

Case report,

Stroke-Like Episodes in Charcot-Marie-Tooth X1 (CMTX1) Disease

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Abstract:

Background: Charcot-Marie-Tooth disease (CMT) is a heterogeneous group of disorders best known for causing inherited forms of peripheral neuropathy. History of CMT disease is not considered relevant in patients presenting with acute central neurologic manifestations of acute stroke. The case described here should alert clinicians to the possibility of transient stroke-like episodes in young patients suffering from CMTX1, X-linked variant of CMT.

Case description: A 21-year-old man presented to our emergency department with acute onset dysarthria, right facial weakness and right hemiparesis, which started 2 hours before his admission. He was treated with intravenous thrombolysis with a suspected diagnosis of acute ischemic stroke with full resolution of symptoms. The following day he experienced another stroke-like episode of acute onset of dysarthria and left facial weakness that resolved within 3 hours. The patient underwent stroke in the young work-up which was normal. MRI of the brain showed symmetric, non-enhancing areas of restricted diffusion in the corona radiata bilaterally and corpus callosum, also demonstrated on T2/fluid-attenuated inversion recovery (FLAIR) sequences. Clinical and familial investigations resulted in diagnosing CMTX1, X-linked variant of CMT.

Discussion: This case illustrates that CMTX1 disease can have central nervous system (CNS) manifestations that could mimic stroke-like neurological deficits with pathological MRI findings. The prognosis of the CNS phenotype of CMTX1 is usually good, with spontaneous resolution without permanent deficits. Promptly identifying the disease is vital to avoid unnecessary investigation and potentially harmful therapeutic intervention.

Interoduction:

Charcot-Marie-Tooth (CMT) disease is 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, there are musculoskeletal changes such as 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 disease. This is the second most common form of CMT, accounting for 10-15% of cases. It 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 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 experienced recurrent episodes of transient central nervous system (CNS) dysfunction associated with white matter abnormalities on magnetic resonance imaging (MRI) of the brain.

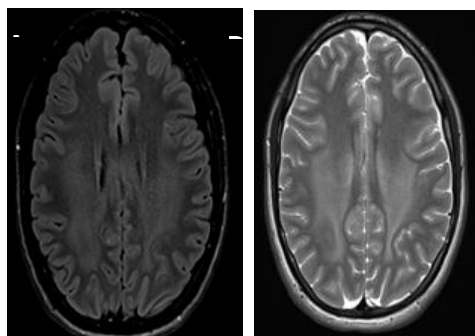


Figure1. MRI of the brain demonstrating symmetric large confluent FLAIR (A) and T2-weighted images (B) hyperintensities in the white matter. FLAIR= fluid-attenuated inversion recovery.

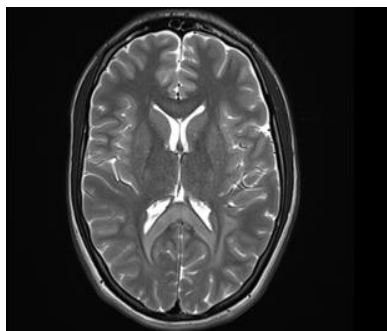


Figure2. T2-weighted images of MRI of the brain demonstrated hyperintense signal in the splenium of the corpus callosum.

Case presentation:

A 21-year-old man, with a history of progressive motor-sensory neuropathy supported by electromyography (EMG) manifesting as bilateral foot drop and progressive gait disorder in the past 6 years, presented to our emergency department with acute onset dysarthria, right facial weakness and right hemiparesis, which started 2 hours before his admission. On his physical exam he had dysarthria, right facial weakness, right hemiparesis and bilateral high arch feet. Computerized tomography (CT) of the head was normal. No hemorrhage, ischemic changes or space occupying lesions were seen. CT angiography (CTA) of the head did not detect large vessel occlusion (LVO).

He was treated with intravenous thrombolysis (IV tPA) with a diagnosis of acute ischemic stroke. He had full resolution of his symptoms within 1.5 hours. The following day he experienced another episode of acute onset of dysarthria and left facial weakness that resolved within 3 hours. 3 days prior to his admission he had fever, fatigue, cough and rhinorrhea. During his admission he was diagnosed with influenza type B virus.

