Case Report

Episodic neurological dysfunction in hereditary peripheral neuropathy

Girish Baburao Kulkarni, Pooja Mailankody, Pawanraj Palu Isnwara, Chandrajit Prasad[1], Veerendrakumar Mustare

Department of Neurology, [1]Neuroradiology, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Abstract

Episodic transient neurological symptoms are an important set of problems presenting to a neurologist in his routine practice. Occasionally, detailed clinical history including past and family history supplemented with focused examination can bring out a rare cause for such symptoms. We describe in this report in a young male presenting with episodic focal neurological dysfunction, with family history of similar episodes in mother and brother. Examination showed features of pes cavus and peripheral neuropathy for which patient was asymptomatic. Mother and brother were established cases of hereditary neuropathy. Imaging on multiple occasions showed reversible white matter abnormalities. Clinical suspicion of X-linked Charcot-Marie-Tooth disease type 1 (CMT1X) was confirmed with detection of mutation in Gap Junction B1 (GJB1) gene, which codes for connexin 32 protein (c.425G>A; p.R142Q hemizygous mutation). Though this mutation has been already reported in CMTX patients, it has not been associated with transient neurological dysfunctions. This is probably the first reported case of CMTX patient with transient neurological dysfunction from India, whose family members had similar episodes.

Key Words

Charcot-Marie tooth disease, connexin-32, magnetic resonance imaging, neurologic manifestations

For correspondence:

Dr. Girish Baburao Kulkarni, Department of Neurology, National Institute of Mental Health and Neurosciences, Hosur Road, Bangalore - 560 029, Karnataka, India. E-mail: gbk5000@rediffmail.com

Ann Indian Acad Neurol 2015;18:111-114

Introduction

Among the hereditary motor sensory neuropathies, X-linked Charcot Marie Tooth Disease type 1 (CMTX) is the second most common disease. It is associated with mutations in Gap Junction B1 (GJB1) gene, which codes for connexin 32 protein present both in central and peripheral nervous systems.[1,2] Patients will have slowly progressive distal lower and upper limb weakness with foot deformities with minimal sensory findings and absent ankle jerks. Rarely, CMTX can also present with transient neurological deficits with signal changes in magnetic resonance imaging (MRI) of the brain.[3,4] In this communication, we describe a patient who was referred to us with the long-standing recurrent focal weakness with white matter changes in MRI, who was found to have CMTX disease.

Access this article online

Quick Response Code:

Website: www.annalsofian.org

DOI: 10.4103/0972-2327.144314

Case Report

A 19-year-old student was admitted with recurrent episodes of right hemiparesis and dysarthria from his age of 8 years. In 2002, he had right-sided hemiparesis with slurring of speech without aphasia developing over few minutes lasting for 10 hours. A computerized tomographic (CT) scan of brain was done, which was normal; electroencephalograph did not show any epileptiform discharges. He was treated with sodium valproate as a case of seizure with Todd's paralysis for next few years and he was asymptomatic. In 2010, he had transient mild distal weakness of the right upper limb while traveling in a bus, which lasted for 20 minutes. The following day he had right upper and lower limb weakness with slurring of speech lasting for 30 minutes. He was evaluated with a magnetic resonance imaging (MRI), which showed T2 hyperintense diffusion-restricting lesions in the splenium of the corpus callosum and internal capsule [Figure 1a-d]. Demyelinating disease was suspected, and he was given oral steroids for 45 days. He improved completely in few days. In July 2013, he had 5 episodes of right hemiparesis without aphasia over 4 days, each lasting 20-30 minutes. Along with weakness, he also had numbness of right side of face, which lasted for about 20 minutes. Again, he was treated with steroids for one month and improved completely. In August 2013, he had

2 more episodes of right hemiparesis and right hemi facial sensory loss lasting 30 minutes. Imaging with MRI July showed bilateral periventricular and centrum semiovale diffusion restricting lesions [Figure 1e-h]. He was referred to us with diagnosis of demyelinating disease for further management and consideration for immunomodulation.

Family history was significant in that maternal grandfather, mother, elder brother, and male cousins from the maternal side had a history of distal limb weakness and wasting. Mother and brother had been seen 15 and 5 years earlier by different treating teams at our hospital and diagnosis of CMT was made. In addition, the mother had a history of long-standing complex partial seizures, bipolar affective disorder, episodic weakness of limbs, and transient vision abnormalities, and the brother had two episodes of right hemiparesis lasting for few days with normal CT scan of the brain.

