CASE REPORT

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The Silent Strain: A Rare Case of Charcot-Marie-Tooth 4H

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Abstract

Charcot-Marie-Tooth disease 4H (CMT4H) is an autosomal recessive demyelinating form of CMT caused by FGD4/FRABIN mutations. CMT4H is typically characterised by early onset and a slow progression of motor and sensory deficits, particularly in the distal extremities, along with foot deformities. Here, we report a patient with CMT4H who presented with gradually worsening flaccid paraparesis. This case represents the second reported instance of CMT4H in an Indian patient, harboring a novel homozygous 1880T >C (p.Phe627Ser) mutation in the FGD4 gene. This case emphasizes the importance of genetic testing in the diagnosis of rare neuromuscular disorders, particularly when clinical findings suggest a hereditary neuropathy with atypical progression.

Introduction

Charcot-Marie-Tooth disease (CMT) is a diverse group of genetically and clinically varied heterogeneous peripheral neuropathies, characterised by the progressive degeneration of distal muscles and loss of sensory function. CMT type 4 (CMT4) is an autosomal recessive demyelinating form of CMT, distinguished by an earlier onset of symptoms. CMT4 is further classified into several subtypes, CMT4A to CMT4J, based on clinical manifestations and genetic causes. Mutations in over 10 different genes, including GDAP1, MTMR2, SBF1, SBF2, NDRG1, HK1, MPZ, EGR2, SH3TC2, PRX, FGD4, FIG4, and SURF1, have been identified as causes of CMT4[1]. CMT type 4H, caused by mutations in the FGD4 gene, typically presents in the first decade of life with slow progression, areflexia, and foot deformities[2]. While most cases of CMT4H have been reported in the Mediterranean region, it is rarely seen in other areas. In this report, we describe a case of CMT4H in an Indian patient.

Case Presentation

A 17-year-old girl presented with a long-standing history of weakness in both lower limbs, which began at the age of 1.5 years. She was born via normal vaginal delivery at 9 months, with early development progressing normally. The symptoms first appeared when she started walking at the age of 1.5 years, with complaints of knee buckling and frequent falls, particularly on uneven surfaces. By school age, she had difficulty climbing stairs and required support to board the bus. At the age of 7 to 8 years, she found it challenging to descend the bus independently and had trouble participating in physical activities, such as running. By the age of 9-10 years, she voluntarily stopped dancing due to a fear of falling. Over time, the weakness has gradually worsened. From the age of 11 years, she initially needed minimal support to squat and stand up. However, in the last seven months, her condition progressed to the point where she now required two-person assistance to rise from a squatting position. In the past year, she also struggled with wearing slippers, having difficulty reaching her feet to place them on and experiencing slippage.

The patient denied any sensory disturbances such as tingling, numbness, paresthesias, or burning sensations. There was no history of autonomic disturbances, including tachycardia, palpitations, flushing, or urinary abnormalities. She reported no sensorimotor complaints in the upper limbs or any signs of cranial nerve involvement. There was no family history of similar complications over the past three generations (Fig. 1).

Physical examination revealed a *pes cavus* deformity (Fig.

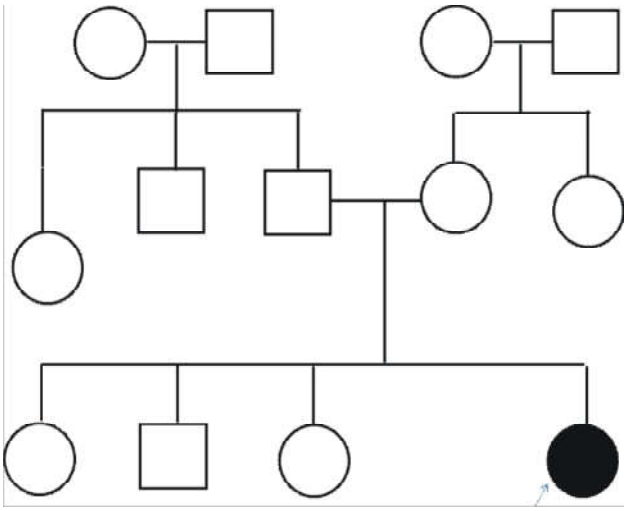

Fig. 1: *Family tree of the patient.*

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2), but the rest of the examination was unremarkable. The central nervous system (CNS) examination showed normal higher mental functions and cranial nerve findings. Motor examination demonstrated generalised hypotonia. Muscle strength in the upper limbs was 4/5 at the shoulders, elbows, and wrists. In the lower limbs, muscle strength was as follows: hip flexion 3/5, hip extension, abduction, and adduction 4/5, knee flexion 3/5, knee extension 4-/5, ankle plantar flexion 2/5, and ankle dorsiflexion 3/5. On sensory examination, the patient showed normal responses to fine touch, crude touch, and pain-temperature sensations in both lower limbs. However, proprioception was impaired up to the knee joints symmetrically in the lower limbs and up to the elbow joints symmetrically in the upper limbs.

