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Case Report

Clumsy Walking Hides a Rare Neuropathy: A Novel de novo *MFN2* Variant Causing Charcot–Marie–Tooth Disease Type 2A in a Child

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Abstract: ***Background*:** Charcot-Marie-Tooth Disease type 2 (CMT2) is a genetically heterogeneous hereditary motor and sensory neuropathy characterized by axonal degeneration. Diagnosis is established through a combination of clinical history, physical examination, electrophysiological studies, and genetic testing. ***Case Presentation*:** We report a case involving a 9-year-old female patient who presented with a two-year history of frequent falls and clumsy gait. Neurological examination revealed a high steppage gait, bilateral foot drop, pes cavus, absent ankle jerks, and impaired dorsiflexion and eversion of both feet. Romberg's sign was positive. There was no involvement of proximal lower limbs, upper limbs, or sensory modalities. Nerve conduction studies and electromyography demonstrated severe axonal neuropathy confined to the distal lower extremities. Genetic analysis via a neuromuscular gene panel identified a novel de novo heterozygous variant (c.262A>C) in the *MFN2* gene, consistent with Charcot-Marie-Tooth Disease type 2A2A. ***Conclusion*:** This case highlights a rare de novo *MFN2* mutation in a pediatric patient with CMT2A2A, underscoring the importance of early recognition and genetic testing in atypical presentations of hereditary neuropathies.

Keywords: Charcot-Marie-Tooth Disease (CMT), Hereditary Neuropathy, CMT Type 2 (CMT2), Axonal Neuropathy, CMT2A2A.

INTRODUCTION

Charcot-Marie-Tooth disease (CMT) is a hereditary motor and sensory neuropathy (HMSN) that comprises of a group of common inherited peripheral neuropathies that are characteristic of being a progressive disease that includes calf muscle atrophy in multiple of its subtypes. The disease causes progressive damage to peripheral nerves, which affects both the motor and sensory functions of the limbs. Some of the clinical manifestations of the disease include distal muscle wasting and weakness, sensory loss, and foot deformities including deformities such as pes cavus and hammer toes [1].

The broad categories that CMT is divided into are CMT1, CMT3, and CMT4, which are demyelinating subtypes, and CMT2, which is an axonal subtype. There is also CMTX, which shares features from both demyelinating and axonal CMT subtypes [2].

According to the literature, CMT2A is a type of primarily axonal disease in which a mutation to the gene MFN2 causes damage to the axons. CMT2A accounts for approximately 20 percent of the axonal subtype of CMT and around 5 percent of all CMT cases making it the most common axonal form [3]. The mutation is inherited in an autosomal dominant pattern. However, some genes inherited in an autosomal recessive pattern have been associated with an early-onset form of the condition. There is also the possibility of acquiring a de novo mutation which is rare among patients who have the condition [4].

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CMT is heterogeneous in its presentation regarding the severity, age of onset, and the specific features of neuropathy associated with the disease. Moreover, associated features vary according to subtype. That being said, some of the common initial presentation features include distal weakness and atrophy associated with pes cavus and foot drop. As the disease progresses, foot deformities such as hammertoes become prominent as well as hand weakness and muscle atrophy. On the other hand, sensory symptoms may present but are less noticeable in most of the subtypes. While other forms of CMT have a potential for disability as the disease progresses, the potential for disability in CMT2A is higher due to the earlier onset of the disease which predisposes the patients to mobility impairment. Many patients end up requiring walking aids, ankle-foot orthoses and in more severe cases wheelchairs. It also affects the upper limb by impairing fine motor tasks. Regarding the sensory component, patients may suffer from pain and fatigue [1].

This report describes an early-onset case of CMT2A in a pediatric patient, characterized by motor and sensory involvement confined to the lower limbs, with complete sparing of the upper limbs. While initial lower limb involvement is typical of CMT2A, upper limb symptoms generally emerge as the disease progresses.

