Case Reports in Neurology

Case Rep Neurol 2015;7:247–252

DOI: 10.1159/000442410
Published online: December 24, 2015

1662–680X/15/0073–0247$39.50/0
www.karger.com/crn

Recurrent Episodes of Stroke-Like Symptoms in a Patient with Charcot-Marie-Tooth Neuropathy X Type 1

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Key Words
Charcot-Marie-Tooth disease · Hereditary motor sensory neuropathy · CMTX1 · Transient neurological symptoms · Magnetic resonance imaging

Abstract
Charcot-Marie-Tooth disease (CMT), also known as hereditary motor sensory neuropathy, is a heterogeneous group of disorders best known for causing inherited forms of peripheral neuropathy. The X-linked form, CMTX1, is caused by mutations in the gap junction protein beta 1 *(GJB1)* gene, expressed both by peripheral Schwann cells and central oligodendrocytes. Central manifestations are known but are rare, and there are few case reports of leukoencephalopathy with transient or persistent neurological deficits in patients with this CMT subtype. Here, we report the case of a man with multiple male and female family members affected by neuropathy who carries a pathologic mutation in *GJB1*. He has experienced three transient episodes with variable neurological deficits over the course of 7 years with corresponding changes on magnetic resonance imaging (MRI). This case illustrates CMT1X as a rare cause of transient neurological deficit and demonstrates the evolution of associated reversible abnormalities on MRI over time. To the best of our knowledge, this report provides the longest period of serial imaging in a single patient with this condition in the English language literature.

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Introduction

Charcot-Marie-Tooth (CMT) disease encompasses a group of inherited disorders affecting the motor and sensory nerves of the peripheral nervous system. It is characterized by progressive weakness and atrophy of distal muscles, high arched feet (pes cavus), and loss of deep tendon reflexes [1]. Five main types of CMT, with multiple subtypes, are described in most classification systems, and more than 60 causative genes are currently known. X-linked Charcot-Marie-Tooth disease type 1 (CMTX1) is an X-linked, semidominant form of CMT. This second most common form of CMT, accounting for 10–15% of cases, is caused by mutations in the gap junction protein beta 1 *(GJB1)* gene located on chromosome Xq13.1, encoding connexin 32 (Cx32) [2, 3]. Cx32 is normally expressed in Schwann cells, oligodendrocytes, and astrocytes, where it is thought to provide a pathway for the diffusion of small molecules and ions directly across the myelin sheath [4]. Most Cx32 mutations are thought to cause inability to form functional gap junctions. Electrophysiologically, CMTX1 shows mixed features of a demyelinating and axonal polyneuropathy [1]. In addition to the common peripheral presentation of CMT, CMTX1 has been reported to have transient central nervous system manifestations [5]. Here, we describe a CMTX1 patient who has experienced multiple episodes of transient central nervous system (CNS) dysfunction associated with white matter abnormalities on magnetic resonance imaging (MRI) of the brain, and demonstrate the temporal progression of his radiological abnormalities over the course of several years.

Case Presentation

A 20-year-old male with diabetes mellitus type 1 and a known personal history of CMTX1 presented to our emergency department with acute-onset dysarthria, tongue deviation, left facial weakness, and left hand numbness developing over the course of about 3 h. He described poor sleep, slight nausea, and mildly elevated blood glucose (183 mg/dl on home testing) in the hours prior to symptom onset. He noted no recent fevers, travel, or strenuous physical exercise. By the time of presentation, his numbness had been improving. On examination, the vital signs were normal. Physical exam findings included a lingual dysarthria and subtle left facial weakness in an upper motor neuron pattern. There was normal strength in all extremities except for ankle dorsiflexion graded at 4-/5, which appeared to be his baseline. There was subjectively decreased sensation in the left upper extremity, primarily in the medial forearm, but not in any specific peripheral nerve distribution. Reflexes were diminished in the upper extremities and absent in the lower extremities bilaterally. The intrinsic muscles of the feet appeared atrophic, with hammer toes and high arches. Plantar reflex was absent bilaterally. Serum electrolytes, renal function, liver function tests, complete blood count with differential, erythrocyte sedimentation rate, and C-reactive protein were all normal. MRI of the brain showed symmetric, nonenhancing areas of restricted diffusion in the corona radiata bilaterally, also seen on T2/fluid-attenuated inversion recovery (FLAIR) sequences (fig. 1e), without edema or mass effect. Intracranial MR angiography was normal.

