Case Report

Pediatric Charcot-Marie-Tooth disease: A case report and diagnostic challenges

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ABSTRACT

Charcot-Marie-Tooth (CMT) disease is a hereditary motor sensory neuropathy affecting about one in 2500 individuals that is characterized by progressive weakness and loss of touch sensation affecting different parts of the body. Despite its significant genetic heterogeneity, CMT is rarely reported in the Indian literature. We report a 10-year-old boy with CMT presented with severe calf pain, bilateral pes cavus deformity, and areflexia. His mother also had similar symptoms, and the diagnosis was confirmed by neuroimaging and nerve conduction studies. This highlights the importance of considering CMT disease in patients with progressive muscle weakness and deformities, especially with a family history of similar symptoms.

Key words: Areflexia, Charcot-Marie-Tooth, Hereditary, Neuropathy, Pes cavus

Charcot-Marie-Tooth (CMT) disease, which was formerly known as "hereditary motor and sensory neuropathy" (HMSN), is a widely recognized inherited peripheral neuropathy that involves motor and sensory nerves and affects individuals of both sexes and all ethnic backgrounds. It can be divided into demyelinating (Type 1) and axonal (Type 2) based on electrophysiology and histopathology. CMT Type 1 is characterized by severely reduced motor nerve conduction velocities (<38 m/s) and segmental demyelination with onion bulb formations, while CMT Type 2 is characterized by normal or mildly reduced velocities and chronic axonal degeneration and regeneration. CMT1 can be further divided into X-linked, autosomal dominant (AD), and autosomal recessive (AR) forms [1]. The most common symptom of CMT is weakness in the feet and ankles. Initial physical findings may include depressed or absent tendon reflexes and weakness of foot dorsiflexion at the ankle. Typical presentation includes bilateral foot drop, symmetrical atrophy of muscles below the knee, pes cavus, atrophy of intrinsic hand muscles (especially the thenar muscles of the thumb), and absent tendon reflexes in both upper and lower extremities.

CASE REPORT

A 10-year-old boy presented with progressive worsening of bilateral calf pain over the past 2 weeks, which had become severe over the past 2 days. The pain was persistent and interfering with the child's sleep and daily activities. He had a history of recurrent leg pain in the past, but there were no signs of fever, early morning stiffness, joint involvement, or arthralgia. However, he had difficulty in walking due to the pain; there was no history of lower limb weakness. He had a similar history of calf pain at 2 years of age for which, he was treated symptomatically and improved.

He was the second child of a non-consanguineous marriage and there were no significant antenatal or perinatal issues. The child's mother had a history of similar episodes of leg pain and pes cavus deformity from childhood, but she had not been fully evaluated. The patient had achieved all developmental milestones for his age, and according to his mother, he was performing well in school, currently studying in fifth standard.

On general examination, the child had a weight of 30 kg (25 percentile) and a height of 138 cm (25–50 percentile). His vital signs were stable. The child had pallor but no icterus, cyanosis, clubbing, lymphadenopathy, or pedal edema. He had severe calf muscle tenderness on both legs and pes cavus deformity bilateral (Fig. 1). His higher mental function and cranial nerve were normal. Bulk, power, and tone of both upper and lower limbs were normal. Deep tendon reflexes were absent in both legs. Blood investigations revealed a normal full blood count, electrolytes, C-reactive protein, liver renal function, and creatine phosphokinase (47 U/ml). Cerebrospinal fluid analysis showed 35 cells with 40% polymorphs and 60% lymphocytes, with elevated protein (190 mg/dL) and normal sugar.

Nerve conduction studies (NCS) showed prolonged distal latency, reduced compound muscle action potential (CMAP) amplitude, significantly reduced conduction velocity, and absent

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F waves in multiple nerves, including the left median, ulnar, and peroneal nerves, as well as the sural and tibial nerves (Table 1). A significant conduction block is noted in the left peroneal nerve. In addition, sensory nerve action potentials were absent in the left median and ulnar nerves and both sural nerves as shown in Table 2. These findings suggest a predominantly demyelinating type of peripheral neuropathy. Magnetic resonance imaging (MRI) spine showed diffuse, symmetrical thickening and hyperintensity of lumbar nerve roots and lumbar plexus components on both sides. There was thickening and hyperintensity of the visualized femoral and sciatic nerve on both sides depicting the diagnosis of inflammatory demyelinating polyradiculopathy (Fig. 2).

The child was treated with a course of oral steroids and NSAIDS for pain management and physical therapy focusing on gait training, therapeutic exercise and postural stabilization, fall risk prevention strategies, serial casting/night splinting, and prevention of secondary impairments. Corrective surgery for pes caves deformity was advised if it interferes with daily activities.