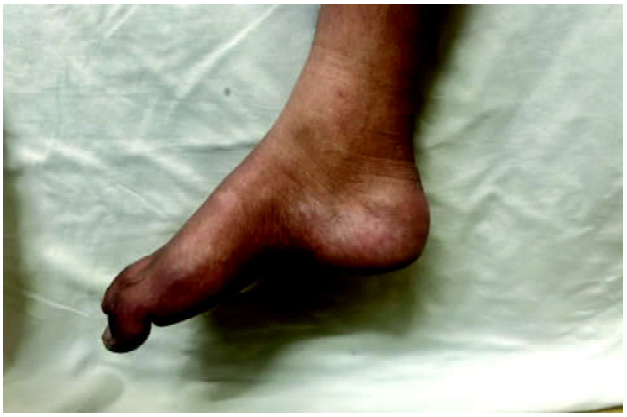

Fig. 2: *pes cavus and hammer toes with distal atrophy of lower limbs.*

Investigations revealed normal creatine kinase levels, along with normal electrolytes, renal function tests, liver function tests, thyroid profile, and haemogram. The HbA1c was 5.2%. Cerebrospinal fluid was normal. Nerve conduction studies (NCS) showed non-recordable motor and sensory conduction velocities, distal latencies, and amplitudes in the median, ulnar, radial, common peroneal, and tibial nerves on both sides (Table I).

The nerve biopsy was not performed as consent was not provided. Whole exome sequencing, revealed a homozygous variation c.1880T>C (p.Phe627Ser) affecting exon 11 of the FGD4 gene (Fig. 3).

Table 1: Nerve conduction studies showed non-recordable motor conduction velocities, distal latencies, and amplitudes in the right median, common peroneal, and tibial nerve.

Nerve	Latency	Amplitude	Duration m/s	Velocity m/s
MNC				
Right Median - APB				
Wrist	NR	NR	NR	
Elbow	NR	NR	NR	NR
Right Peroneal				
Ankle	NR	NR	NR	
Knee	NR	NR	NR	NR
Right Tibial				
Ankle	NR	NR	NR	
Knee	NR	NR	NR	NR

Treatment

Physical and occupational therapy was started.

Discussion

CMT4 is an autosomal recessive form of CMT and mutation in the *FGD4* gene is implicated as the cause of this disease. FGD4 encodes a protein called frabin, which belongs to the family of Rho guanine nucleotide exchange factors (RhoGEFs) that activate Rho GTPases, such as Cdc42 and Rac1, by catalysing the exchange of GDP for GTP[3]. Mutations in FGD4 cause CMT4H by disrupting the normal function of frabin and impairing the signalling pathways that regulate the actin cytoskeleton and myelination in Schwann cells[2]. Mutations in FGD4 causes CMT4H by disrupting the normal function of frabin and impairing the signalling pathways that regulate the actin cytoskeleton and myelination in Schwann cells[4]. Our patient had foot deformities since childhood along with other typical neurological features which developed gradually. The proband had both motor and sensory involvement which was demonstrated by the electrophysiological studies. CMT4H is characterised by distal weakness at the onset of symptoms which was seen in our case as well[5]. We identified a homozygous variation c.1880T>C

Gene[a] (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
FGD4 **(+)** (ENST00000534526.7)	Exon 11	c.1880T>C **(p.Phe627Ser)**	Homozygous	Charcot-Marie-Tooth disease type 4H	Autosomal recessive	Uncertain Significance

Fig. 3: *Whole exome sequencing showing homozygous variation c.1880T>C (p.Phe627Ser) affecting exon 11 of the FGD4 gene.*

(p.Phe627Ser) affecting exon 11 of the FGD4 gene that has not been published in literature before.

Conclusion

The gradual and slowly progressive nature of the disease underscores the heterogeneity of CMT4H, and the findings highlight the importance of genetic testing for definitive diagnosis in cases where clinical features suggest a hereditary neuropathy. This case emphasizes the significance of recognizing rare genetic mutations in the differential diagnosis of childhood-onset neuropathies and the value of early intervention with physical and occupational therapy to manage symptoms and improve quality-of-life. The report also contributes to the growing body of knowledge on CMT4H, encouraging further research and awareness in diverse populations.

References

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