A review of the patient's pediatric records revealed that he had experienced two prior episodes of unilateral weakness at ages 13 and 14 years, separated by 10 months. The first episode involved the left side and the later episode the right. Both were of sudden onset but gradual evolution over the course of hours to their peak severity, and each resolved completely over the course of several days. At the time of the first episode, the patient was admitted to the hospital and evaluated with cerebrospinal fluid (CSF) studies and brain MRI.

His CSF showed no evidence of infection and was negative for oligoclonal bands, intrathecal immunoglobulin synthesis, and other markers of inflammation. MRI of the brain at that time demonstrated abnormalities in T2/FLAIR and diffusion-weighted MRI sequences in the bilateral centrum semiovale, right parietal lobe, and splenium of the corpus callosum without gadolinium enhancement (fig. 1a), similar to but more widespread than in the most recent presentation. No immediately precipitating event could be identified including vaccination, infection, or travel. He was initially diagnosed with acute disseminated encephalomyelitis (ADEM) and treated with methylprednisolone. A follow-up MRI 3 months after the initial presentation had demonstrated nearly complete resolution of the lesions (fig. 1b), and MR spectroscopy obtained 9 months after the initial event was unremarkable.

The second episode consisted of right-sided weakness and ataxia and resulted in another hospital admission with repeated imaging. MRI of the brain at this time demonstrated large, nonenhancing T2/FLAIR hyperintensities in the bilateral centrum semiovale, the splenium of the corpus callosum, the left greater than right corticospinal tracts, and the left greater than right cerebellar peduncle (fig. 1c). The CSF was again bland. A tentative diagnosis of recurrent ADEM was made, and treatment with steroids was provided. The patient again improved quickly and had recovered to his baseline at a 6-month outpatient follow-up.

Further evaluation continued in the outpatient setting, with symptoms of peripheral neuropathy becoming apparent. Nerve conduction studies and electromyography demonstrated low amplitude sensory and motor responses with sensory conduction velocities in the 38- to 46-m/s range and motor conduction velocities in the 37- to 54-m/s range. Distal latencies and F-waves were also variably prolonged. The findings were suggestive of a mild-to-moderate sensorimotor polyneuropathy with mixed axonal and demyelinating features. A detailed pedigree of other affected family members revealed that the patient's mother, maternal grandfather, maternal aunt, and a male first cousin (son of the affected aunt) also have neuropathy, although none reported stroke-like episodes. About 2 years after his initial presentation, genetic testing confirmed a T467G (Leu156Arg) hemizygous disease-associated mutation in the gene for Cx2 *(GJB1)*.

Four years after his initial presentation, after about 3 years free of episodes, a fourth brain MRI was obtained to evaluate the progression of the extensive white matter lesions seen at the time of the second event (fig. 1d). This study showed a small nonenhancing area of T2/FLAIR hyperintensity in the left cerebellar peduncle, with the previously seen signal in the right cerebellar peduncle, centrum semiovale, and splenium of the corpus callosum all resolved. Three years later, at the time of his most recent episode, the T2/FLAIR hyperintensity in the left cerebellar peduncle had also resolved (fig. 1e).

