Case Report

From Genes to Gait: Childhood-Onset Charcot-Marie-Tooth Disease Type 2A: A Case Report

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Abstract

Background: Charcot–Marie–Tooth disease type 2A (CMT2A) is an inherited axonal neuropathy commonly associated with pathogenic variants in the MFN2 gene. Childhood-onset disease is often associated with early gait impairment and progressive distal weakness. Here we present a 7-year-old Indian boy with progressive lower-limb weakness, frequent falls, and steppage gait beginning at 3.5 years of age, clinically showing features of neuropathy and later Whole-exome sequencing identified a heterozygous pathogenic MFN2 variant, confirming autosomal-dominant CMT2A.Progressive childhood steppage gait associated with pescavusand distal areflexic weakness should prompt evaluation for hereditary neuropathy. Early electrophysiological and molecular confirmation facilitates timely multidisciplinary management and family counselling.

Keywords: Charcot–Marie–Tooth disease; CMT2A; MFN2; pediatric neuropathy; pescavus; steppage gait.

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Introduction

Charcot-Marie-Tooth disease (CMT) is the most common inherited disorder of the peripheral nervous system, with a population prevalence of roughly 1 in 2,500.[1] The disease is genetically and clinically heterogeneous and is partitioned electrophysiologically into demyelinating (CMT1),axonal (CMT2)and intermediate forms.[2] Within the axonal group, type 2A (CMT2A) is the single most frequent subtype and is overwhelmingly caused by pathogenic variants in MFN2.[1,3]

Childhood-onset CMT2A is recognized as a more severe phenotype than adult-onset disease, with earlier loss of independent ambulation and a higher burden of additional features such as optic atrophy, vocal-cord paresis and pyramidal signs.[4-6] The MFN2 gene encodes mitofusin-2, a mitochondrial membrane protein involved in mitochondrial fusion and axonal transport. Variants affecting the GTPase domain, including p.Arg94Trp, have been associated with severechildhood-onset phenotypes.[5,6] Clinical manifestations may include distal weakness, foot deformities, gait impairment, optic atrophy, and pyramidal features.[1,7]

The present case report describes a 7-year-old boy, with early-onset progressive distal motor neuropathy caused by a heterozygous pathogenic MFN2 p.Arg94Trp variant. The report highlights the clinico-genetic diagnostic approach, electrophysiological profile, multidisciplinary management, and short-term functional outcome.

Case Presentation

Master K, a 7-year-and-0-month-old boy, presented with a history of progressive lower-limb weakness since the age of 3.5 years .He was the second-born child of a non-consanguineous marriage, Birth history was unremarkable,Immunization was up to date , Developmental history showed normal acquisition of milestones and lived in a household classified as lower-middle socioeconomic status .The presenting concerns were progressive difficulty walking and running, frequent tripping and falls, difficulty retaining slippers on his feet, and visible thinning of the lower-limb musculature. There was no upper-limb weakness: he combed his hair, raised both arms overhead, buttoned clothing and fed himself with his hands without difficulty. Proximal lower-limb function was preserved; he rose from sitting unaided. Cranial-nerve symptoms were systematically ruled out (no anosmia, no visual blurring, no diplopia, no ptosis, no squint, no food-pocketing, no hearing loss, no nasal regurgitation, no voice change, no tongue deviation). He had no respiratory distress, no involuntary

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movements, no oculomotor abnormalities and no head bobbing. There were no autonomic, bowel or bladder symptoms; no recent intramuscular injection or trauma; no heat intolerance, abnormal sweating or pica.

