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Case Study

Case Study of a Rare Pathogenic DHTKD1 Mutation Associated with CMT2Q

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Abstract

Introduction: CMT is a hereditary neuropathy that has diverse presentations and genetic causes. The DHTKD1 gene is associated with CMT2Q.

Case Presentation: A proband with a pathogenic DHTKD1 mutation was evaluated with laboratory, clinical, genetics and electrophysiological testing.

Discussion: Although previous studies have shown the DHTKD1 mutation to present at a younger onset, our case study shows a milder later onset presentation.

Conclusion: CMT mutations, especially DHTKD1 mutations that involve the mitochondria may have more variable presentations. This is a rare mutation that needs to be investigated further.

Introduction

Charcot-Marie-Tooth (CMT) disease refers to a group of diverse hereditary motor and sensory neuropathies. As the affected nerves slowly degenerate, the initial presentation will often be weakness of the muscles and decreased sensation of the lower legs and feet, which can manifest as foot drop, abnormal gait, and balance problems. Other commonly reported symptoms of CMT include changes in the structure of the feet, such as pes cavus and hammertoes [1]. CMT primarily affects the peripheral nervous system and can cause symptoms that vary significantly between different affected individuals. For example, a parent who has few symptoms may have a child that presents with significantly more symptoms. CMT can be divided into two major types. CMT type 1 (also known as demyelinating type), which is characterized by abnormal myelin that typically leads to slowed nerve conduction velocities. CMT type 2 (also known as axonal type) is characterized by abnormalities with the axon and usually does not present with slowed nerve conduction velocities.

CMT2Q is a subtype of autosomal dominant CMT disease type 2. It typically presents during adolescence or adulthood with slowly progressive bilateral distal muscle weakness and atrophy. Other manifestations of CMT2Q include diminished deep tendon reflexes, pes cavus, and mild to moderate sensory impairment. DNA sequencing analysis of

individuals with CMT2Q revealed a heterozygous loss of function mutation of the DHTKD1 gene on chromosome 10p14 [2]. One study looked at a five-generation family of eight affected individuals with CMT disease type 2. DNA sequencing analysis revealed that all eight had a nonsense mutation in exon 8 of DHTKD1, which was absent in unaffected individuals of this family, as well as in 250 unrelated normal individuals. In addition, *in vitro* studies have shown that DHTKD1 silencing led to decreased energy production, as evidenced by a reduction in ATP, total NAD (+) and NADH, and NADH levels. Thus, DHTKD1 appears to have a role in mitochondrial energy production, and its deficiency may be a contributing factor to the neurological deficits found in CMT2Q [3].

Methods

One female subject with a known pathogenic mutation in the DHTKD1 gene was retrospectively analyzed with genetic and clinical data. Genetic data included the Invitae hereditary motor and sensory neuropathy panel. Clinical data which included the subject's history, physical exam findings, and nerve conduction study results obtained *via* chart review.

Results

Subject 1 is a 68-year-old female with a past medical history of gallbladder disease who presented to the clinic (02/25/16) for increased difficulty with balance and walking. Her first reported symptoms were problems with her gait and increased clumsiness around her mid-50s. However, she was able to ambulate without assistive devices and denied any numbness in her hands and/or feet. She also denies any difficulties reaching motor milestones nor did she notice any motor deficits throughout her childhood and reported being able to keep up with her peers physically. She also denied any family history of neuropathy, gait instability, and foot deformities (including pes cavus, pes planus, and hammertoes). She previously received an EMG at an outside facility, which revealed evidence of a length-dependent sensorimotor peripheral neuropathy with both axonal and demyelinating features.