He had no known cardio-vascular risk factors. His BMI was 19. During his admission heart rate was monitored and he underwent metabolic and coagulation profiles examinations. Toxic screen was negative. Test results showed that he did not have occult vascular risk factors, hypercoagulability or autoimmune disease. Trans-thoracic echocardiography ruled out cardio-embolic source for embolism. Doppler and contrast injection of agitated saline negated patent foramen ovale (PFO) or septal defects. Fabry disease was negated. His family history was positive for a grandfather with CMT. His mother was not diagnosed with CMT but shared the same foot structure with hammer-toes and high arches feet. His nerve conduction studies demonstrated symmetric axonal- demyelinating sensory-motor polyneuropathy. MRI of the brain demonstrated symmetric bilateral abnormalities in T2/ fluid-attenuated inversion recovery (FLAIR) and restricted diffusion, without enhancement after Gadolinium injection. FLAIR and T2-weighted sequences showed symmetric, bilateral, hyperintense areas in the cerebral white matter (figure 1A, B) and in the splenium of the corpus callosum (figure 2). Diffusion-weighted imaging (DWI) showed hyperintensity with reduced apparent diffusion coefficient (ADC) in the same distribution (figures 3, 4).

The patient was discharged in his baseline condition without any remnants of his stroke-like symptoms. 12 months after his admission he had no progression of symptoms and did not experience additional acute episodes. Follow-up MRI of the brain was normal.

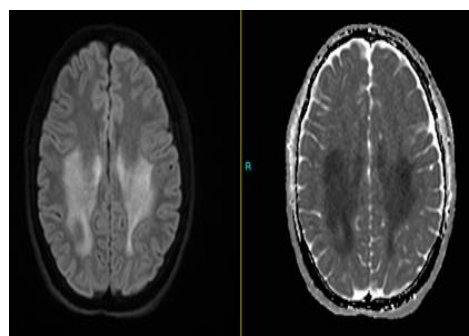


Figure 3. DWI sequence showing bilateral symmetrical confluent cerebral deep white matter hyperintensity (A) with reduced ADC (B), demonstrating a restricted diffusion of water molecules in the corresponding areas. DWI = Diffusion-weighted imaging; ADC = apparent diffusion coefficient.

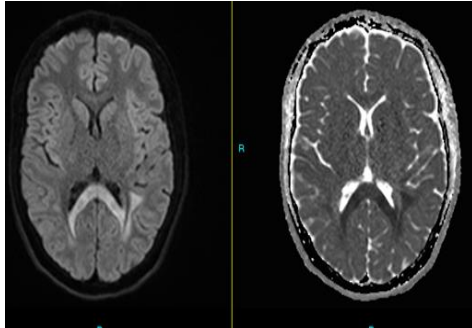


Figure 4. DWI sequence showing hyperintensity in the splenium of the corpus callosum (A) with reduced ADC (B), demonstrating restricted water diffusion. DWI = Diffusion-weighted imaging; ADC = apparent diffusion coefficient.

Discussion and conclusions:

CMTX1 is caused by mutations in the Gap-Junction Beta-1 gene (GJB1), encoding connexin-32, expressed in Schwann-cells and oligodendrocytes (7,8). The typical clinical manifestation is of slowly progressive motor sensory neuropathy. Nerve conduction studies in CMTX1 show variable results, but typically, there is mild to intermediate slowing of motor

conduction velocities. Compound muscle action potentials are almost always reduced in amplitude, indicating axonal loss. Definitive diagnosis is done by genetic testing for GJB1. There are few case reports and small series on central neurological deficits in patients with this CMT subtype. Overt CNS manifestations tend to be episodic and of acute to subacute onset, frequently described as stroke-like as in our case. In the acute phase, characteristic abnormalities are seen on MRI shows an increased T2/FLAIR-weighted signal, sometimes associated with restricted diffusion but without contrast enhancement. The most frequently involved areas include the posterior centrum semiovale, splenium of the corpus callosum, and the middle cerebellar peduncles (8). These stroke-like episodes in CMTX1 patients were usually triggered by febrile illness, altitude changes, vaccination or strenuous exercise. In the case presented the trigger was Influenza type B infection. Cases such as the patient reported here should alert clinicians of the possibility of CMTX1 disease in the differential diagnosis of stroke-like acute onset neurological deficits, especially in young males with a personal or family history of peripheral neuropathy. The prognosis of the CNS manifestations of CMTX1 is usually good, with spontaneous resolution and no permanent deficit; therefore, prompt identification of these episodes is vital to avoid unnecessary investigations and potentially harmful therapeutic intervention.

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