Examination revealed bilateral pescavus and hammer toes; no thickened nerves were seen. Motor examination revealed mild distal small muscle wasting in feet and hand, with mild toe grip weakness. Touch and joint position and pain sensation were normal but vibration sense was impaired in lower and upper limbs. Reflexes were sluggish in upper limbs and absent in lower limbs. Plantars were flexor bilaterally with inability to perform heel walking. Cardiac examination was normal and there were no bruits.

His routine hematological, biochemical, cardiac, immunological, thyroid, vitamin B12, homocysteine, electroencephalogram, and intra- and extracranial magnetic resonance angiography (MRA) were normal. Nerve conduction studies revealed sensory motor axonal and demyelinating neuropathy. All sensory nerve action potentials (SNAPs) were absent in both limbs, with motor nerve conduction velocities being 34-39 m/s with mild prolonged distal latencies. Visual-evoked potential showed prolonged P100 latency in both eyes as well as somatosensory-evoked potentials. Brainstem-evoked auditory responses were normal bilaterally. Auditory evaluation did not show any deafness. Serial imaging with MRI of the brain revealed T2 hyperintense signal changes in posterior limb of bilateral internal capsule (left > right) and splenium of corpus callosum in 2010; these were diffusion-restricting [Figure 1a-d]. In July 2013, MRI July revealed T2 hyperintense, T1 isointense diffusion-restricting lesions in bilateral centrum semi ovale and internal capsule [Figure 1e-h]. Repeat MRI in August 2013 in our hospital showed disappearance of the centrum semi ovale lesions [Figure 1i-l]. Nerve conduction studies of both his mother

