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Tehreem Arshad
Shifa International Hospital, Islamabad

Muhammad Jawad Hassan
National University of Medical Sciences, Rawalpindi, Pakistan

Arsalan Ahmad
Shifa International Hospital, Islamabad

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A CASE OF CHARCOT-MARIE-TOOTH DISEASE TYPE 2O (CMT 20) ASSOCIATED WITH DYNC1H1 AND SLC12A6 MUTATIONS

Tehreem Arshad[1], Muhammad Jawad Hassan[2], Arsalan Ahmad[1]
[1]Department of Neurology, Shifa International Hospital, Islamabad
[2]Department of Biological Sciences, National University of Medical Sciences, Rawalpindi, Pakistan

Corresponding Author: Arsalan Ahmad *Department of Neurology, Shifa International Hospital, Islamabad* ***Email:*** *arsalanahmad65@gmail.com*

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ABSTRACT
Charcot-Marie-Tooth disease (Charcot Marie-Tooth) comprises of a variety of hereditary diseases affecting the peripheral nervous system. Charcot Marie-Tooth2 is a subgroup caused by defects in the axon of the peripheral nerve cells. Charcot Marie-Tooth Type 20 is an uncommon type that affects less than one in a million people and is linked to specific genetic abnormalities. We report a case study of a 66-year-old individual with Charcot Marie-Tooth Type 20, diagnosed on clinical presentation and identified through genetic analysis. Electromyography and nerve conduction studies supported the diagnosis of an axonal sensorineural neuropathy. A comprehensive genetic neuropathies panel led to the identification of mutations in SLC12A6 and DYNC1H1 gene. This case adds to our growing understanding of Charcot Marie-Tooth Type 20 and paves the path for new therapeutic options targeting specific genetic abnormalities, providing hope for improved patient management approaches in the future.

KEYWORDS: Charcot Marie-Tooth Type 20, DYNC1H1, SLC12A6, Mutation, Neuromuscular

INTRODUCTION
Charcot-Marie-Tooth disease (CMT) is a diverse group of inherited progressive neurodegenerative disease affecting peripheral nerves. CMT covers a wide range of clinical manifestations, from mild sensory deficiencies to severe motor impairments. The condition causes progressive muscle weakness, atrophy, varied sensory loss, and poor coordination, which has a substantial negative impact on the quality of life.[1] Additional characteristics may include abnormal gait, scoliosis, cognitive impairment, and spasticity.[1] CMT is a common genetic neuromuscular illness globally, with an estimated prevalence of 1 per 2,500 persons and a global impact on 2.6 million people.[2] Charcot-Marie-Tooth disease is categorized into different types according to clinical and genetic features, with Type 2 (CMT2) distinguished by the presence of axonal degeneration, as opposed to the demyelination seen in Type 1 (CMT1).[2] According to the median motor nerve conduction velocity, CMT type 1, CMT type 2, and intermediate CMT are classified: <38 m/s, >38 m/s, and 25–45 m/s respectively.[3]

More than 100 distinct genes have been identified; these genes are crucial for many various biological processes, including protein degradation, myelination, axonal transport, and mitochondrial function.[4] Individuals with CMT often experience life-long impairment in motor function, sensation, and general quality of life. CMT1 is the most prevalent form making up two-thirds of cases.[3] MFN2 gene mutations are the cause of CMT2A, which accounts for 20% cases of axonal CMT.[4] Literature study revealed a few Pakistani studies expanding the genetic pool of CMT.

In this case report, we present a detailed clinical description of a patient diagnosed with a rare subtype of CMT2. Additionally, we discuss the genetic basis of CMT2 and its implications for disease understanding. By sharing this case, we contribute to the growing knowledge surrounding CMT2, emphasizing the importance of accurate diagnosis and comprehensive management.

