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CENTRALLY INVOLVED X-LINKED CHARCOT-MARIE-TOOTH DISEASE PRESENTING AS A STROKE-MIMIC

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X-linked Charcot-Marie-Tooth disease type 1 (CMTX1) is the second most common hereditary motor sensory neuropathy (HMSN) representing an estimated 10%–15% of occurrences. CMTX1 arises from mutations in the gap-junction beta-1 gene (*GJB1*) on chromosome Xq13.1, which encodes the gap-junction protein connexin-32.[1] Rather unique to CMTX1, among other forms of HMSN, is CNS involvement in a minority of patients with CMTX1.

We discuss the case of a 28-year-old man who presented with abrupt-onset severe dysarthria initially interpreted as being symptoms of stroke. In subsequent workup, his presentation was found to be due to previously undiagnosed CMTX1.

Case. A 28-year-old man presented to a community hospital after experiencing the acute onset of profound dysarthria. He was emergently evaluated by a stroke neurologist via our academic center's telemedicine stroke service and was found to have an NIH stroke score of 2 points for dysarthria with no other apparent focal deficits. A noncontrasted head CT was normal. Although the presentation was within the time window for acute therapies, thrombolytics were not given because of mild symptoms and the absence of further localizing examination features.

The patient was transported to our medical center and his dysarthria resolved over the course of several hours. His examination was notable for pes cavus, mild weakness of ankle dorsi- and plantar-flexion, and absent lower extremity deep-tendon reflexes. Family history was notable for high arches and ankle instability in his mother. MRI obtained at arrival showed symmetric diffusion restriction in the splenium of the corpus callosum and posterior subcortical white matter (figure). Electrodiagnostic studies demonstrated markedly slowed peripheral motor nerve conduction velocities (peroneal = 26.0 m/s and ulnar = 35.1 m/s), reduced motor amplitudes (peroneal = 0.6 mV and ulnar = 5 mV), and absent distal sensory potentials (ulnar and sural) consistent with HMSN.

Further history revealed that the patient had been admitted for 2 previous episodes of transient neurologic dysfunction at ages 10 and 14 years. Records from those admissions showed that on both presentations, MRI had shown similar findings. In each case, acute demyelinating encephalomyelitis had been suspected resulting in treatment with high-dose corticosteroids. Repeat MRI at 6-month follow-up in each case had shown complete resolution of the lesions.

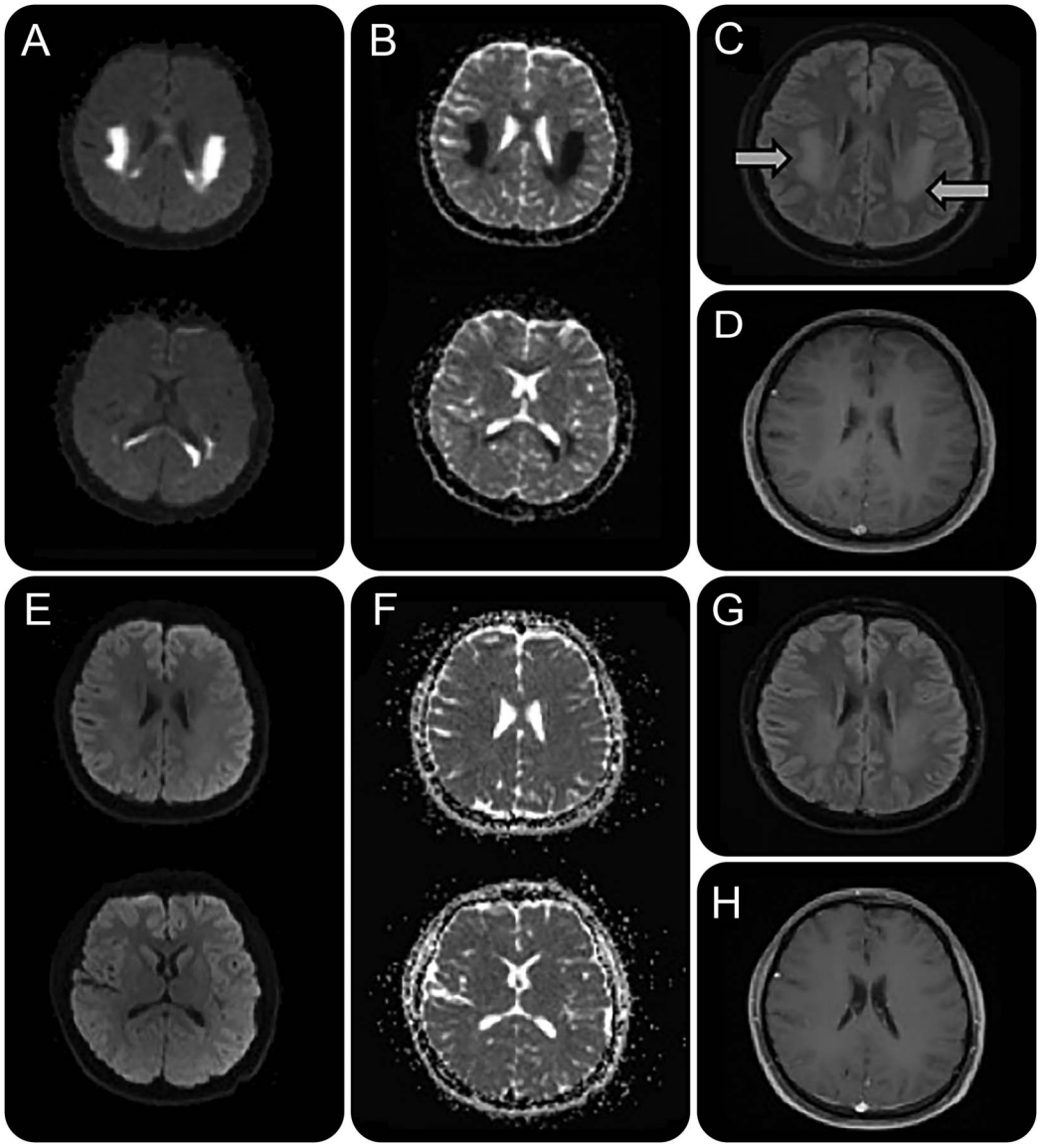
Genetic testing of the patient confirmed a known pathogenic *GJB1* mutation (c.G271A, p.V91M). At 6-month follow-up, he had experienced no further symptoms, and repeat MRI showed near-complete resolution of the previously observed white-matter abnormalities (figure).