Genetic testing identified a novel MFN2 mutation not previously reported, and both parents tested negative for the mutation, indicating a likely de novo origin.

CASE PRESENTATION

We report the case of a 9-year-old girl with a two-year history of progressive gait difficulties, characterized by frequent falls and clumsiness, as observed by her father. There was no upper limb or sensory symptoms. No history suggestive of cranial nerve symptoms.

She was born full-term, and her birth history was uneventful with no complications during pregnancy and delivery and no neonatal intensive care unit admission. She appropriately achieved her developmental milestones. Her family history consisted of non-consanguineous parentage with no neurological and developmental conditions among her parents and two siblings.

On general examination, the patient appeared well with no dysmorphic features. Respiratory, cardiovascular, abdominal, genitourinary, and ENT systems were unremarkable, and cranial nerves were intact. Upper limb neurological examination revealed normal tone, strength, and sensation. In the lower limbs, there was marked weakness in dorsiflexion and foot eversion (MRC grade 2/5) and mild weakness of toe extensors and plantarflexion (MRC grade 4/5), with preserved strength at the hip and knee. Deep tendon reflexes were notable for brisk knee jerks and absent ankle jerks. Light touch sensation was intact, but proprioceptive responses were inconsistent, with a positive Romberg sign. Gait assessment demonstrated a bilateral high-steppage gait, foot drop, and pes cavus; she was unable to walk on heels or toes, though Gower's sign was negative. Cerebellar and spinal examinations were otherwise unremarkable.

Laboratory investigations revealed normal creatine phosphokinase (104 U/L) and folic acid levels (14.1 ng/mL). Magnetic resonance imaging of the lumbosacral spine was unremarkable. Nerve conduction studies were performed on both upper and lower limbs. In the lower limbs, sensory nerve action potentials were reduced bilaterally, distal latencies were moderately prolonged, and compound motor action potentials were severely reduced. In contrast, upper limb studies demonstrated preserved conduction and normal amplitudes. Overall, the findings were consistent with a motor and sensory axonal neuropathy predominantly affecting the lower limbs. Electromyography of the right tibialis anterior revealed high-amplitude, rapidly firing neurogenic potentials, indicative of chronic partial denervation.

Genetic testing was notable for a negative PMP22 deletion analysis. A neuromuscular gene panel identified a heterozygous c.262A>C (p.Ile88Leu) variant in the MFN2 gene (NM_014874.4), classified as likely pathogenic for Charcot–Marie–Tooth disease axonal type 2A2A. Parental testing was negative for this variant, confirming a de novo mutation.

Correlation of the clinical phenotype with genetic findings established a diagnosis of de novo Charcot–Marie–Tooth disease type 2A2A. The patient was referred for comprehensive ophthalmological evaluation to exclude optic neuropathy and for audiological assessment; both were unremarkable. The clinical course has remained relatively stable, and longitudinal follow-up is ongoing to monitor disease progression and potential musculoskeletal complications.

DISCUSSION

Charcot-Marie-Tooth disease is a hereditary condition with multiple subtypes, characterized by progressive sensory and nerve dysfunction [5].

The patient described in this case report has CMT2A subtype, which is the most common subtype of the disease. It is caused by a mutation in the MFN2 (mitofusin-2) gene. MFN2 hereditary motor and sensory neuropathy (MFN2-HMSN) is a classic axonal peripheral sensorimotor neuropathy, inherited in either an autosomal dominant (AD) manner (~90%) or an autosomal recessive (AR) manner (~10%). MFN2-HMSN is characterized by more severe involvement of the lower extremities than the upper extremities, distal upper-extremity involvement as the neuropathy progresses, more prominent motor deficits than sensory deficits [6].