CASE PRESENTATION
The patient, 66-year-old male with no known comorbidities, was first seen in March 2017 when he presented with tingling of left big toe and right thumb. Examination showed reduced pinprick in the medial aspect of left big toe. Nerve conduction study done in May 2017 was consistent with Tarsal Tunnel Syndrome affecting left side more than right (Table 1). He was seen again in October 2020, when he complained of numbness left medial side of big toe and the lateral edge of the foot. Neurological examination revealed decreased pin prick in the left lateral and medial aspect of the foot. Higher mental functions, cranial nerves, motor system, and cerebellar exams were unremarkable. A repeat Nerve Conduction studies/Electromyography, done in October 2020, showed non recordable sensory nerve action potentials in bilateral sural, superficial peroneal, lateral and medial plantar nerves, reduced Compound Muscle

Action Potential (CMAP) amplitude of the left tibial motor nerve and a conduction block in the right tibial motor nerve, that indicated a predominantly axonal sensory neuropathy (Table 2). Needle Electromyography of the left tibialis anterior, gastrocnemius (medial head), Vastus lateralis, middle and lower lumbar paraspinal muscles was unremarkable. He visited neurology clinic in February 2023, he had subjective memory problems and decreased hearing. Pure tone Audiometry showed mild bilateral high frequency sensorineural hearing loss. Serum immunofixation and serum protein electrophoresis was unremarkable. Serum copper levels were normal.

Table 1 (a) Motor Nerve Conduction Studies (NCS)- 2017

Motor (Right)						Motor (Left)					
Nerve Tested	**Site**	**Lat (m)**	**Amp (mV)**	**C.V**	**F-wave**	**Nerve Tested**	**Site**	**Lat (m)**	**Amp (mV)**	**C.V**	**F-wave**
Median APB	Wrist	3.6	9.5	-	27.3	**Median APB**	Wrist	3.3	9.1	-	29.9
	Elbow	8.3	8.5	53			Elbow	7.7	8.6	52	
Ulnar ADM	Wrist	3.0	11.5	-	28.9	**Ulnar ADM**	Wrist	3.0	13.1	-	29.5
	B-Elbow	7.2	10.2	50			B-Elbow	7.9	12.4	45	
	A-Elbow	9.3	9.4	52	-		A-Elbow	9.8	11.5	53	-
Tibial	Ankle	5.2	7.5	-	-	**Tibial**	Ankle	5.2	6.8	-	-
	Knee	15.8	4.4	41	51.2		Knee	1.8	33	46	54.0

Table 1(b): Sensory Nerve Conduction Studies (NCS)- 2017

Sensory Right				Sensory Left			
Nerve Tested	**Lat (m)**	**Amplitude (mV)**	**C.V**	**Nerve Tested**	**Lat (m)**	**Amplitude (mV)**	**C.V**
Median	3.4	21	54	**Median**	3.4	23	57
Ulnar	2.9	20	63	**Ulnar**	2.8	19	56
Radial	1.9	33	91	**Radial**	2.1	29	63
Sural	2.1	61	73	**Sural**	2.1	74	67
Superficial Peroneal	2.1	24	54	**Superficial Peroneal**	2.1	33	67
Lateral Plantar	2.2	3	74	**Lateral Plantar**		N-R	
Medial Plantar	2.5	6	93	**Medial Plantar**		N-R	

Table 2 (a): Motor Nerve Conduction Studies (NCS)- 2020

Motor Right						Motor Left					
Nerve Tested	**Site**	**Lat (m)**	**Amp (mV)**	**C.V**	**F-wave**	**Nerve Tested**	**Site**	**Lat (m)**	**Amp (mV)**	**C.V**	**F-wave**
Median APB	Wrist	3.39	7.53		29.1	**Median APB**	Wrist				-
	Elbow	9.12	6.61	43.6	-		Elbow				-
Tibial	Ankle	4.20	5.00			**Tibial**	Ankle	5.20	2.86		
	Knee	15.50	2.42	31.9	56.0		Knee	16.60	1.86	31.6	57.8
Peroneal EDB	Ankle	4.15	2.53		53.4	**Peroneal EDB**	Ankle	4.15	2.55		57.4
	B-Knee	14.10	2.52	34.2	-		B-Knee	13.20	1.68	33.1	-
	A-Knee	16.05	2.42	51.3	-		A-Knee	15.35	1.62	51.2	-
H-Reflex		N-R				**H-Reflex**		N-R			

