

X-linked Charcot–Marie–Tooth Disease Presenting with Stuttering Stroke-like Symptoms

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Abstract

X-linked Charcot–Marie–Tooth disease (CMTX1) is the second most common form of Charcot–Marie–Tooth disease (CMT). It is caused by a mutation in the gap junction β 1 (*GJB1*) gene, which encodes for connexin-32. In addition to the peripheral neuropathy and foot deformities observed in classic CMT, central nervous system symptoms and magnetic resonance imaging (MRI) signal abnormalities in the brain have been reported in patients with CMTX1. Here we describe two cases of adolescent males who presented with stuttering neurologic deficits that were initially suggestive of acute ischemic stroke and were ultimately diagnosed with genetically confirmed CMTX1. Both patients had evidence of T2 hyperintensity and decreased diffusion on MRI in the centrum semiovale, posterior corona radiata, posterior periventricular white matter, and corpus callosum. Though rare, these cases illustrate the importance of comprehensive neurologic history, physical examination, and appropriate diagnostic evaluation.

Keywords

- ▶ X-linked Charcot–Marie–Tooth disease
- ▶ gap junction β 1 gene
- ▶ neuropathy
- ▶ stroke-like symptoms

Introduction

X-linked Charcot–Marie–Tooth (CMTX1) disease is caused by mutations in the gap junction β 1 (*GJB1*) gene (connexin-32), which is present in both the central nervous system (CNS) and peripheral nervous system.¹ CMTX1's clinical phenotype consists of progressive muscle atrophy, weakness, areflexia, variable sensory abnormalities, and, occasionally, CNS manifestations.² The diagnosis is based on clinical presentation, electromyography, and nerve conduction studies that demonstrate slowed nerve conduction velocities with demyelinating features. Sequencing of the *GJB1* gene detects approximately 90% of cases.³ More than 400 different mutations in the *GJB1* gene have been identified, and transient CNS deficits with associated white matter abnormalities on

magnetic resonance imaging (MRI) have been reported in patients with CMTX1.^{2,4,5}

Here we report two previously healthy adolescent patients who presented with stuttering stroke-like episodes and were ultimately diagnosed with CMTX1 disease with CNS features.

Case 1

A 13-year-old male presented with isolated right facial weakness and was diagnosed with Bell's palsy and treated for Lyme disease with doxycycline. His facial weakness improved temporarily, but he returned to the emergency department hours later with recurrent facial weakness, dysarthria, and right upper extremity weakness and numbness. He was admitted,

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placed on standard stroke precautions, and given aspirin. His neurologic exam was notable for a mild, fluctuating right upper and lower facial droop, decreased right-hand strength, brisk right biceps and right patellar tendon reflexes, diminished ankle reflexes, pes cavus deformity of his feet, and mild muscle wasting in his distal lower extremities. Additional history revealed travel to the mountains in New York and California the week prior to presentation.

Cerebrospinal fluid (CSF) analysis was normal. MRI showed asymmetric restricted diffusion in the bilateral centrum semi-ovale, posterior corona radiata, and lateral aspects of the splenium of the corpus callosum, with superior extension of the left to the left precentral gyrus with associated T2 hyperintense signal corresponding to areas of restricted diffusion (►Fig. 1A–C). Magnetic resonance (MR) angiography was normal. Electromyography and nerve conduction studies showed evidence of a mild-to-moderately severe and chronic sensorimotor demyelinating neuropathy consistent with CMTX1. Genetic testing demonstrated a hemizygous L76P variant (c.227T > C (p.Leu76Pro (L76p)) of the *GJB1* gene.

Case 2

A 14-year-old right-handed boy presented after 2 days of stuttering symptoms of tongue tingling and right facial weakness while traveling to Bermuda on a cruise. He was treated with diphenhydramine for a possible allergic reaction, with resolution of symptoms. The following evening, the symptoms returned prompting treatment with prednisone for possible Bell's palsy by the cruise physician. The next morning, he was brought to an emergency room in Bermuda where he complained of right leg weakness. He was managed according to a stroke protocol and transferred to our facility for further diagnostics and management. His examination was notable for ankle weakness, decreased vibration sense in lower extremities, absent lower extremity reflexes, and pes cavus deformity of his feet. Additional history revealed bilateral foot weakness since childhood.

