CASE REPORT

Charcot-Marie-Tooth Disease: From Steppage Gait to Nephropathy

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Abstract

A previously healthy 9-year-old boy was referred to the pediatric neurology outpatient clinic for steppage gait. Objectively, he had claw toes and slight muscular atrophy of the intrinsic muscles of hands and feet, almost absent Achilles and rotulian reflexes, slight retraction in the dorsiflexion of the feet. Electromyography revealed severe and demyelinating sensorimotor polyneuropathy. The multiplex ligation-dependent probe amplification study of the peripheral myelin protein 22 gene revealed no changes. The next generation sequencing panel detected heterozygous variant c.395T> C in inverted formin-2 gene (Cr. 14), which causes Charcot-Marie-Tooth disease E and focal segmental glomerulosclerosis. Autosomal dominant intermediate Charcot-Marie-Tooth disease E is an uncommon variant of the disease (prevalence < 1/1,000,000) characterized by mixed axonal-demyelinating physiology that shares Charcot-Marie-Tooth and focal segmental glomerulosclerosis features. This report shows the importance of a complete diagnostic workup, which allowed genetic diagnosis, optimizing clinical surveillance, and reinforcing the importance of a multisystemic evaluation and multidisciplinary management.

Keywords: Child; Charcot-Marie-Tooth Disease/diagnosis; Charcot-Marie-Tooth Disease/genetics; Glomerulosclerosis, Focal Segmental/genetics; Microfilament Proteins/genetics; Mutation/genetics

Introduction

Charcot-Marie-Tooth disease is the most prevalent inherited peripheral neuropathy in children, representing the largest group of inherited neuromuscular diseases, with a variety of phenotypes, inheritance patterns, and causal genes.

Affected people often experience weakness and progressive atrophy of distal muscles, reduced tendon reflexes, and deformities in the feet and hands. Three subtypes of Charcot-Marie-Tooth disease were distinguished through electrophysiological and neuropathological studies. The autosomal dominant disease of Charcot-Marie-Tooth disease type 1, the demyelinating variant, is the most prevalent form, and is electrophysiologically characterized by reduced motor nerve conduction velocities of the median nerve (motor nerve conduction velocities < 38 m/s) as well as segmental demyelination, segmental remyelination, and hyperplasia of Schwann cells causing onion bulb formations on histopathological examination. Most cases are caused by mutations in the peripheral myelin protein 22 (*PMP22*) gene and myelin protein zero (*MPZ*) gene. Type 2 Charcot-Marie-Tooth disease is an axonal form associated with normal or subnormal nerve conduction velocities and axonal degeneration. The intermediate form of Charcot-Marie-Tooth disease combines demyelinating and axonal characteristics in which patients of the same family may have subnormal or reduced nerve conduction velocities (motor nerve conduction velocities between 25-45 m/s).[1,2]

Since the initial description, several cases of renal involvement have been reported in association with Charcot-Marie-Tooth disease. The common mechanisms underlying the two clinical entities remain at issue. In patients with Charcot-Marie-Tooth, an increased prevalence of glomerulopathies, mainly focal and segmental glomerulosclerosis, have been documented.[3] The estimated prevalence of focal segmental glomerulosclerosis in Charcot-Marie-Tooth is 1/400 patients with Charcot-Marie-Tooth, compared with 1/1,000,000 in the general population.[4]

Case Report

A 9-year-old boy was born to nonconsanguineous parents. He had no significant family, antenatal, and

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perinatal history. Psychomotor development was normal. The patient was referred to the pediatric neurology outpatient clinic for steppage gait. Reference to toe position from the beginning of autonomous walking at 12 months, associated with frequent falls. Without suspected hearing loss, cramps, or myalgia. Objectively, he had claw toes (Fig. 1) and slight muscular atrophy of the intrinsic muscles of hands and feet (Fig. 2). Neurological examination showed almost absent Achilles and rotulian reflexes, slight retraction in dorsiflexion of the feet, walking starting with the forefoot, foot hanging, and excessive flexion of hips and knees, and no ability to walk on his heels. No changes in tactile, proprioceptive, and vibratory sensitivity. Appropriate investigations were ordered, including electromyography which revealed severe and demyelinating sensorimotor polyneuropathy, with an important axonal component (tibial nerve conduction velocity 12.5 m/s). The multiplex ligation-dependent probe amplification study of the *PMP22* gene revealed no changes. Targeted next generation sequencing panel detected heterozygous variant c.395T> C in gene *INF2* (Cr. 14), which causes Charcot-Marie-Tooth E and focal segmental glomerulosclerosis, both with autosomal dominant inheritance. The patient was referred to pediatric nephrology, non-nephrotic proteinuria was detected (24-hour urine protein excretion test 20.1 mg/m^2/h), and the renal function was normal (urea 30 mg/dL, creatinine 0.41 mg/dL). Therefore, nephroprotective therapy measures were initiated (dietary recommendations with the avoidance of excessive sodium and excessive protein intake) and regular 24-hour urine protein excretion tests were initiated. In addition, he was referred to physical and rehabilitation medicine outpatient clinic (starting physiotherapy), otorhinolaryngology (awaiting evaluation), and genetics (parents awaiting genetic result).

