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 noncontrast CT was normal. Although the presentation was within the time window for acute therapies, thrombolitics 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 CMTX1.5

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
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. 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. 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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Author contributions: Patrick Nicholson: concept and design and preparation of manuscript. Stefan M. Pulst: concept and design and critical revision of manuscript for intellectual content.

Study funding: No targeted funding reported.
Disclosure: Dr. Nicholson reports no disclosures. Dr. Pulst serves on the editorial boards of the Journal of Cerebellum, NeuroMolecular Medicine, CONTINUUM, Experimental Neurology, Neurogenetics, Nature Clinical Practice Neurology, and Current Genomics; holds patents for Nucleic acids encoding ataxin-2 binding proteins; Nucleic acid encoding Schwannomin-binding proteins and products related thereto, Transgenic mouse expressing a polynucleotide encoding a human ataxin-2 polypeptide, Methods of detecting spinocerebellar ataxia-2 nucleic acids, Nucleic acid encoding spinocerebellar ataxia-2 and products related thereto, Schwannomin-binding proteins, and Compositions and methods for spinocerebellar ataxia; receives publishing royalties from Churchill Livingston, AAN Press, Academic Press, and Oxford University Press; receives license fee payments from Cedars-Sinai Medical Center; has served on the speakers’ bureau of Athena Diagnostics, Inc.; has received research support from NIH and the National Ataxia Foundation; is a paid consultant for Ataxion Therapeutics and Takeda Pharmaceuticals; and provided expert testimony for Hall & Evans, LLC. Go to Neurology.org/ng for full disclosure forms. The Article Processing Charge was paid by the authors.

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Received August 3, 2016. Accepted in final form December 12, 2016.

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Centrally involved X-linked Charcot-Marie-Tooth disease presenting as a stroke-mimic

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*Neurol Genet* 2017;3;
DOI 10.1212/NXG.0000000000000128

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