The patient was previously evaluated at a private hospital where preliminary investigations were performed; he had no asthma, seizure disorder, recurrent respiratory tract infections, prior hospitalizations or surgeries.There was no family history of neuromuscular disease. [Figure 1]

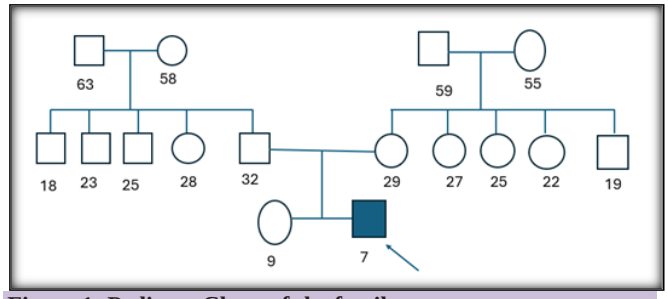


Figure 1: Pedigree Chart of the family

Clinical findings: On examination the patient was awake, playful, afebrile and well-hydrated, with no pallor, icterus, cyanosis, clubbing, lymphadenopathy or oedema. Vital signs were age-appropriate: heart rate 104/min and regular with all peripheral pulses palpable and capillary refill below 2 seconds, respiratory rate 26/min, blood pressure 100/60 mmHg (10th–50th centile) and SpO_2 98% on room air. Anthropometry placed him on the 10th–25th centile for height (117 cm), weight (18 kg) and body-mass index (13.15 kg/m²). There were no dysmorphic features, no neurocutaneous markers, no kyphoscoliosis, and no frontal bossing, polydactyly or syndactyly. The most striking general finding was bilateral pescavus and lower limb wasting present. There was no toe clawing, no palpable peripheral nerves, no skin trophic changes and no fixed contractures. [Figure 2].Neurological examination is reported in [Table 2] and other systems were norm.

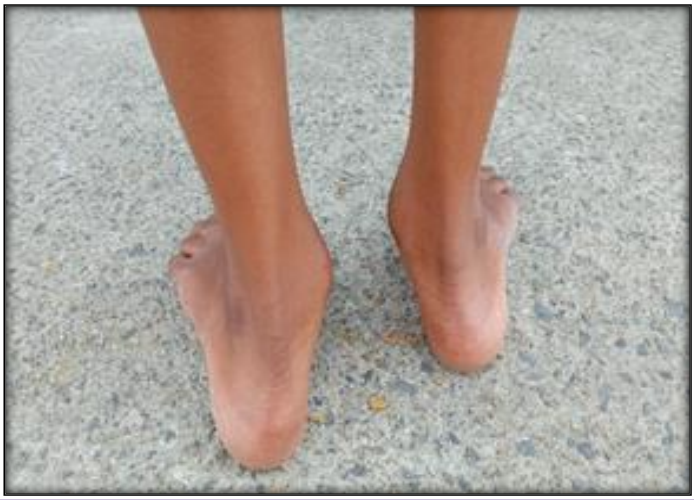


Figure 2: Clinical photograph of the lower limbs showing pescavusand lower limb wasting.

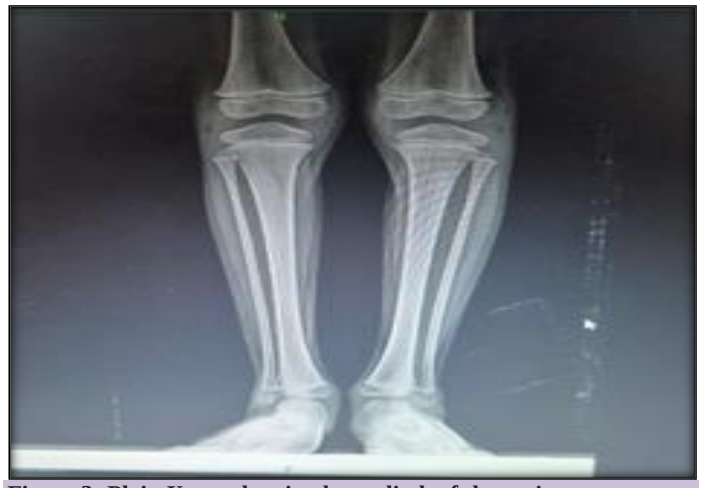


Figure 3: Plain X-ray showing lower limb of the patient.