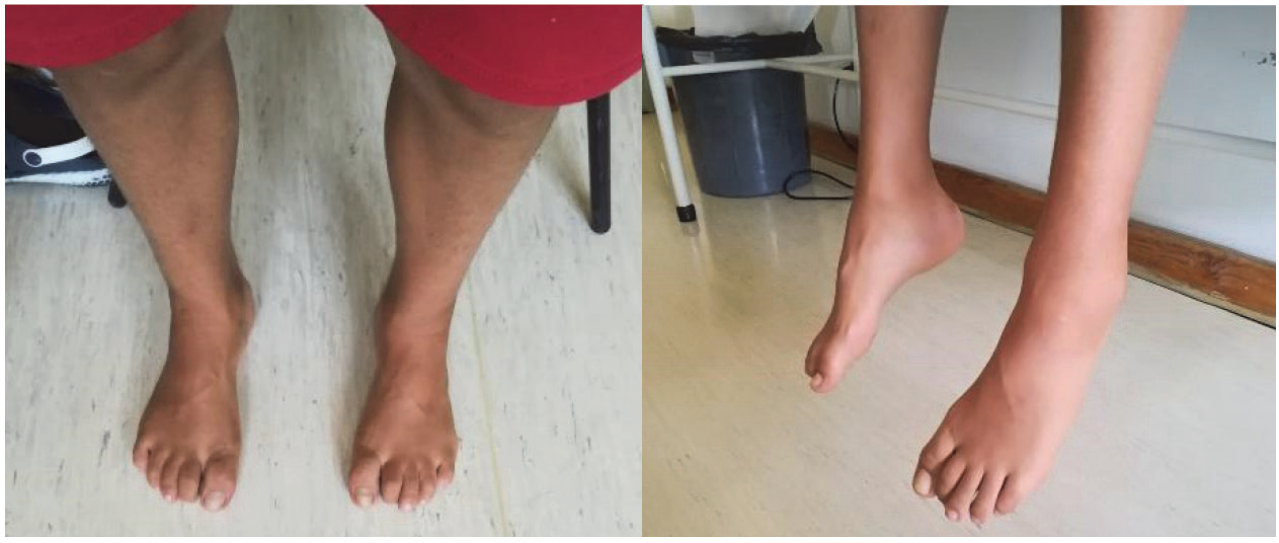

Figure 1. Claw toes.

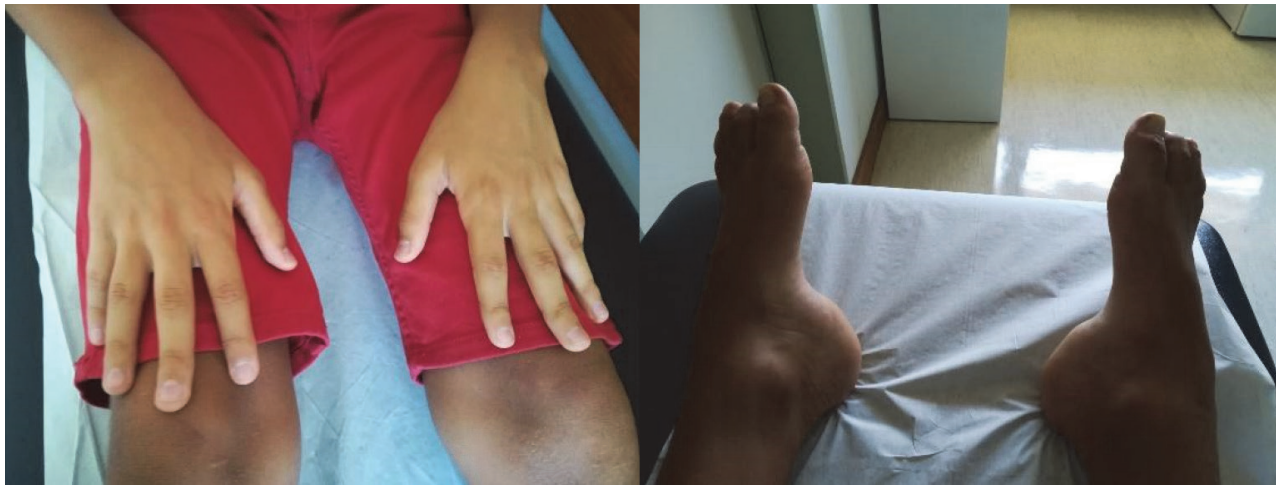

Figure 2. Muscular atrophy of the intrinsic muscles of hands and feet.