Table 2(b): Sensory nerve conduction studies-2020

Sensory Right				Sensory Left			
Nerve Tested	**Lat (m)**	**Amplitude (mV)**	**C.V**	**Nerve Tested**	**Lat (m)**	**Amplitude (mV)**	**C.V**
Median	3.33	20.10	63.7	**Median**			
Ulnar	2.88	21.90	61.1	**Ulnar**			
Radial	2.37	33.90	60.6	**Radial**			
Sural		N-R		**Sural**		N-R	
Superficial Peroneal		N-R		**Superficial Peroneal**		N-R	
Lateral Plantar		N-R		**Lateral Plantar**		N-R	

Sensory Right				Sensory Left			
Nerve Tested	**Lat (m)**	**Amplitude (mV)**	**C.V**	**Nerve Tested**	**Lat (m)**	**Amplitude (mV)**	**C.V**
Medial Plantar		N-R		**Medial Plantar**		N-R	

Table 2(c): Electromyography (EMG)- 2020

Muscle Tested	**Insertional Activity**	**Spontaneous Activity**			**Motor Unit**			**Recruitment**	**Interference**
		Fibs	**PSW**	**Mis**	**Amp**	**Dur**	**Poly**		
Tibialis Anterior	-	0	0	0	N	N	0	N	Full
Gastrocnemius: Medial Head	-	0	0	0	N	N	0	N	Full
Vastus Lateralis	-	0	0	0	N	N	0	N	Full
Lumbar Paraspinal (Middle)	-	0	0	0					
Lumbar Paraspinal (Lower)	-	0	0	0					

Abbreviations:

Fibs: Fibrillation potentials, **PSW:** Positive sharp waves, **Mis:** Motor unit recruitment, **Amp:** Amplitude, **Dur:** Duration, **Poly:** Polyphasic potentials, **N:** Normal

N-R: No Response, **Lat (m):** Latency, **Amp (mV):** Amplitude in millivolts (mV), **C.V:** Conduction velocity: **APB**, abductor pollicis brevis: **ADM**, abductor digiti minimi muscle: **FDI**, first dorsal interosseous muscle: ***EDB*,** extensor digitorum brevis

Patient's grandmother had numbness and weakness of limbs which started at age of 50. His son also has symptoms of peripheral neuropathy, including pes cavus. Based on clinical symptoms and family history he was advised genetic testing.

A Comprehensive Neuropathies Panel (Invitae, USA) test was performed on the patient's peripheral blood DNA. Sequence analysis as well as deletion/duplication testing of the panel's 111 genes identified three variants: c.3163A-T (p.Met1055 Leu) in the SLC12A6 gene, c.13493C>T (p.Ser4498Phe) in the DYNC1H1 gene, and a pathogenic variant (heterozygous deletion of the

entire coding sequence) in the SMN1 gene. Autosomal dominant Charcot-Marie-Tooth disease is linked to the SLC12A6 gene (PMID: 31439721) and particularly, the DYNC1H1 gene (MedGen UID: 481850) is associated with CMT20.

Genetic counselling for his children was done and they were offered genetic testing.

DISCUSSION

isease is a heterogeneous group of inherited peripheral neuropathies that mostly affect the limbs and are characterized by increasing muscular weakening and sensory loss.[1] There are several subtypes of , and among the uncommon varieties is Charcot-Marie-Tooth Type 20 (Charcot Marie-Tooth Type 20). Gene DYNC1H1 on chromosome 14q32.31 encodes cytoplasmic dynein 1 heavy chain 1, and mutations in this gene cause Charcot Marie-Tooth Type 20 (OMIM:600112). The mutation alters the usual cellular processes involved in maintaining axons, leading to the characteristic symptoms of the disease.[4]

The most prevalent diseases resulting from DYNC1H1 mutations are Spinal muscular atrophy with lower extremity predominance 1 and Charcot Marie-Tooth Type 20.[5] People affected with DYNC1H1 mutations often present in early childhood with delayed motor milestones, aberrant gait, slowly progressing weakness, and wasting of the distal lower limbs, as well as pes cavus deformity. Transient paresthesia and neuropathic lower limb symptoms have also been observed.[6] Muscle cramping and foot pain have previously been documented as early signs of illness.[7] Over a 5-year follow-up period, a prospective study revealed a gradual decline in muscle strength and an increase in disability in type 2.[7] Ambulation typically last throughout adulthood.6 Despite this variability, the overall trend is of chronic progression, with symptoms persisting and often worsening over time.

