CASO CLÍNICO/CASE REPORT

Generalized Epilepsy in a Patient with *GBJ1* X-Linked Charcot-Marie-Tooth Disease

Epilepsia Generalizada em Doente com Doença de Charcot-Marie-Tooth Ligada ao X por Mutação do Gene *GBJ1*

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Abstract

Charcot-Marie-Tooth (CMT) disease is an inherited neuropathy known for its genetic and phenotypic heterogeneity. Although unusual, the involvement of the central nervous system (CNS) has also been reported, including epilepsy.

A 23-year-old man who at the age of 8 started to develop a gait disturbance. His neurological examination revealed distal weakness, muscular atrophy of the four limbs and decreased deep tendon reflexes. The electromyogram and nerve conduction study revealed a chronic symmetric axonal sensorimotor polyneuropathy. Next generation gene panel sequencing identified a hemizygous variant on *GJB1* gene (c.547C>T, p.R183C) consistent with X-linked CMT. At the age of 21, he developed recurrent unprovoked tonic-clonic seizures. An electroencephalogram was consistent with a generalized epilepsy.

The association of CMT disease with epilepsy is rare. *GJB1* encodes the gap junction protein connexin32, which is expressed primarily in Schwann cells of peripheral nerves but also in oligodendrocytes and certain neuronal populations, possibly explaining the CNS manifestations.

Resumo

A doença de Charcot-Marie-Tooth (CMT) é uma neuropatia hereditária reconhecida por sua heterogeneidade genética e fenotípica. Embora incomum, também há relatos do envolvimento do sistema nervoso central (SNC), incluindo epilepsia.

Homem de 23 anos que aos 8 anos se apresenta com alterações da marcha. Ao exame neurológico apresentava fraqueza muscular distal, atrofia dos quatro membros e hiporreflexia generalizada. O eletromiograma e estudo de condução nervosa revelaram sinais de polineuropatia sensitivo-motora axonal simétrica crónica. O estudo genético identificou uma variante hemizigótica no gene *GJB1* (c.547C>T, p.R183C) consistente com CMT ligada ao X. Aos 21 anos, desenvolveu crises tónico-clónicas recorrentes, não provocadas. O eletroencefalograma foi compatível com epilepsia generalizada.

A associação da doença CMT com epilepsia é rara. O gene *GJB1* codifica a proteína conexina32, que é expressa principalmente nas células de Schwann dos nervos periféricos, mas também nos oligodendrócitos e determinadas populações neuronais, possivelmente explicando as manifestações do SNC.

Introduction

Charcot-Marie-Tooth (CMT) disease encompasses a variety of inherited neuropathies, affecting 1 in 2500 patients.[1–3] It is primarily an autosomal dominant disease, most often caused by a duplication in the peripheral myelin protein-22 gene (*PMP22*).[4] However, shortly after the first descriptions of CMT, an affected family having X-linked inheritance was reported.[5] It is now known that the X-linked pattern of CMT (CMTX) is the second most common form.[6] Affected males who are hemizygous for the mutation have moderate to severe clinical manifestations, showing onset of symptoms in early childhood, while heterozygous females are usually less affected, with mild clinical signs, probably due to random X-inactivation.[2,7]

CMT disease has a marked genetic and phenotypic heterogeneity.[8] It typically affects both motor and sensory peripheral nerves, enclosing demyelinating and axonal forms.[1] Although unusual, the involvement of the central nervous system (CNS) has also been reported, including epilepsy.[1,2,9,10] The association of CMT disease with epilepsy is rare, and most of the published cases are related to *PMP22* gene duplications in CMT1A subtype. Its underlying mechanisms are still unknown.[1,2]

We describe the case of a patient diagnosed with CMTX affecting *GJB1* gene in middle childhood, who also developed generalized epileptic seizures. We aim to contribute to unravel the clinical pleomorphism of CMT disease and specifically delineate the neurological spectrum of *GJB1*.

Case Report

A 23-year-old male, son of healthy and non-consanguineous parents, that at the age of 8 started to develop a gait disturbance with frequent drops and muscle weakness in lower legs. Regarding clinical background, the patient was born with 39 weeks after a pregnancy and a natural childbirth with no complications. His psychomotor development was considered normal. The neurological examination revealed a weakness of the distal muscles of upper and lower limbs (Medical Research Council Scale for muscle strength: bilateral wrist extensors – grade 4/5, bilateral wrist flexors – grade 4/5; bilateral finger extension – grade 4/5; bilateral finger abduction – grade 4/5; bilateral leg flexion /extension - grade 4/5; bilateral ankle dorsiflexors – grade 2/5; bilateral plantar flexion – grade 3/5; bilateral ankle invertors/evertors – grade 4/5) [11]. Atrophy was observed in the intrinsic hand muscles, especially the thenar muscles of the thumb, as well as in the distal leg muscles. Deep tendon reflexes were decreased. Plantar responses were flexor. There was a mild postural tremor of the upper limbs. The remaining neurologic examination was unremarkable, namely no ataxia or sensory impairment were observed. The patient had *cavus* feet, but no other skeletal deformations, like scoliosis. The motor deficits remained stable, with a mild to moderate gait disability.