Discussion

Autosomal dominant intermediate Charcot-Marie-Tooth E is an uncommon variant of the disease (prevalence < 1 / 1,000,000) characterized by mixed axonal-demyelinating physiology that shares Charcot-Marie-Tooth and focal segmental glomerulosclerosis features. This form is defined as a dominant Charcot-Marie-Tooth E phenotype and is the third most frequent intermediate disease. The clinical manifestations of Charcot-Marie-Tooth E include age of onset between 5 and 28 years, proteinuria, mild to severe weakness, *pes cavus,* reduced tendon reflexes, sensory or sensorineural loss, and cramps.[5] Genetic testing is the gold standard of the diagnostic evaluation and is necessary for the confirmation of subtype-specific diagnoses.

Inverted formin-2 (*INF2*) gene is located on chromosome 14q32.33 and encodes inverted formin-2, which is expressed in the cytoplasm of Schwann cells and renal podocytes, affecting both the peripheral nervous system and the renal glomerulus. Podocyte dysfunction plays a central role in the pathogenesis of Charcot-Marie-Tooth E.[6,7] The prevalence of *INF2* mutations in association with Charcot-Marie-Tooth/focal and segmental glomerulosclerosis is much higher (75%) compared to isolated focal segmental glomerulosclerosis (12%-17%) and is null in isolated Charcot-Marie-Tooth, suggesting that *INF2* mutations may be the link between Charcot-Marie-Tooth and focal segmental glomerulosclerosis.[1,6,8] Neurological features of Charcot-Marie-Tooth E include slowly progressive distal muscle weakness and atrophy in the upper and lower limbs, distal sensory loss in the extremities, reduced or absent deep tendon reflexes, and foot deformities. In Charcot-Marie-Tooth E patients, the clinical neurologic symptoms are similar to those in other forms of the disease. The sensorimotor polyneuropathy typically presents with the involvement of the anterior and lateral compartment muscles of the lower leg and progresses lengthwise.

Neurological symptoms typically appear before the onset of proteinuria, meanly 3.3 years earlier.[6] Nerve biopsy reveals both axonal and demyelinating changes and nerve conduction velocities vary from the demyelinating to the axonal range (between 25-50 m/s).

Focal segmental glomerulosclerosis is one of the most common histological patterns of acquired glomerular disease leading to end-stage kidney disease.[7] The clinical features of focal segmental glomerulosclerosis include a wide spectrum of pathologies, from isolated non-nephrotic proteinuria to corticosteroid-resistant nephrotic syndrome and a reduction of the glomerular filtration rate that can be associated with progression to end-stage kidney disease.[3,6] Charcot-Marie-Tooth/ focal segmental glomerulosclerosis patients most often present as asymptomatic proteinuria without profound hypoalbuminemia or edema. Charcot-Marie-Tooth associated focal segmental glomerulosclerosis usually has a faster progression to end-stage kidney disease compared to isolated focal segmental glomerulosclerosis, with a median age onset of proteinuria of 14.5 years and end-stage kidney disease at 20 years.[1,6] To date, there is no significant evidence that earlier onset of proteinuria may be associated with faster progression to end-stage kidney disease or more severe chronic kidney disease, once there is significant inter and intrafamilial phenotypic variability with a wide range of age at presentation and end-stage kidney disease.[8] The diagnosis of focal segmental glomerulosclerosis is based on the detection of segments of sclerosis limited to some glomeruli.

Mild or moderate sensorineural hearing loss may also be associated, as found in 27% of patients, compared to the approximately 5% prevalence in overall Charcot-Marie-Tooth. Thirty-six genes were described to be involved in inherited peripheral neuropathy and hearing loss, including *INF2*. Since the cranial nerves are part of the peripheral nervous system and are wrapped by Schwann cells, hearing loss associated with Charcot-Marie-Tooth disease can be due to cochlear impairment and/or auditory nerve dysfunction.[3,6,9] Currently, specific disease-modifying therapy is not available for Charcot-Marie-Tooth E. In genetic focal segmental glomerulosclerosis disorders, dietetic measures (avoidance excessive sodium and excessive protein intake) and supportive measures are the focus (angiotensin converting enzyme inhibitors or angiotensin receptor blockers to control proteinuria, diuretics to control edema). Prognosis generally is poor, and the management of end-stage kidney disease is currently supportive.