On physical exam, she was found to have significantly reduced strength on great toe dorsiflexion and mildly reduced strength for foot eversion bilaterally. Her toes had reduction in sensation to light touch, vibration, and proprioception. Her deep tendon reflexes were diffusely areflexic. She was also found to have an abnormal gait and positive Romberg's sign. Nerve conduction studies demonstrated reduced amplitudes of the peroneal response off the tibialis anterior, as well as reduced amplitude of the left median and ulnar sensory response. Her left sural sensory response was absent. These findings showed evidence of an axonal CMT. Thus, a referral to genetic counselling was provided where an Invitae hereditary motor and sensory neuropathy panel revealed she carries a pathogenic mutation in DHTKD1 consistent with autosomal dominant CMT2Q. During genetic counselling, she reports that her sister (71 years old) also has peripheral neuropathy and is undergoing genetic evaluation. It is implied that her sister likely has CMT2Q as well, and that her two sons although asymptomatic currently have 50% risk.

Five years later follow up (04/29/21), she reported significant fatigue in her legs and feet, in addition to a left foot drop. She complained of decreased gait speed and worsening of balance, especially when changing direction during ambulation. She also reports associated pain at the bottom of her feet that is relieved with ice, stretching, and exercise.

Rehabilitation Presentation

She was also referred to physical therapy (02/25/16) for activity recommendations, balance, and gait concerns. Her assessment revealed force production deficits, more distally than proximally, in line with her diagnosis of CMT2Q. She also demonstrated altered gait with foot drop. As testing progressed, she was noted to have more fatigue, decreased activity tolerance, and decreased balance. It was deemed that she had no need for ongoing outpatient physical therapy, and she was encouraged to include balance exercises in her daily routine.

Discussion

Charcot-Marie-Tooth disease type 2 is characterized by adolescent to adulthood onset of symmetrical slowly progressive predominantly lower distal muscle weakness and atrophy with diminished deep tendon reflexes, pes cavus, and sensory impairment [4]. Most cases of CMT will exhibit weakness in adolescence or early adulthood. However, Subject 1 was essentially asymptomatic during childhood to adolescence and began first displaying symptoms in mid to late adulthood, starting with altered gait. Since then, her disease course has progressed slowly, and her symptoms appear to be mostly confined to her distal lower extremities. Her toes demonstrate reduced strength and sensation, but the most concerning symptom to her is impairments in gait and balance. However, she can ambulate independently, perform her ADL's, and maintain an exercise program highlighting the mild progressive course of CMT2Q. She is diffusely areflexic but does not endorse significant atrophy or pes cavus. Genetic screening revealed that she does possess a pathogenic mutation of DHTKD1, which has been identified to cause CMT2Q [3]. Specifically, it is a nonsense mutation in DHTKD1 that is associated with CMT2Q, but the molecular mechanism behind this has not been completely elucidated. One study demonstrated how knocking out DHTKD1 in mice recreates major aspects of the CMT2 phenotypes. These mice had progressive weakness and atrophy in distal limbs, as well as decreased nerve conduction velocity. DHTKD1 is involved with lysin and tryptophan catabolism within the mitochondria and this study also demonstrated how a DHTKD1 deficiency leads to impaired mitochondrial energy production and the accumulation of metabolites. These metabolites then led to myelin structure damage and axonal degeneration. Interestingly, mice that were fed one of the metabolites (2-aminoadipic acid) were found to also have phenotypes like CMT2Q phenotypes [5]. Thus, these findings illustrate a possible link between metabolic disorders and mitochondrial insufficiency to the pathogenesis of peripheral neuropathies. The slow onset and mild progression of CMT2Q, as seen in Subject 1 compared to other subjects who present earlier could reflect the variability of presentations seen in most mitochondrial disease processes.

Conclusion

CMT is a heterogenous genetic disease, and as a result, different mutations in different genes can lead to the production of similar symptoms. In the case of CMT2Q, deficiencies in DHTKD1 appear to present with a later onset and cause mild distal weakness/atrophy and sensory loss when compared to other types of CMT. With the advancement of molecular genetic studies, further underlying causes of the different types of CMT will be elucidated, allowing more accurate diagnosis and improvements in the development of therapy strategies.

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