CME

The CNS phenotype of X-linked Charcot-Marie-Tooth disease

More than a peripheral problem

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X-linked Charcot-Marie-Tooth disease (CMTX) is the second most common form of inherited demyelinating neuropathy, next to CMT type 1A, which is caused by duplication of the *PMP22* gene.[1] CMTX is caused by mutations in *GJB1*, the gene encoding connexin32 (Cx32), which belongs to a highly conserved family of proteins that form gap junctions in vertebrates. Myelinating Schwann cells express Cx32, which likely forms gap junctions between the layers of the myelin sheath, thereby providing a shorter pathway for the diffusion of small molecules and ions directly across the myelin sheath.[2] Oligodendrocytes also express Cx32, which participates in the gap junction coupling of oligodendrocytes and astrocytes.[3]

More than 240 different *GJB1* mutations have been described (http://molgen-www.uia.ac.be/CMTMutations/DataSource/MutByGene.cfm). Most patients with CMTX, including those with a deletion of the *GJB1* gene, have a similar degree of neuropathy, indicating that most mutations probably cause a loss of function.[1] In agreement, many Cx32 mutants do not form functional gap junctions,[4] often related to their aberrant trafficking to the cell membrane.[5] In addition to their peripheral neuropathy, many patients have asymptomatic evidence of brain involvement, such as abnormal brainstem auditory evoked responses (BAER).[6,7] Patients have also been found to have abnormal brain MRI results in association with transient CNS symptoms.[8-11] Here, we report a patient who had two episodes resembling acute demyelinating encephalomyelitis (ADEM), the first episode preceding the diagnosis of CMTX.

Case report. A 12-year-old boy presented in January 1999 with three consecutive episodes of transient neurologic dysfunction, over the course of 3 days, with complete recovery between each episode. Initially, he had numbness of the right face and arm, paresis of the right arm and face, and dysarthria, lasting 4 hours. The following day, he developed the same symptoms, and mild right leg weakness, lasting 10 hours. On day 3, he developed a complete motor aphasia, right arm weakness, dysphagia, and loss of gag reflex, lasting 4 hours. MRI (on day 3) showed abnormally increased T2 signal and reduced diffusion in the posterior portion of the centrum semiovale bilaterally (figure 1, A and B), as well as in the splenium of the corpus callosum (figure 1, C and D). These lesions spared the subcortical U fibers and did not enhance (not shown). Three-dimensional time-of-flight MR angiography of the intracranial vessels, electroencephalography, and CSF were normal, including a normal lactate level (1.1 mmol/L) and no oligoclonal bands. Laboratory tests, including complete blood count, electrolytes, renal function, coagulation parameters, urinalysis, and urine toxicology screen, were negative. A Lyme antibody titer was normal. Varicella zoster and Epstein-Barr antibody titers were consistent with prior infections. Very long chain fatty acid levels were normal. A diagnosis of probable ADEM was made and he was treated with high-dose IV corticosteroids for 3 days.

A subsequent outpatient evaluation revealed high-arched feet, hyporeflexia at the ankles, and minimal weakness in ankle dorsiflexion. There was a family history of CMT—in his mother, two maternal uncles, a maternal aunt and her son, the maternal grandmother, and the maternal great-grandmother. None of these family members reported similar transient neurologic episodes. The patient's mother had normal results on brain MRI; the other affected family members did not have brain MRI performed. Sequencing *GJB1* (performed by Athena Diagnostics, Worchester, MA) from the patient revealed a C to T mutation at nucleotide position 285, predicted to result in an amino acid change from arginine to tryptophan at codon 75 (R75W). Other family members were presumed to have the same mutation.