Discussion

The clinical features of CMTX1, an X-linked semidominant disorder, are characteristic of most dominant CMT forms. Patients have slowly progressive weakness and atrophy with onset in distal leg muscles, usually manifesting first as difficulty running and frequently sprained ankles. The age of onset is 10 years or younger in most affected males. Heterozygous females with CMTX1 are frequently asymptomatic or minimally symptomatic. However, they may develop mild clinical manifestations at an older age (as with this patient's mother), or have subclinical evidence of peripheral neuropathy on electrophysiological studies [6]. Nerve conduction studies in CMTX1 show variable results, but typically, there is an intermediate (30–40 m/s) or even mild (>40 m/s) slowing of motor conduction velocities. Compound muscle action potentials are almost always reduced in amplitude, indicating axon

loss [7]. Axon loss occurs even in early disease stages, suggesting an underlying mixed axonal and demyelinating pathology; this distinguishes CMTX1 from most other CMT forms associated with mutations in myelin-related genes [4].

In addition to peripheral neuropathy, CMTX1 patients often have subclinical CNS involvement that can be detected by brainstem auditory evoked potentials [8]. Overt CNS manifestations tend to be episodic and of acute to subacute onset, frequently described as stroke-like as in this case [3, 5, 9, 10]. Brain MRI obtained during the acute phase of a stroke-like event usually shows an increased T2/FLAIR-weighted signal, sometimes associated with restricted diffusion but without contrast enhancement. Involvement has been described most frequently in the posterior centrum semiovale, splenium of the corpus callosum, and sometimes the middle cerebellar peduncle [11, 12]. These abnormalities have variously been described both as resolving completely or persisting even once patients are asymptomatic [9, 10]. Abnormal MRIs have also been reported in patients without stroke-like symptoms [2, 13]. Disruption of the gap junction-mediated coupling between oligodendrocytes and astrocytes likely leads to an inability of these cells to properly regulate ion and fluid exchange, which may explain the restricted diffusion seen on MRI of the patient with CMTX1 in the acute phase of their illness [14]. Such dysregulation may at least in part explain why stressors like high altitude, intense exercise, febrile illness, hyperventilation, and concussion have been found to precipitate the acute events [4]. Although no clear precipitating events were found for any of this patient's episodes, it is worth noting that he also has diabetes, and it is tempting to speculate that metabolic stress related to this condition could have been a contributor.

This case serves as a reminder that exacerbation of central CMTX1 disease is a consideration in the differential diagnosis of stroke-like acute-onset neurological deficit with diffusion-weighted positive MRI, or an unusual ADEM-like illness. The prognosis of the CNS phenotype of CMTX1 is usually spontaneous resolution without permanent deficit; therefore, promptly identifying the disease is vital to avoid unnecessary investigation and potentially harmful therapeutic intervention. The central white matter lesions on MRI in CMTX1 have been described previously as either fully or partly reversible [9, 10]. In the patient reported here, some white matter signal changes persisted for 3 years but were found to fully resolve (at least at the level of 1.5-tesla resolution) by 6 years. We believe this report, spanning 7 years in total, represents the longest period of serial CNS imaging in a single CMTX1 patient yet described in the English language literature. The findings described herein suggest that the central lesions of CMTX1 are likely to be fully reversible but may persist for several years after an event.

Statement of Ethics

Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor of this journal.

Disclosure Statement

The authors have nothing to declare.