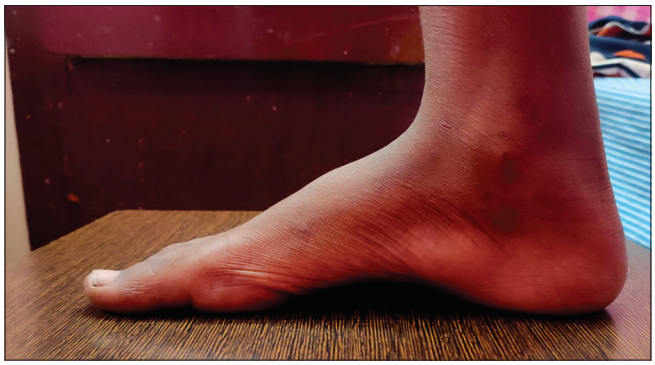

Figure 1: Typical foot of patient with Charcot-Marie-Tooth, showing pes cavus

Genetic evaluation was advised to confirm the diagnosis and to classify the specific type and the parents were advised about the need for close follow-up and physiotherapy.

DISCUSSION

CMT disease is a genetically and clinically heterogeneous group of disorders found in 1 in 2500 individuals that are characterized by progressive weakness and loss of touch sensation affecting different parts of the body [2]. In this case, the main clinical features were bilateral calf pain, areflexia, pes cavus deformity, and a similar complaint in the mother. The diagnosis of hereditary neuropathy was supported by NCS and MRI of the spine. There is limited literature reporting the foot deformities associated with the various types of HMSNs. While the history, clinical examination, and inheritance of different types of CMT vary, genetic evaluation is required to identify the underlying mutation.

CMT is caused by mutations in over 80 genes, with the majority of neuropathies being demyelinating, although up to one-third of cases may present as primary axonal disorders [3]. Clinical manifestations of CMT are heterogeneous but patients often experience distal weakness, loss of sensation, and foot deformities such as pes cavus and hammer toes that may appear in the first or second decade of life. Although the disease progresses slowly throughout a patient's lifespan, some individuals may exhibit severe, rapidly progressive disability in early childhood.

CMT is classified into two types based on upper limb motor conduction velocities (MCV): CMT1 (demyelinating) with MCV <38 m/s, and CMT2 (axonal) with MCV more than 38 m/s. Demyelinating CMT shows uniformly slow MCVs, whereas acquired demyelinating neuropathies exhibit patchy slowing.

Table 1: Motor nerve conduction study

Nerve/sites	Muscle	Latency (ms)	Amplitude (mV)	Segments	Latency difference (ms)	Distance (mm)	Velocity (m/s)	Duration (ms)
L Median-APB								
Wrist	APB	8.29	7.3	Wrist-APB		70		15.23
Elbow	APB	18.9	6.0	Elbow-wrist	10.00	170	17	16.19
L Ulnar-ADM								
Wrist	ADM	6.50	5.2	Wrist-ADM		70		14.12
B Elbow	ADM	18.12	4.0	B Elbow-wrist	11.62	180	15	15.94
L Peroneal-EDB								
Ankle	EDB	5.92	2.6	Ankle-EDB		50		11.56
B Fib	EDB	24.29	0.6	B Fib head-Ankle	18.38	270	15	12.25
R Peroneal-EDB								
Ankle	EDB	5,83	2.5	Ankle-EDB		50		11.02
B Fib head	EDB	26.25	1.6	B Fib head ankle	20.42	170	13	12.21
L Tibial-AH								
Ankle	AH	7.25	2.8	Ankle-AH		50		21.44
Knee	AH	28.62	1.2	Knee-ankle	21.37	320	15	21.98
R Tibial-AH								
Ankle	AH	7.94	3.1	Ankle-AH		50		17.10
Knee	AH	29.88	1.5	Knee-ankle	21.94	320	15	19.40

APB: Abductor pollicis brevis, ADM: Abductor digiti minimi, EDB: Extensor digitorum brevis, AH: Abductor hallucis

Table 2: F Waves

Nerve	F Latency ms	M Latency ms
L Peroneal-EDB	Absent	8.3
L Tibial-AH	Absent	9.7
R Peroneal-EDB	Absent	8.1
R Tibial-AH	Absent	8.8
L Median-APB	61.8	9.4
L Ulnar-ADM	Absent	7.5

APB: Abductor pollicis brevis, ADM: Abductor digiti minimi, EDB: Extensor digitorum brevis, AH: Abductor hallucis