Regarding complementary diagnostic exams, routine laboratory tests were normal. The electrophysiological findings were consistent with a chronic, symmetrical sensorimotor axonal polyneuropathy with greater involvement of the distal segments of the lower limbs. In lower limbs, motor conduction velocity was reduced (35.3 m/s), distal motor latency was within the norm, and the distal compound muscle action potential (CMAP) were reduced in amplitude and slightly dispersed. Sensory conduction velocities were also reduced both in the upper (36.9 m/s, median nerve) and lower limbs (33.7 m/s, sural nerve). Sensory nerve action potentials (SNAP) of the superficial peroneal nerve were absent bilaterally and decreased in the upper limbs. Electromyography examination showed signs of chronic denervation with muscle unit potentials of increased amplitude and duration, with greater involvement of distal muscles. Signs of ongoing denervation such as fibrillation potentials were also described. Next generation targeted gene panel sequencing, with 277 genes and a mean depth coverage of 377x, identified a hemizygous, missense variant on *GJB1* (c.547C>T, p.R183C), classified as pathogenic. His parents were not available for genetic study.

At the age of 21, he developed recurrent unprovoked tonic-clonic seizures, both awake and asleep, with no specific time pattern. He had no memory for the events, and he denied any subjective symptoms preceding the events compatible with an aura. Myoclonic jerks were not perceived. No seizure precipitants were identified, such as sensitivity to flashing lights, sleep deprivation or fatigue, nor other stressors namely high altitude, intense exercise, febrile illness, or hyperventilation. Regarding clinical background, there was no history of previous febrile seizures, head trauma, CNS infection or family history of epilepsy. An electroencephalogram (EEG) showed generalized 3-4Hz polyspike/ spike-and-slow-wave complexes, consistent with a generalized epilepsy (**Fig. 1**). During intermittent photic stimulation (IPS), there was no photoparoxysmal response. A brain magnetic resonance imaging (MRI) - 1.5 Tesla with a dedicated protocol for epilepsy excluded any structural abnormalities. Further investigation, including with metabolic

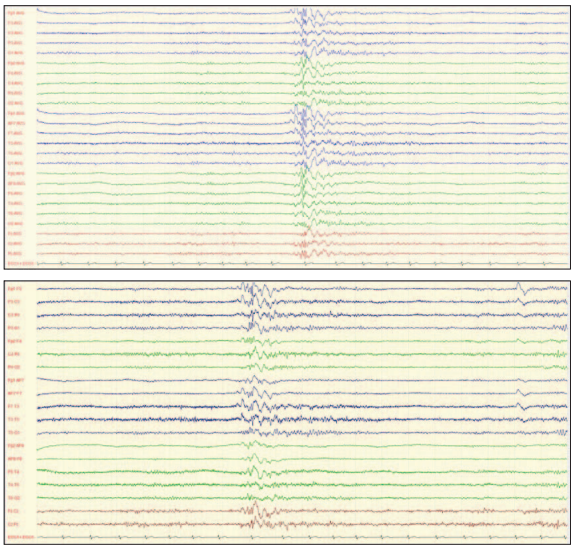

Figure 1. Interictal EEG: Generalized 3-4Hz polyspike/spike-and-slow-wave complexes, with a bifrontal amplitude maximum, superimposed on a normal EEG background (Common average reference, 20 mm/sec, 120 µV/cm, HFF: 70 Hz, LFF: 1,0Hz)

tests and cerebrospinal fluid examination were normal. He was then treated with levetiracetam 500 mg twice a day, with seizure-freedom for a follow-up period of 2 years.

Subject has given his written informed consent to publish this case report.

Discussion

In this case report, we describe a patient with a clinical presentation of a symmetric sensorimotor polyneuropathy with intermediate conduction velocities in the 1st decade of life, compatible with CMTX resultant from a *GJB1* mutation, who posteriorly fulfil the diagnostic criteria for a generalized epilepsy (recurrent unprovoked generalized tonic-clonic seizures, EEG with generalized epileptiform discharges and a normal brain MRI). This association, to the best of our knowledge, has not been reported before.