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DOI: 10.1159/000442410

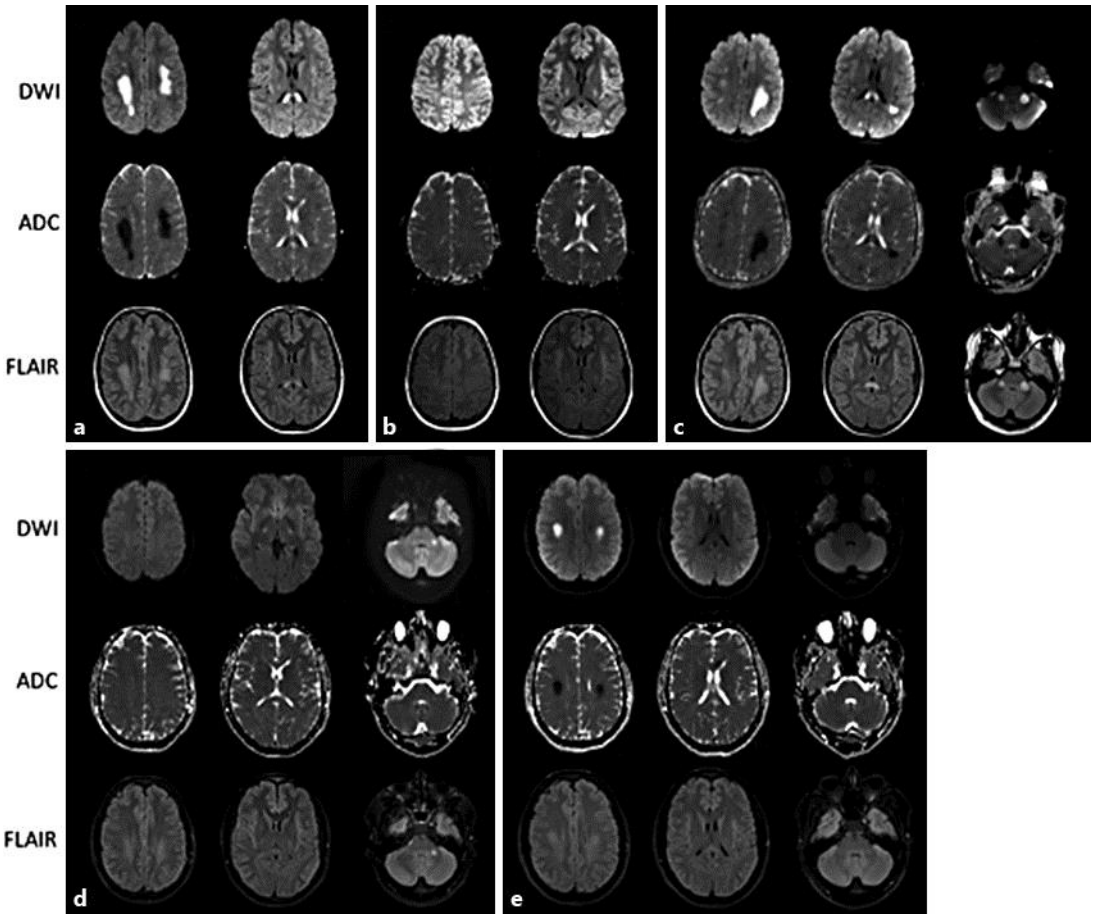

Fig. 1. Progression of cerebral white matter lesions associated with CMTX1 in a single patient over 7 years. DWI = Diffusion-weighted imaging; ADC = apparent diffusion coefficient. **a** Initial presentation in September 2007 associated clinically with right-sided weakness demonstrates diffusion-weighted and FLAIR signal in the left greater than right centrum semiovale and the splenium of the corpus callosum. **b** Follow-up imaging in December 2007 with near-complete resolution of the DWI and FLAIR hyperintensities. **c** Second exacerbation of stroke-like symptoms in July 2008 associated with left-sided weakness and large hyperintensities in the bilateral centrum semiovale, corticospinal tracts, splenium of the corpus callosum, and the right cerebellar peduncle on DWI and FLAIR sequences. **d** Follow-up imaging in December 2011 demonstrates resolution of lesions in the right cerebellar peduncle, bilateral centrum semiovale, and splenium of corpus callosum, with a residual small area of FLAIR hyperintensity in the left cerebellar peduncle. **e** Presentation in November 2014 with dysarthria, left-sided weakness, and dysesthesia demonstrating restricted diffusion and FLAIR hyperintensity in the right greater than left corona radiata and left genu of the corpus callosum. The previously visualized signal in the left cerebellar peduncle has resolved.