In November 2002, at age 15, he presented again

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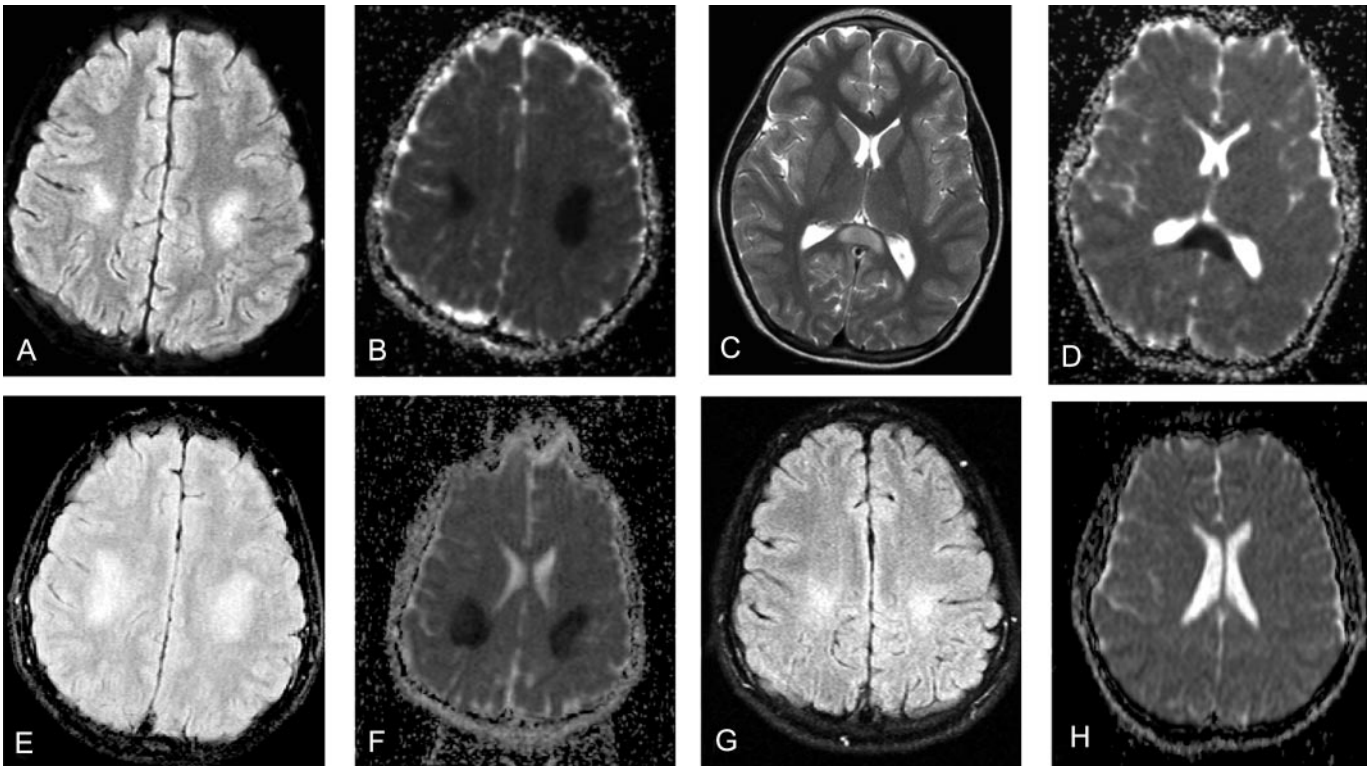

Figure 1. Episode 1: Axial fat-suppressed fluid attenuated inversion recovery (FLAIR) (A) (repetition time/echo time/inversion time 9,000/119/2,200 msec) through the centrum semiovale shows the bilaterally symmetric regions of abnormal T2 hyperintensity. Calculated apparent diffusion coefficient map (ADC) (4,000/100) (B) demonstrates the reduced diffusion as hypointensity in the same regions. Axial fat-suppressed FLAIR (C) shows the abnormal hyperintensity in the splenium with corresponding reduction in diffusion shown on ADC (D). Episode 2: Axial fat-suppressed FLAIR (E) shows the recurrent T2 signal abnormality in similar regions to episode 1. ADC (F) reveals reduction in diffusion in the affected areas. Eleven-week follow-up: Axial fat-suppressed FLAIR (G) shows mild residual T2 signal abnormality with resolution of the lesions on ADC (H).

with 2 days of mild right arm weakness and worsening handwriting. After wrestling with his brother on the second day, he developed a severe hemiparesis of the left face and arm, dysarthria, and dysphagia, lasting about 8 hours, which then resolved completely over several hours. MR performed 2 days later again showed symmetric abnormally increased T2 signal and diffusion reduction in the posterior frontal and parietal white matter bilaterally, in approximately the same distribution as the MR 4 years earlier (figure 1, E and F), again with no abnormal enhancement. Routine laboratory studies and CSF were normal, and oligoclonal bands were absent. He was not treated with corticosteroids and had recovered completely without any specific therapy. Repeat brain MRI performed 11 weeks later showed a return to normal diffusion and improvement in the abnormal T2 signal with some mild areas of persistently increased T2 signal in the white matter (figure 1, G and H).