More than 400 different mutations have been described in *GJB1*, which encodes the gap junction protein connexin32 (Cx32).[6,12,13] Cx32 is composed by 4 transmembrane domains that link 2 extracellular loops and 1 intracellular loop as well as intracellular N- and C-terminal domains.[7,14] It is expressed primarily in Schwann cells of peripheral nerves, playing an important role in the homeostasis of myelinated axons.[1,7,15] In the presence of a mutation, most of them being missense, Cx32 fails to form functional gap junction channels, or lead to channels with altered gating properties.[16,17] The reported rare missense variant, located at exon 2, affects the 2nd extracellular loop of the Cx32, and has previously been reported in CMTX affected patients.[7,17] The R183C variant is a non-conservative amino acid substitution, which is likely to impact secondary protein structure as these residues differ in polarity, charge, size, and other properties.[7,17] This substitution occurs at a position that is conserved across species and in silico analysis predicts this variant as probably damaging to protein structure/function. Multiple missense variants at the same codon (R183H/S/P) and in nearby residues have been reported in Human Gene Mutation Database in association with *GJB1*-related disorders,[18] supporting the functional importance of this region of the protein.

Besides the classic presentation with neuropathy, involvement of CNS has also been reported in clinical phenotypes of patients with CMT disease, including cognitive impairment, pyramidal signs, ataxia, and cerebral white matter abnormalities.[1,2,8,9,14,19–22] Particularly for *GJB1* disorders, SNC manifestations can appear as fixed abnormalities or acute, self-limited and recurrent episodes of transient neurologic dysfunction (especially upper motor neuron weakness and dysarthria), known as stroke-like episodes, that may occur after a metabolic stress (Abrams, 2020; Panas *et al*, 2001; Paulson *et al*, 2002; Srinivasan *et al*, 2008 Wilmshurst and Ouvrier, 2011). Panas *et al* (2001) reported that EEG recordings during these episodes showed moderate diffuse slowing.[14] Only a few reports have described the association between epilepsy and CMT disease. Both focal, without a consistent topography [1,2,9], and generalized epilepsy[10] have been reported. Myoclonic epilepsy in combination with peroneal muscular atrophy was first described by Smith *et al* (1978). Posteriorly, Routsonis *et al* (1984) studied a Greek family with CMT peroneal muscular atrophy, in which some affected members had epilepsy. Epilepsy with myoclonic seizures can be associated to CMT1A with duplication of *PMP22* gene.[10] Intractable generalized tonico-clonic seizures were also described in an 11-year-old patient with CMT1A due to *PMP22* gene duplication.[10] Abid *et al* (2014) reported a patient who suffered from a hereditary neuropathy type CMT1A with a duplication of the *PMP22* and temporal lobe epilepsy.[2]

The underlying pathophysiologic mechanism of CNS manifestations, including epilepsy, is not completely understood.[15] However, CNS dysfunction in CMT1A is supposedly related to the expression of *PMP22* mRNA and its protein in the CNS.[21,24] Furthermore, Cx32 is also expressed in oligodendrocytes and certain neuronal

populations.[2,14,16,23] Loss of functional Cx32 gap junction channels within CNS could lead to increased susceptibility to abnormalities of the intercellular exchange of ions and small molecules.[16,23] Central involvement in CMTX was proved by slowing of central conduction in brainstem auditory evoked responses.[25] Central myelin involvement may be related to altered oligodendrocyte function or to the role of the *GJB1* gene during CNS development.[14] It is still controversial whether epilepsy in CMT patients are a part of the same phenotypic spectrum or a random epiphenomenon.[1,2,10] Careful genotype/phenotype correlations have revealed a far greater complexity in CMT disease than previously thought. In the cases reported in the literature, exhaustive analyses of the patients and their families were performed to discard the possibility of two different entities occurring together.[1,2,10] Likewise, the hypothesis of a coexisting disease was also extensively analysed in our patient, but a genetic generalized epilepsy (mono or polygenic) remains a possibility.

To conclude, we report an association of generalized epilepsy and CMTX due to *GJB1* mutation that has not been reported in the literature, to the best of our knowledge. Our case is in concordance with current literature supporting epilepsy as a possible CNS manifestation of CMT disease. Further studies are still needed to confirm this hypothesis and explain in detail its pathophysiological mechanisms. Elucidating the clinical manifestations of *GJB1* mutation in both peripheral and central nervous system is important not only for a prompt clinical diagnosis but also for the development of targeted treatments in the future. ■

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IM and JJR: Conception, drafting the article and final approval of the version to be submitted.

JM and FS: Critical review and final approval of the version to be submitted.

AG: Critical review with intellectual contribution and final approval of the version to be submitted.

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