Table 1: Neurological Examination Findings

Parameter	Findings
Higher mental functions	Conscious, oriented, and age appropriate
Cranial nerves	Intact cranial nerve examination (I–XII)
Tone	Normal in upper limbs; decreased bilaterally in lower limbs
Power	Upper limbs: MRC grade 5/5; lower limbs: MRC grade 3/5 distally
Deep tendon reflexes	Knee, ankle, and supinator reflexes absent bilaterally; biceps and triceps reflexes preserved
Plantar response	Bilateral extensor plantar response
Sensory examination	Pain and light-touch sensations preserved
Gait	Bilateral steppage gait
Cerebellar signs	Absent

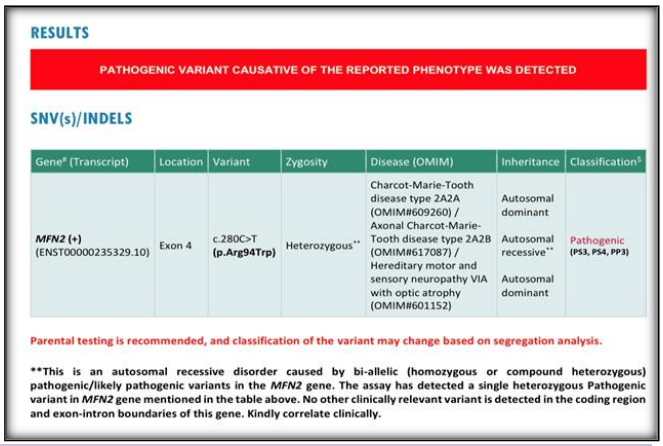
A plain radiograph of the lower limbs was normal, ruling out an occult bony cause for the gait disturbance. [Figure 3] A bedside ophthalmologic assessment showed no optic atrophy and no retinitis pigmentosa, an important negative given the well-described co-segregation of MFN2 variants with optic atrophy in HMSN VIA.[3,5]

Table 2: Nerve-conduction-study findings

Nerve / modality	Site	Latency (ms)	Amplitude	Conduction velocity (m/s)	Interpretation
Left peroneal — motor	Ankle	1.25	0.3 µV	—	Severely reduced amplitude
Left peroneal — motor	Knee	16.67	—	0.00 (non-recordable)	Non-recordable CV ankle–knee
Right sural — sensory	Mid-calf	1.79	29.7 µV	55.87	Preserved sensory response

Left ulnar — motor	Wrist	1.25	10.2 mV	—	Within normal limits
Left ulnar — motor	Elbow	4.79	9.2 mV	45.20	Normal conduction velocity
Left ulnar — sensory	Digit 5	1.33	1.5 µV	60.15	Within normal limits

Nerve-conduction studies were the pivotal electrophysiological investigation (Table2). The pattern shows the length-dependent axonal motor neuropathy with relative preservation of sensory and upper-limb conduction, exactly the electrophysiological signature expected for CMT2A and quite different from a CMT1-type demyelinating pattern.[2,4]


RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

SNV(s)/INDELS

Gene* (Transcript)	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification$
MFN2 (+) (ENST00000235329.10)	Exon 4	c.280C>T (p.Arg94Trp)	Heterozygous**	Charcot-Marie-Tooth disease type 2A2A (OMIM#609260) / Axonal Charcot-Marie-Tooth disease type 2A2B (OMIM#617087) / Hereditary motor and sensory neuropathy VIA with optic atrophy (OMIM#601152)	Autosomal dominant Autosomal recessive** Autosomal dominant	Pathogenic (PS3, PS4, PP3)

Parental testing is recommended, and classification of the variant may change based on segregation analysis.

**This is an autosomal recessive disorder caused by bi-allelic (homozygous or compound heterozygous) pathogenic/likely pathogenic variants in the *MFN2* gene. The assay has detected a single heterozygous Pathogenic variant in *MFN2* gene mentioned in the table above. No other clinically relevant variant is detected in the coding region and exon-intron boundaries of this gene. Kindly correlate clinically.

Figure 4: Genetic Variant Analysis of the patient

Final diagnosis

Charcot-Marie-Tooth disease type 2A (CMT2A), an autosomal-dominant axonal hereditary motor and sensory neuropathy, confirmed by the convergence of (i) a clinical phenotype of childhood-onset distal lower-limb weakness with pescavus and steppage gait, (ii) an NCS pattern of length-dependent axonal motor neuropathy with sensory and upper-limb sparing, and (iii) a heterozygous pathogenic MFN2 c.280C>T (p.Arg94Trp) variant.