Discussion. CNS involvement of CMTX1 can cause transient neurologic dysfunction in men and more rarely in women carriers.[2–4] This is likely related to the presence of connexin-32 in oligodendrocytes as well as Schwann cells. Abnormal connexin-32 disrupts transport of ions through gap junctions, causing instability of the affected myelin and leading to central and peripheral nervous system manifestations of CMTX1.[2]

The p.V91M mutation in our patient had previously been associated only with peripheral neuropathy.[5,6] This patient's phenotype is notable for 2 reasons. In adolescence, the white-matter lesions were misdiagnosed and treated as encephalomyelitis, whereas the sudden onset in adulthood suggested a vascular etiology. Evaluated via telemedicine, the patient would have been a candidate for thrombolytic therapy had it not been for the relative contraindication of an NIH stroke scale of 2. This highlights that the CNS involvement in CMTX1, although rare, should be considered in the differential for acute stroke in young patients. Family history is important, and may aid in diagnosis, as it did in this case. Presentations can be clinically heterogeneous, with symptoms lasting hours to weeks and including relatively rapid onset of hemiparesis, sensory loss, dysarthria, aphasia, and even complete paralysis.

Despite clinical heterogeneity, imaging findings appear to be stereotyped with diffusion restriction in the posterior subcortical white matter (most often bilateral) and splenium of the corpus callosum on

Figure MRI



Brain MRI obtained at presentation (A–D) showed hyperintensity on diffusion tensor sequences (A) and corresponding hypointensity on apparent diffusion coefficient sequences (B) in the posterior cortical white matter and splenium of the corpus callosum. Fluid-attenuated inversion recovery (FLAIR) sequence demonstrated corresponding T2 hyperintensity (arrows in box C), whereas postgadolinium T1 sequence showed no associated contrast enhancement (D). Brain MRI obtained at 6-month follow-up (E–H) showed near-complete resolution of the leukoencephalopathy (diffusion tensor [E], apparent diffusion coefficient [F], FLAIR [G], and T1 postgadolinium [H] sequences are shown). There was persistence of only very mild FLAIR signal abnormality (G).

MRI.[2–4] It is interesting to note that in addition to predisposing factors of infection and physical exertion, change to high-altitude locations has been associated with development of white-matter lesions in CMTX1.[3] MRI lesions in the splenium and posterior white matter are shared in patients with CMTX1 and individuals with high-altitude cerebral edema. Common to both is apparent diffusion coefficient hypointensity of the lesions indicating cytotoxic edema.[7] Although MRI findings aid in diagnosis, CT imaging may be completely normal (as in this case). If expedited MRI is obtained, recognition of the stereotyped MRI patterns described above is of clinical utility. Fortunately, the profound leukoencephalopathy on MRI is reversible. This case illustrates that CMTX1 is an important diagnosis to include when considering nonvascular causes of acute stroke-like presentations in young patients.

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