was increased, onion bulb formation due to proliferated schwann cell cytoplasm surrounding axons and extensive segmental demyelination and remyelination. A final diagnosis of Charcot Marie Tooth disease was made. Patient was started physiotherapy including hand grip exercises, orthotics i.e. AFO (ankle foot orthosis) for walking and Splints

for hands were applied, attendant counselling was done and a two month follow up was advised.

Discussion

Charcot-Marie-Tooth (CMT) disease is the most common inherited neurologic disorder with an estimated prevalence of 17 to 40/10,000. ³Slowly progressive distal weakness, muscle atrophy, and sensory loss due to an inherited peripheral neuropathy was described independently in 1886 by Charcot and Marie in France and by Tooth in England. A few years later, Dejerine and Sottas recognized and described a more severe, infantile form of inherited neuropathy. More recently the disease has been categorized in five types (Table 1)

Table 1. Charcot-Marie-Tooth (CMT) disease-Types ⁴

Type	Characteristic
CMT1	Dominantly inherited, hypertrophic, predominantly demyelinating form
CMT2	Dominantly inherited predominantly axonal form
Dejerine-Sottas	Severe form with onset in infancy
CMTX	inherited in an X-linked manner
CMT4	includes the various demyelinating autosomal recessive forms of Charcot-Marie-Tooth disease

In a large study of German individuals with a CMT1 phenotype (776), Gess et al. found the following percentages: CMT1A (51%), CMTX1 (9%), and CMT1B (5%). Sixty-six percent of subjects with a CMT1 phenotype had a genetic diagnosis. Of those with a CMT2 phenotype, 11% had CMTX1, 8% had CMT2A, and 6% had the rare giant axonal neuropathy. Thirty-five percent of individuals with CMT2 had a genetic diagnosis.⁵

The main features of CMT are a combination of lower motor neuron-type motor deficits and sensory signs and symptoms, reflecting the sensory-motor neuropathy. Length-dependent paresis and muscle atrophy develops, with areflexia, although a subset of patients will retain deep tendon reflexes, especially in the axonal forms. The chronic nature of the motor neuropathy will result in foot deformity (eg, *pes cavus*), hammertoes and high-arched feet. Involvement of the hands may follow as the disease progresses. Sensory symptoms are less frequent than in acquired chronic neuropathies, but may point to specific gene

involvement. Signs of sensory system dysfunction are common (70%) and include loss of vibration and joint position sense followed by decreased pain and temperature sensation in stocking and glove distribution. Clinical features do not distinguish between the demyelinating or axonal forms.⁶

A three-generation family history with attention to other relatives with neurologic signs and symptoms should be obtained. Ancillary diagnostic tests include electrophysiological studies and sural nerve biopsy. Recently, peripheral nerve MRI and skin biopsy have emerged as potential diagnostic aids in certain types of hereditary neuropathies, though further research studies are needed. EMG and nerve conduction studies (NCS) distinguish two major types - the demyelinating form, which is characterized by symmetrically slowed nerve conduction velocity (NCV; usually <38 m/s), and the axonal form, which is associated with normal or subnormal NCV and reduced compound muscle action potential. Sural nerve biopsies from patients with the demyelinating type reveal segmental demyelination and onion bulb formation, whereas the nerve biopsies from patients with the axonal form show axonal loss, absent or few onion bulbs and no evidence of demyelination⁶

Management is by a multidisciplinary team of neurologists, physiatrists, orthopedic surgeons, and physical and occupational therapists; special shoes and/or ankle/foot orthoses (AFOs) to correct foot drop and aid walking; gripping exercises for hand weakness; orthopedic surgery as needed for severe pes cavus deformity and hip dysplasia; acetaminophen or nonsteroidal anti-inflammatory agents for musculoskeletal pain; tricyclic antidepressants, carbamazepine or gabapentin for neuropathic pain.⁷

References

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