According to a recent study, some mutations in the DYNC1H1 dimerization domain were associated with an Neuromuscular Disorder phenotype in individuals with reduction lower limb strength but mostly retained upper limb strength.[5] The axonal sensorineural involvement identified on Nerve Conduction studies is consistent with DYNC1H1 mutations, known to affect axonal transport. The relative preservation of motor function aligns with the described phenotypic variability in DYNC1H1-related disorders, which can range from severe early-onset forms to milder, later-onset presentations like in our patient. [5]

Literature review shows a very few genetically confirmed cases of in Pakistan. A case series from Pakistan presented clinical symptoms of , including pes cavus with autosomal recessive nature of their condition. However, no genetic testing was done.[8] Another study identified pathogenic mutations in SH3TC2, HK1, REEP1, and MFN2 in five consanguineous Pakistani families. These mutations have been linked to 2A, dHMN5B (DSMA5B), 4C, and 4G, respectively.[9] In consanguineous Pakistani families, a previously identified missense mutation in the MFN2 gene and a new nonsense mutation in the GAPD1 gene were found to cause 2A and 4A, respectively.[10]

Our patient was found to have heterozygous mutations in DYNC1H1 and SLC12A6. Heterozygous Mutation in Exon 23 c.3163A>T (p.Met1055Leu) is identified in SLC12A6 gene. This mutation causes the neutral and non-polar amino acid leucine to occur at codon 1055 of the SLC12A6 protein (p.Met1055Leu), in place of the neutral and non-polar amino acid methionine. Population databases have this variant (rs749430190, gnomAD 0.01%). Nevertheless, there is no literature reporting this variant in people with diseases associated to SLC12A6. Heterozygous Mutation in Exon 75 c.13493C>T (p.Ser4498Phe) was identified in DYNC1H1. At codon 4498 of the DYNC1H1 protein (p.Ser4498Phe), this sequence alteration swaps the neutral and polar serine for the neutral and non-polar phenylalanine. It is not found in population databases (gnomAD no frequency). Until now, this mutation has not been documented in the literature in people with DYNC1H1-related disorders.

Challenges are faced in diagnosing this condition due to its phenotypic variability and similarity to other Charcot Marie-Tooth subtypes. The specific phenotype observed in this patient appears milder compared to typical presentations of Charcot Marie-Tooth Type 20. For instance, the p.Ser4498Phe mutation in DYNC1H1, though not previously reported, might have a reduced penetrance or expressivity, leading to a milder clinical course. It is crucial to consider whether these mutations are indeed pathogenic in this context or if they represent variants of uncertain significance. Further studies, including familial genetic analysis and functional studies, would be necessary to confirm the pathogenic role of these mutations.

The patient had a positive family history of similar symptoms, suggesting an inherited nature of the disease. Genetic variants play a vital role in clinical diagnosis and prognosis. Treatment is symptomatic. A multidisciplinary team, which frequently consists of orthopaedic surgeons, neurologists, physiatrists, and physical and occupational therapists, evaluates and treats affected patients.[1] While there is currently no cure for Charcot Marie-Tooth Type 20, growing research into gene therapy and molecular therapies shows hope for the disease's future.[4] Despite significant advancements in genetic testing and molecular diagnostics, understanding the molecular mechanisms driving the axonal degeneration in Charcot Marie-Tooth2 remains a critical research area.

CONCLUSION

This case involves a rare combination of mutations in the DYNC1H1, SMN1 deletion and SLC12A6 genes, which has not been widely reported in the literature, especially in the context of Charcot Marie-Tooth Type 20. The patient's relatively mild phenotype despite carrying these

mutations, and the presence of symptoms like tarsal tunnel syndrome, which is uncommon in Charcot Marie-Tooth Type 20, are significant and should be highlighted. Further research is needed to elucidate the synergistic effects of these mutations on the clinical phenotype and to explore potential targeted therapeutic interventions.

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Tehreem Arshad; concept, case management, manuscript writing
Muhammad Jawad Hassan; genetic testing, manuscript writing
Arsalan Ahmed; case management, manuscript revision
All the authors have approved the final version of the article and agree to be accountable for all aspects of the work.