CSF showed an elevated protein of 139 mg/dL but was otherwise unremarkable. MRI revealed symmetric foci of T2 and FLAIR (fluid-attenuated inversion recovery) hyperintensity of the centrum semiovale, posterior corona radiata, posterior periventricular white matter, and, to a lesser extent, the splenium of the corpus callosum with marked decreased diffusion in the areas of T2 prolongation (►Fig. 1D–F). MR angiography was unremarkable. Electromyography and nerve conduction studies revealed electrophysiological evidence of a demyelinating neuropathy primarily in the arms and a mixed demyelinating and axonal neuropathy in the legs with chronic denervation throughout. A hemizygous mutation (c.425G > A (p.Arg142Lgn)) was identified in the *GJB1* gene.

Discussion

CNS manifestations of CMTX1 can include dysarthria, dysphagia, aphasia, extremity weakness, respiratory distress, ataxia, paresthesias, and cranial neuropathies. These can be stuttering, transient, or sustained. Stroke-like events have

been described in individuals with CMTX1, and CNS involvement can precede clinical signs of peripheral neuropathy, making the diagnosis challenging.⁶ In both cases described here, the initial presenting symptoms were stuttering and asymmetric, mimicking a vascular etiology, although signs of peripheral neuropathy including pes cavus were present on examination. Fluctuating episodes of Bell's palsy were also noted in both cases, which may have been secondary to either bilateral white matter involvement or lower motor neuron involvement, as CMTX1 is both a central and peripheral neurologic disease. CMTX1 presenting with Bell's palsy as an initial manifestation has not been previously described. Episodes can begin suddenly or progress over days, and can last for several weeks, often with a fluctuating course. Attacks can be provoked by travel to high altitudes, fevers, or intercurrent illnesses, or can be unprovoked.^{4,7,8} In case 1, the recent travel to altitude possibly provoked his episode, whereas the flight to cruise boat transition may have provoked the symptoms in case 2.

CNS events in patients with CMTX1 and CNS involvement can be recurrent.^{4,5,7} On further history, the patient in case 1 had a transient episode of slurred speech and ataxia 4 years prior. During that hospitalization, he was found to be influenza A positive, and his symptoms were attributed to the viral infection after a head computed tomography (CT) and lumbar puncture were unrevealing. His symptoms spontaneously resolved after 2 days. The patient in case 2 did not have any prior episodes of transient neurologic dysfunction.

The MRI pattern of CMTX1 is unique and can assist with the diagnosis. There are some similarities to methotrexate toxicity, although this would be apparent on history. MRI changes in CMTX1 classically show nonenhancing signal abnormalities in the periventricular deep white matter, middle cerebral peduncles, centrum semiovale, and the corpus callosum, often with a posterior predominance. Additionally, T2 abnormalities in CMTX1 typically spare the subcortical U-fibers distinguishing it from other white matter disorders such as acute disseminated encephalomyelitis. MRI signal abnormalities usually resolve within a few months.¹ Interestingly, despite bilateral MRI findings in both cases, neither patient demonstrated bilateral symptoms. Nerve conduction studies commonly show “intermediate range” slowing of nerve conduction velocities ranging between 30 and 45 m/s, as well as mildly prolonged distal motor and F wave latencies.^{1,2,6} The CSF of these patients is typically normal, supporting the idea that inflammation is not a primary etiology of this disorder.⁵

Various mutations in the *GJB1* gene have been associated with clinical and MRI evidence of CNS involvement. The exact mechanism through which CNS damage occurs is unknown; however, it is suspected to be secondary to disruption of gap junction communication between oligodendrocytes and astrocytes. Disruption of gap junction mediated coupling between oligodendrocytes and astrocytes is thought to lead to dysregulation of fluid exchange, resulting in the diffusion restriction abnormalities that are often identified on MRI in these patients.⁵ Additionally, it has been hypothesized that physiologic stressors such as hypoxia and infections lead to decreased gap junction coupling between oligodendrocytes