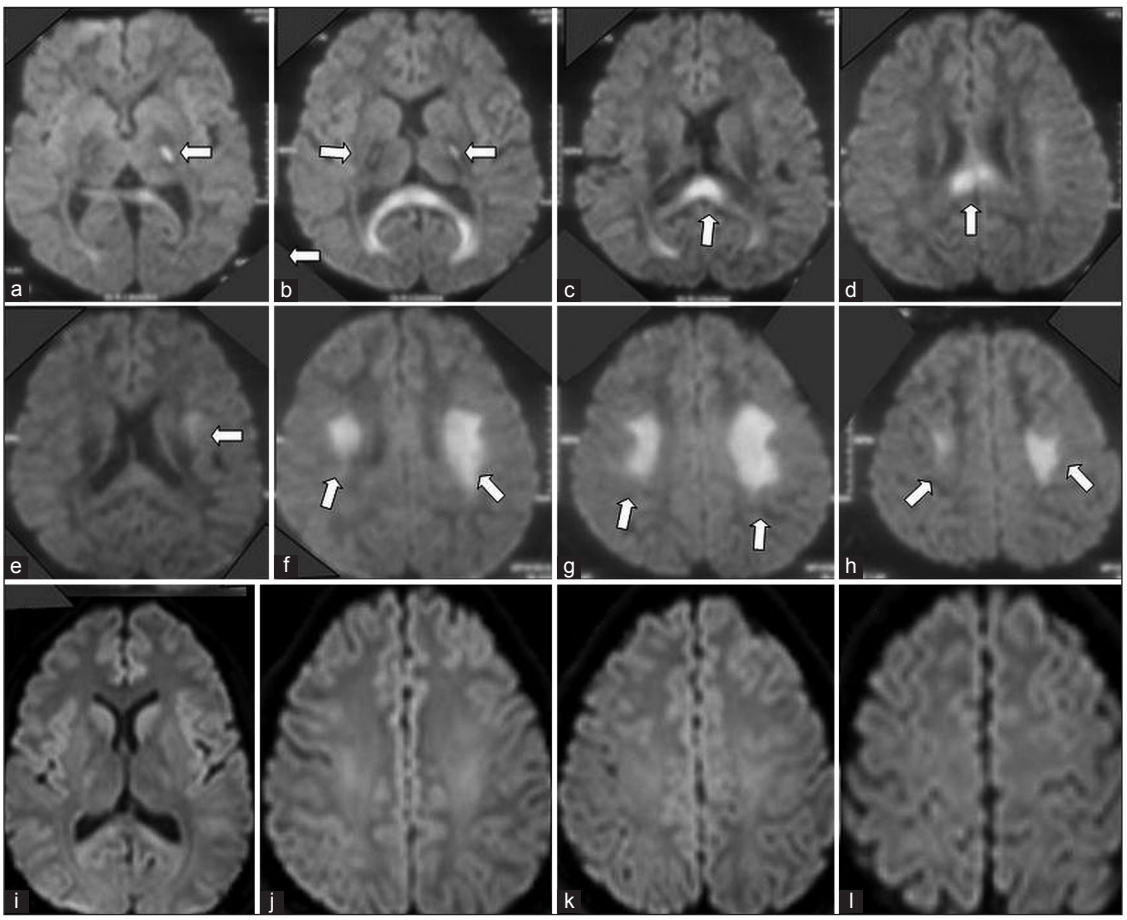

Figure 1: Magnetic resonance imaging of the brain: Diffusion-weighted sequences during 2010 episode (a-d) showing restricting lesions in left posterior limb of internal capsule and splenium of the corpus callosum. Lesions involving bilateral subcortical white matter and centrum semi ovale (e-h) during July 2013 episode. Resolution of the changes (i-l) in the repeat imaging done after 1.5 months. Arrows showing abnormalities

and brother were consistent with sensory motor axonal and demyelinating neuropathy. In 2013, MRI of the mother revealed diffusion-restricting lesions in the posterior limb of bilateral internal capsule (images not shown). Patient did not consent for a lumbar puncture.

The GJB 1 (CX32) gene at Xq13.1 was sequenced to investigate for the presence of mutation in the coding region and promoter 2 region. Molecular genetic testing was positive for c.425G>A; p.R142Q mutation (hemizygous) in GJB1 gene. The C.425 G>A mutation is a point mutation in coding region causing amino acid substitution from Arginine to glycine in 142nd position. The patient was asymptomatic at the time of discharge for his episodic symptoms. He was treated conservatively without steroids and was given the information regarding his diagnosis and about the transient episodes associated with his disease.

Discussion

Our patient presented with episodic transient focal motor symptoms over eleven years with resolving subcortical, splenial, and internal capsule white matter lesions. He and other family members had features of CMTX (with transient events in mother and brother) confirmed by genetic testing.

X-linked Charcot-Marie-Tooth disease presents with distal muscle involvement in form of weakness and sensory disturbances, hyporeflexia, and foot deformities. Motor nerve conduction velocities are reduced (males > females). There are reports of various transient neurological dysfunctions in the form of hemiparesis, paraparesis, monoparesis, ataxia, and dysarthria lasting for few minutes to hours to days occasionally persistent deficits.[3-16] Almost all patients had childhood onset of symptoms, though few studies have reported adult onset of symptoms.[5,13] Attacks are provoked by stressors in the form of travel to high altitudes or infection but can also be spontaneous. MRI shows signal changes in corpus callosum, frontoparietal white matter, and rarely middle cerebellar peduncle, with sparing of subcortical U fibers. The lesions could persist for few months in the absence of symptoms. Around 240 different *GJB1* mutations have been described. The mutation c.425G>A; p.R142Q mutation (hemizygous) has been previously described.[17] In addition, there is report of this mutation in CMTX with associated deafness in one of the patient.[18] However, there are no reports of transient neurological symptoms described with this mutation in the literature. As per our search, there are no genetically proven CMTX with transient neurological symptoms reported from India.

Connexin 32 protein is a gap junction protein found in Schwann cells in peripheral nerves (PN) and oligodendrocytes in the central nervous system. The gap junctions in PN form an easier way for the diffusion of small molecule sand ions between the covering myelin sheath layers. In the central nervous system, gap junctions help in coupling of oligodendrocytes and astrocytes. The Connexin 32 mutations lead to peripheral and central myelination defects and dysfunctions in gap junctions leading to loss of fluid regulation and diffusion restriction and transient neurological deficits.[13-16]

Compared to other patients reported in the literature, our patient was not a known case of CMTX when presented with transient neurological symptoms and had no predisposing factors (stress, infection, etc.). His mother and brother had features of CMTX with episodic transient neurological deficits. His mother also had psychiatric symptoms and long-standing seizures. This also may be a window of opportunity for further search in to the pathogenesis of weakness, white matter changes, and genetic defect in this disease.