MFN2 (mitofusin-2) gene is responsible for the regulation of the fusion of the outer membrane of the mitochondria. This function is crucial for maintaining mitochondrial health, distributing mitochondrial DNA, and enabling mitochondria to respond to metabolic demands. Also, the protein is involved in transporting mitochondria along the neuron's axons [5]. Researches has shown that mitofusin 2 is also increased at tethering sites between the mitochondria and the endoplasmic reticulum. The tethering of mitochondria to the endo plasmic reticulum is required for intercommunication during signalling involving calcium uptake. Neuronal damage in CMT2A could be a consequence of impaired endoplasmic reticulum–mitochondrial apposition. Increased intracellular calcium transfer caused by MFN2 alterations may induce apoptosis [6].

The prevalence of the disease in the Middle East is not well studied or reported. However, globally, it is one of the most common inherited peripheral neuropathies. The reports on the global prevalence ranges widely from 40 per 100,000 to 82 per 100,000 with CMT1 and CMT2 being the most common subtypes [2].

The phenotypic appearance and clinical features of CMT are directly correlated to the malfunction of the mitofusin-2 protein. Although it is heterogeneous in its clinical course and features, patients do share some characteristics. Initially, patients with CMT2A might develop delayed motor milestones and walking difficulties. That being said, the age of onset of the disease determines the features that the patient might present with. The most common feature that patients initially present with is distal lower limb muscle weakness and atrophy, which may manifest with pes cavus, foot drop, as well as frequent falls. Moreover, as the course of the disease progresses, foot deformities such as hammertoes and contractures might manifest in more severe cases. Upper limb involvement generally develops at later stages, and it involves loss of dexterity and muscle weakness in the hands. Some patients, however, have upper limb sparing. Apart from the motor symptoms, some sensory features may also manifest, such as distal sensory loss, most commonly in the lower limbs, but it may also progress and affect the hands. Various sensory components are affected, such as proprioception, vibration, and light touch. Some senses may be spared, such as temperature and pain. Moreover, patients may experience tingling, numbness, or even burning sensations on their feet. Patients with an earlier onset might also experience sensory ataxia as the disease progresses [1].

The symptoms associated with CMT2A may vary widely according to the age of onset, the specific mutation associated with the MFN2 gene, and the mode of inheritance. They may range from simply sensory disturbances to muscle wasting and foot deformities, and even progress to loss of ambulation to the extent that a wheelchair may be needed for the patient. It is a highly heterogeneous disease [4].

It is rare for the age of onset to be in infancy (under 2 years); however, it is usually associated with a more severe disease progression. It is most commonly diagnosed in childhood between 2 and 10 years of age. It is brought to the parents' attention when they realize their child has frequent falls, a clumsy gait, and maybe even pes cavus or other foot deformities. If the patient has a stable course of the disease, they might be diagnosed in adolescence between 11 years to 18 years. A small percentage of patients who have a particularly stable course present in adulthood. Patients might have a long, stable course for the disease with minimal progression, but some patients may have rapid progression, especially those who have the CMT2A subtype [1].

The clinical spectrum of peripheral neuropathies associated with MFN2-related neuropathies is varied. One example is research done by Fridman *et al*., [4], which focused on patients with the MFN2 mutation who had an early onset of the disease. The research revealed that patients with early onset of the disease had a more rapid progression of the disease, higher disability resulting from the disease, and often had upper and lower limb involvement. On the other hand, a report done by Bombelli *et al*., [7], revealed a patient with upper motor neuron and pyramidal signs such as brisk reflexes and spasticity. Also, a study done involving a cohort of children who have CMT2A by Züchner *et al*., [3], found that scoliosis, progressive hand involvement, and optic atrophy were seen often in more advanced cases.

CONCLUSION

Charcot–Marie–Tooth disease presenting in children under 10 years of age is rare, and early recognition requires careful clinical evaluation, thorough neurological examination, and appropriate electrodiagnostic and genetic investigations. A high index of suspicion is essential, particularly in patients presenting with subtle distal weakness or gait abnormalities. This case highlights a novel de novo MFN2 c.262A>C (p.Ile88Leu) variant that has not been previously

reported in the literature, expanding the mutational spectrum of CMT2A and underscoring the importance of genetic testing in paediatric axonal neuropathies.

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