Therapeutic intervention

A multidisciplinary supportive plan was instituted at diagnosis, in line with published consensus management for CMT.[2,7,8]Includes Physiotherapy,Ankle foot orthoses,Genetic counselling,Ophthalmological surveillance and Nutritional counselling.The patient was reviewed at the combined paediatric-neurology clinic approximately six months after the whole-exome-sequencing report and after AFO fitting and physiotherapy initiation. Clinically he remained stable and was ambulant in his bilateral solid AFOs.

Discussion

This case highlights the classical clinical presentation and diagnostic pathway of childhood-onset Charcot–Marie–Tooth disease type 2A (CMT2A) associated with a pathogenic MFN2 variant.[1,2]

CMT2A is among the most severe forms of inherited axonal neuropathy in children and is commonly linked to variants in the MFN2 gene.[3] Mitofusin-2 plays a critical role in mitochondrial fusion, mitochondrial trafficking, and maintenance of axonal integrity. Dysfunction of this protein particularly affects long peripheral axons, explaining the characteristic length-dependent pattern of distal weakness and muscle wasting seen in affected individuals.[4] Previous studies have demonstrated that variants involving the GTPase domain of mitofusin-2, particularly substitutions affecting the Arg94 residue, are associated with earlier disease onset and more severe phenotypes.[5,6]

The clinical profile of the present child is consistent with these observations. Symptoms began at approximately 3.5 years of age with progressive gait difficulty and frequent falls, followed by distal lower-limb weakness and development of pescavus. Despite significant distal motor involvement, proximal strength and upper-limb function remained preserved at presentation, which is a recognized pattern during the early stages of CMT2A.[5] The preserved sensory examination and sural sensory responses on nerve conduction study also correlate with reports describing predominantly motor axonal involvement in pediatric MFN2-related neuropathies.[1,5]

The electrophysiological findings were central to narrowing the differential diagnosis. The markedly reduced peroneal motor amplitude with preserved conduction velocities in unaffected nerves indicated an axonal rather than demyelinating neuropathy. Preservation of ulnar motor conduction velocity helped differentiate the condition from CMT1A and other hereditary demyelinating neuropathies.[2] Similarly, the absence of proximal weakness, calf pseudohypertrophy, and myopathic electrophysiological features argued against muscular dystrophy. Distal spinal muscular atrophy and hereditary spastic paraplegia were also considered; however, the molecular finding of a pathogenic MFN2 variant established the diagnosis conclusively.

In the present case,developmental milestones attained normally and the absence of spasticity, hyperreflexia, sensory level, bowel or bladder involvement, or other upper motor neuron signs made an alternative central nervous system disorder less likely.

The case also demonstrates the clinical utility of early genetic testing in pediatric neuromuscular disorders. Whole-exome sequencing shortened the diagnostic process and enabled disease-specific counselling and surveillance planning. Identification of an MFN2 pathogenic variant prompted ophthalmologic monitoring because optic atrophy and retinal involvement have been reported in association with CMT2A and hereditary motor sensory neuropathy type VIA.[4,5]

At present, no disease-modifying therapy has been approved for CMT2A, and management remains supportive.[7] The multidisciplinary approach used in this child included physiotherapy, gait training, stretching exercises, ankle–foot orthoses, nutritional optimization, and genetic counselling.[2,7]

Prognosis in CMT2A is variable but trends towards more severe disease in childhood-onset cases and with variants affecting the GTPase domain of mitofusin-2.[4-6] The largest natural-history study of CMT2A reported that the proportion of patients who become non-ambulant rises substantially over a decade of

follow-up, with childhood-onset disease showing the steepest decline.[4]

Conclusion

This case reinforces the importance of considering hereditary axonal neuropathy in children presenting with progressive steppage gait, pescavus, and distal weakness. Early electrophysiological evaluation followed by molecular confirmation facilitates timely diagnosis, appropriate counselling, multidisciplinary rehabilitation, and long-term surveillance planning.

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Conflicts of interest

There are no conflicts of interest.

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