References

1. Bergoffen J, Scherer SS, Wang S, Scott MO, Bone LJ, Paul DL, *et al*. Connexin mutations in X-linked Charcot–Marie–Tooth disease. Science 1993;262:2039-42.
2. Ionasescu V, Ionasescu R, Searby C. Correlation between connexin 32 gene mutations and clinical phenotype in X-linked dominant Charcot–Marie–Tooth neuropathy. Am J Med Genet 1996;63:486-91.
3. Panas M, Karadimas C, Avramopoulos D, Vassilopoulos D. Central nervous system involvement in four patients with Charcot-Marie-Tooth disease with connexin 32 extracellular mutations. J Neurol Neurosurg Psychiatry 1998;65:947-8.
4. Panas M, Kalfakis N, Karadimas C, Vassilopoulos D. Episodes of generalized weakness in two sibs with the C164T mutation of the connexin32 gene. Neurology 2001;57:1906-8.
5. Paulson HL, Garbern JY, Hoban TF, Krajewski KM, Lewis RA, Fischbeck KH, *et al*. Transient central nervous system white matter abnormality in X-linked Charcot-Marie-Tooth disease. Ann Neurol 2002;52:429-34.
6. Schelhaas HJ, Van Engelen BG, Gabreëls-Festen AA, Hageman G, Vliegen JH, Van Der Knaap MS, *et al*. Transient cerebral white matter lesions in a patient with connexin 32 missense mutation. Neurology 2002;59:2007-8.
7. Lee MJ, Nelson I, Houlden H, Sweeney MG, Hilton-Jones D, Blake J, *et al*. Six novel connexin32 (GJB1) mutations in X-linked Charcot-Marie-Tooth disease. J Neurol Neurosurg Psychiatry 2002;73:304-6.
8. Hanemann CO, Bergmann C, Senderek J, Zerres K, Sperfeld AD. Transient, recurrent, white matter lesions in X-linked Charcot-Marie-Tooth disease with novel connexin 32 mutation. Arch Neurol 2003;60:605-9.
9. Taylor RA, Simon EM, Marks HG, Scherer SS. The CNS phenotype of X-linked Charcot-Marie-Tooth disease: More than a peripheral problem. Neurology 2003;61:1475-8.
10. Siskind C, Feely SM, Bernes S, Shy ME, Garbern JY. Persistent CNS dysfunction in a boy with CMT1X. J Neurol Sci 2009;279:109-13.
11. Anand G, Maheshwari N, Roberts D, Padeniya A, Hamilton-Ayers M, van der Knaap M, *et al*. X-linked hereditary motor sensory neuropathy (type 1) presenting with a stroke-like episode. Dev Med Child Neurol 2010;52:677-9.
12. Basu A, Horvath R, Esisi B, Birchall D, Chinnery PF. Recurrent stroke-like episodes in X-linked Charcot-Marie-Tooth disease. Neurology 2011;77:1205-6.
13. Balice-Gordon RJ, Bone LJ, Scherer SS. Functional gap junctions in the Schwann cell myelin sheath. J Cell Biol 1998;142:1095-104.
14. Nagy JI, Rash JE. Connexins and gap junctions of astrocytes and oligodendrocytes in the CNS. Brain Res Brain Res Rev 2000;32:29-44.
15. Rash JE, Yasumura T, Dudek FE, Nagy JI. Cell-specific expression of connexins and evidence of restricted gap junctional coupling between glial cells and between neurons. J Neurosci 2001;21:1983-2000.
16. Sargiannidou I, Vavlitou N, Aristodemou S, Hadjisavvas A, Kyriacou K, Scherer SS, *et al*. Connexin32 mutations cause loss of function in Schwann cells and oligodendrocytes leading to PNS and CNS myelination defects. J Neurosci 2009;29:4736-49.

17. Available from: http://molgen-www.uia.ac.be/CMTMutations/DataSource/MutByGene.cfm) [Last accessed on 2014 August 01].
18. Stojkovic T, Latour P, Vandenberghe A, Hurtevent JF, Vermersch P. Sensorineural deafness in X-linked Charcot-Marie-Tooth disease with connexin 32 mutation (R142Q). Neurology 1999;52:1010-4.

How to cite this article: Kulkarni GB, Mailankody P, Isnwara PP, Prasad C, Mustare V. Episodic neurological dysfunction in hereditary peripheral neuropathy. Ann Indian Acad Neurol 2015;18:111-4.
Received: 18-08-14, **Revised:** 05-09-14, **Accepted:** 07-09-14

Source of Support: Nil, **Conflict of Interest:** None declared.