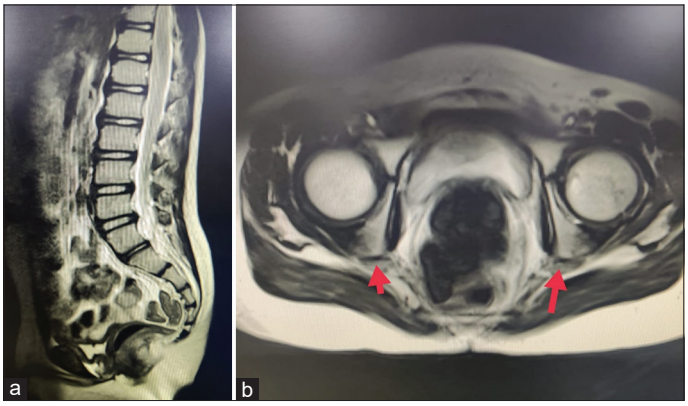

Figure 2: The T2-weighted MRI of the spine displays noticeable thickening of the lumbar nerve roots (a) Sagittal, (b) Axial

Intermediate forms with MCVs between 25 and 45 m/s may aid in genetic diagnosis [4].

There are different types of CMT based on inheritance patterns; (AD) CMT1 is the most common form of CMT, presenting with lower limb motor symptoms, distal weakness, atrophy, sensory loss, hyporeflexia, and foot deformity. The upper limb involvement is later and patients usually have normal lifespans. X-linked CMT1 is caused by mutations in the GJB1 gene encoding connexin 32 (C×32), a gap junction protein expressed in Schwann cells [5].

AD CMT2 patients may present with profound sensory impairment and complications of sensory loss, including ulcerations, osteomyelitis, and amputations [6]. Motor involvement is usually less than sensory involvement. AR CMT is less common than AD CMT. AR CMT1 is classified as CMT4, while AR CMT2 is usually just called AR CMT2. CMT4 cases have early, infantile-onset and may result in early loss of ambulation. Nerve biopsies can be useful for genetic diagnosis. Certain forms of CMT present with MCVs in the intermediate range (25–45 m/s), including dominant intermediate (DI)-CMTB caused by DNM2 mutations [7].

According to most authors, cavovarus is the most common foot deformity in CMT [8]. Joo *et al*. found out that the most common deformities encountered by CMT are pes cavus, forefoot adduction, midfoot supination, and pes varus deformity [9] and Wines *et al*. study also shows 66% are Cavo varus, 22% planovalgus, and 12% with no significant deformity [8].

The electrophysiological studies conducted on this 10-year-old boy revealed the absence of sensory nerve action potentials in the sural, left median, and ulnar nerves, as well as, reduced CMAP and conduction velocity in the right peroneal nerve, and conduction block in the left peroneal nerve. These findings differ from other studies that have shown that neurophysiological abnormalities are present in all children with CMT1A from the age of 2 years. Motor conduction slowing progresses during the first 6 years of life and then stabilizes, while CMAP amplitude is reduced from an early age and the normal increase with age is limited. In younger children, median sensory responses may be recorded [10].

The diagnosis and evaluation of CMT still heavily rely on a thorough history and physical examination. Although genetic testing plays a crucial role in confirming a diagnosis after electrodiagnostic testing, in cases where there is a family history of confirmed CMT, immediate genetic testing may be appropriate, particularly when a relative has a known pathogenic variant. However, it is important to note that inheritance patterns of CMT can be complex due to the highly variable expression of the disease, which means that some oligosymptomatic relatives may be missed during genetic testing. In addition, sporadic CMT is common and may be caused by de novo pathogenic variants. Therefore, despite the widespread availability of genetic testing, electrodiagnostic testing remains important in many cases of CMT.

There is no cure for CMT but treatment is available to slow down the progression of the disease and improve the quality of life of patients which includes orthopedic surgery to correct deformities such as scoliosis and high-arched feet, physical therapy to improve muscle strength and range of motion, occupational therapy to help with daily activities and adaptive devices, medications to manage pain, and other symptoms and genetic counseling and testing for family planning.

Some of the emerging therapies that are being researched for CMT are stem cell therapy to repair nerve damage, hormone therapy, and gene therapy to slow down the disease progression, gene silencing, and gene replacement therapies to target specific genetic causes of CMT. These therapies are still in preclinical or clinical trial stages, and more research is needed to determine their safety and efficacy for CMT patients [11,12].

CONCLUSION

CMT is an unusual clinical entity that can present as familial demyelinating peripheral neuropathy, areflexia, and foot anomalies like pes cavus. A proper clinical examination, detailed history, and family history are essential for a definitive diagnosis. A high index of suspicion by clinicians is necessary to establish a timely and accurate diagnosis of CMT. Although CMT can be inherited with other neuromuscular conditions, it typically has a slow progression, and treatment is mainly physiotherapy and other supportive measures.

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