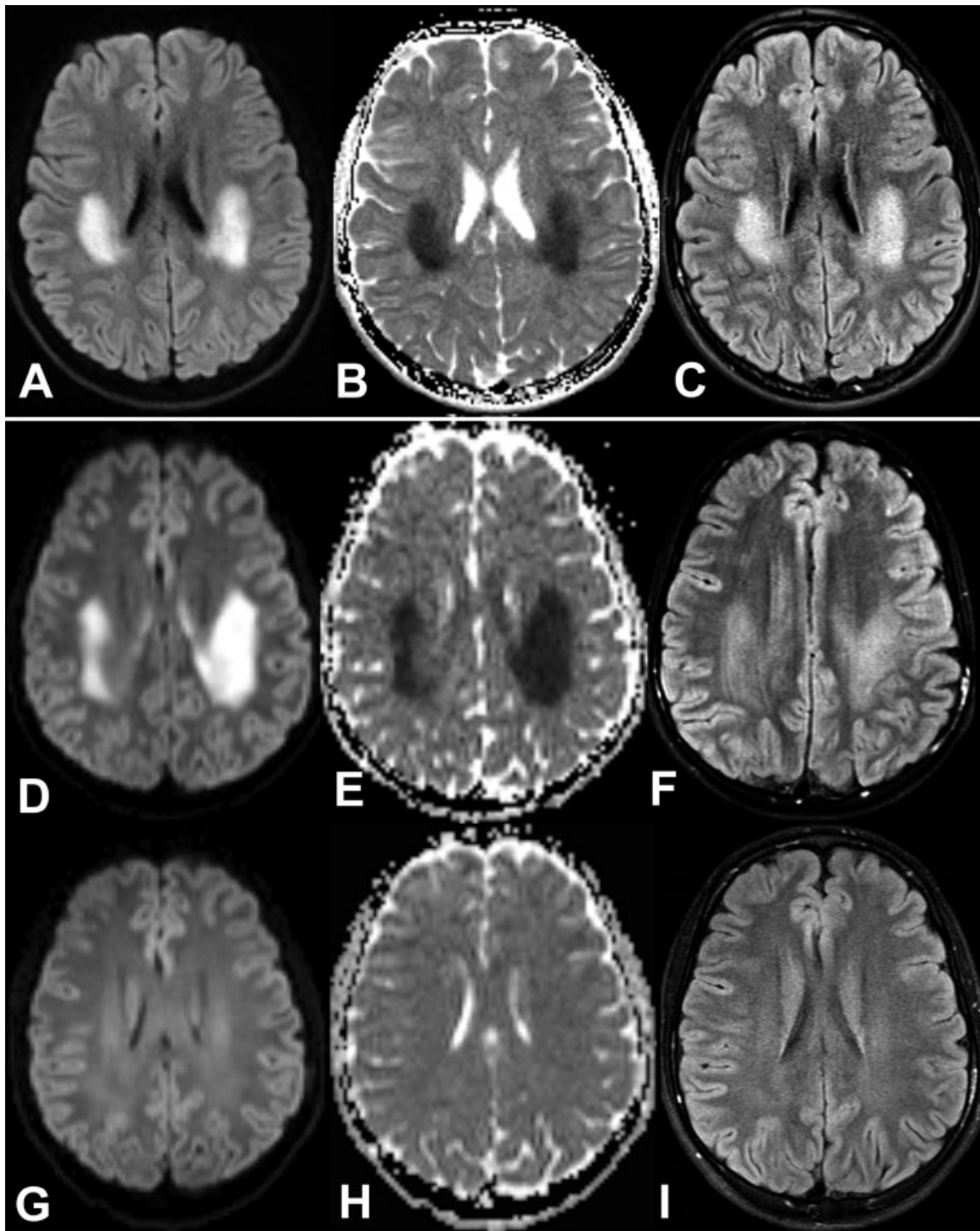


Fig. 1 Brain MRI images of X-linked Charcot–Marie–Tooth disease from patients in case 1 (A–C) and case 2 (D–F) demonstrating markedly reduced diffusion on DWI (diffusion-weighted imaging) (A,D) and ADC (apparent diffusion coefficient) maps (B,E), with corresponding T2 hyperintensity on T2 FLAIR (fluid-attenuated inversion recovery) sequences (C,F). (G–I) Follow-up imaging for case 2 at 4 months postinitial presentation showed near complete resolution of the signal abnormalities.

and astrocytes. Specifically, it has been shown that fluctuations in oxygen exposure lead to CSF acidosis, which is believed to cause closure of gap junctions.^{8,9} Similarly, proinflammatory cytokines released during infections inhibit glial gap junctions, which can also lead to decreased gap junction coupling.⁹ Thus, patients with CMTX1 who have

fragile gap junction communication due to mutations in connexin-32 may be more vulnerable to metabolic stressors leading to transient neurologic deficits.

Treatment for CMTX1 is supportive and focuses on management of the peripheral neuropathy, which may include physical therapy and the use of orthotics. Avoidance of

known triggers is advised. In our patients, symptoms completely resolved within 1 to 2 days of hospitalization, and neither patient has had a recurrence. Follow-up MRI for case 2 at 4 months shows near complete resolution of signal abnormalities (►Fig. 1G–I). The patient in case 1 did not have follow-up imaging performed.

As an X-linked recessive disorder, males with CMTX1 disease have moderate-to-severe sensory/motor neuropathy, whereas females have mild or no symptoms. In the cases presented here, both of the patients' mothers were asymptomatic, although they both had a sensory neuropathy on examination.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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