The multiorgan involvement that characterizes Charcot-Marie-Tooth E disease requires a multidisciplinary evaluation. Based on hearing loss underdiagnosed cases, auditory acuity should be evaluated in every patient suffering from Charcot-Marie-Tooth E. At the same time, the quantitative measurement of protein excretion should be performed by the measurement of total protein/creatinine ratio on a spot urine sample or 24-hour urine collection. Measurement of the protein/ creatinine ratio on a spot urine sample is preferably performed on a first morning specimen due to the large degree of variability in urinary protein levels throughout the day. Timed 24-hour urine measurement is a more accurate method of measuring protein in the urine. However, in infants and children, especially in those who

are not toilet trained, this method tends to be difficult to perform. Therefore, the calculation of a protein/creatinine ratio in a spot urine sample is an acceptable alternative to a 24-hour urine collection for protein, especially in the pediatric population. Until now, in our clinical center, no screening for proteinuria was routinely performed in this subtype of Charcot-Marie-Tooth disease, leading to late or underdiagnosing of Charcot-Marie-Tooth/focal segmental glomerulosclerosis. Therefore, the early referral of Charcot-Marie-Tooth E patients to a nephrology outpatient clinic associated with regular clinical and analytical surveillance is essential, since multisystemic involvement, namely renal, may not be present at an early stage. Furthermore, some patients are only diagnosed with end-stage kidney disease.

Therefore, regular multidisciplinary surveillance should take place to implement measures that modify Charcot-Marie-Tooth E natural history, thereby improving prognosis. Moreover, genetic counselling should be made available to all patients and families.

This report shows the importance of a complete diagnostic workup, which allowed genetic diagnosis, optimizing clinical surveillance, and reinforcing the importance of multisystem evaluation and multidisciplinary management. Regular multidisciplinary surveillance should take place to implement interventions that are directed to the preservation of the quality of life of children with Charcot-Marie-Tooth E.

WHAT THIS CASE REPORT ADDS

- Until now, in our clinical center, no screening for proteinuria was routinely performed in Charcot-Marie-Tooth E disease, leading to late or underdiagnosing of Charcot-Marie-Tooth/focal segmental glomerulosclerosis. Therefore, the early referral of Charcot-Marie-Tooth E patients to a nephrology outpatient clinic associated to regular clinical and analytical surveillance is essential, since multisystemic involvement, namely renal, may not be present at an early stage.
- To the best of our knowledge, there are very few cases described in the literature of patients with Charcot-Marie-Tooth E disease.
- Accurate diagnose and early multidisciplinary management of Charcot-Marie-Tooth E patients allow for supportive interventions directed at the preservation of quality of life.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication

Consent for publication was obtained.

Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

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Doença de Charcot-Marie-Tooth: De Marcha em Pontas a Nefropatia

Resumo

Criança de 9 anos, sexo masculino, previamente saudável, referenciada para consulta de neuropediatria por marcha em pontas. Objetivamente apresentava dedos dos pés em garra e atrofia muscular discreta dos músculos intrínsecos das mãos e pés, reflexos aquilianos e rotulianos quase ausentes, ligeira retração na dorsiflexão dos pés. A eletromiografia revelou polineuropatia sensoriomotora severa e desmielinizante. O estudo por amplificação multiplex de sondas dependente de ligação do gene proteína de mielina periférica 22 não revelou alterações. O painel de sequenciação de nova geração detetou a variante c.395T>C, em heterozigotia, no gene formina invertida 2 (Cr. 14), causadora de doença Charcot-Marie-Tooth-E e glomeruloesclerose segmentar focal. A doença autossómica dominante de Charcot-Marie-Tooth E é uma variante rara da doença Charcot-Marie-Tooth (prevalência < 1/1 000 000), causada por alterações axonais e desmielinizantes, que partilha as características da Charcot-Marie-Tooth e glomeruloesclerose segmentar focal. O artigo apresentado traduz a importância de uma abordagem diagnóstica completa, que permitiu o diagnóstico genético e vigilância clínica otimizada, reforçando assim a relevância da avaliação multissistémica e seguimento multidisciplinar.

Palavras-chave: Criança; Doença de Charcot-Marie-Tooth/diagnóstico; Doença de Charcot-Marie-Tooth/genética; Glomeruloesclerose Segmentar Focal/genética; Mutação/genética; Proteínas dos Microfilamentos/genética