Discussion. This patient initially presented with an unusual ADEM-like attack, was subsequently found to have CMTX, and then presented again with another ADEM-like attack. ADEM-like attacks have been described in individuals with other *GJB1* mutations, including T55I, E102deleted, R142W, and R164W, C168Y.[8-11] These patients had various combinations of dysarthria; dysphagia; expressive aphasia; mono-, para-, hemi-, and quadriparesis; disorientation; ataxia; incoordination; and cranial neuropathies. Episodes began suddenly or progressed over days, typically lasting hours to days, sometimes fluctuating or recurring multiple times during a period of several weeks. Patients seem to recover completely without any specific therapy. Individual attacks seem to be provoked by travel to high altitudes, respiratory distress, or fever/infection, but can be unprovoked. The CSF is normal, suggestive that inflammation is not a primary etiology. Therefore, high dose corticosteroids may not be beneficial. The diagnosis of CMTX should be considered in a patient who has a family history of CMT and an unusual ADEM-like illness, especially with white matter findings on MRI.

MRI obtained acutely shows increased T2-weighted signal, sometimes associated with reduction in diffusion but no abnormal enhancement, predominantly in the posterior centrum semiovale, splenium of the corpus callosum, and sometimes the middle cerebellar peduncles.[8-11] The MRI lesions are largely confluent in the deep white matter and spare

Table *Summary of CNS mutants, their phenotypes, and the localization of the mutant protein (if known) in transfected cells*

Mutation	Phenotype	Localization[5,18]
W24C	EPR[12]	ND
M34V	EPR*	Golgi & GJP
A39V	EPR[26]	ER
T55I	Abnormal MRI[8]	ER
D66N	EPR†	ND
R75W	Abnormal MRI	Golgi
M93V	EPR[27]	Golgi & GJP
E102 deleted	Abnormal MRI[11]	ND
E109 stop	Abnormal MRI[12]	ND
R142W	Abnormal MRI[9]	Golgi
R164Q	Abnormal MRI[13]	Golgi
R164W	Abnormal MRI[10]	Golgi
C168Y	Abnormal MRI[9]	ND
R183H	Abnormal MRI[14]	Golgi & GJP
T191 frameshift	EPR[12]	ND

* Dr. Steven Scherer, unpublished.
† Dr. Richard Sater, personal communication.

EPR = extensor plantar responses; ER = endoplasmic reticulum; ND = not determined; GJP = gap junction plaques.

the subcortical U fibers. These abnormalities have been reported to persist for months, even after the patient is asymptomatic, and may or may not resolve completely.[9,11] Abnormal MRI have also been reported in patients with CMTX who were not reported to have had an ADEM-like illness. One patient with an E109stop mutation had increased T2-weighted signal in the midbrain and small foci of increased T2-weighted signal in the cerebral white matter.[12] One patient with the R164Q mutation was reported to have demyelination in the white matter on the left side in the frontoparietal area,[13] whereas one patient with the R183H mutation was just reported to have central demyelination.[14]

Other *GJB1* mutations have been associated with clinical findings suggestive of CNS involvement. Extensor plantar responses have been found in patients with W24C, M34V, A39V, D66N, M93V, and T191frameshift (table), although a congenital spastic paraparesis may be the cause in the patient with the W24C mutation. MRI findings were not reported in these cases, so it is possible that extensor responses are not associated with MRI findings. Extensor plantar responses may be underappreciated, because the weakness of the extensor muscles would likely disguise them.

Many *GJB1* mutations are associated with subclinical evidence of CNS involvement. Patients with one of 14 different mutations have central slowing of BAER.[6,7] Subclinical central conduction slowing has also been shown by visual evoked potentials and central motor evoked potentials; one of these patients had normal results on brain MRI, whereas the others were not reported to have had an MRI.[15,16] Another patient with CMTX had hypoperfusion of the cerebellum shown on SPECT (iodine-123-N-isopropyl-p-iodoamphetamine), but reportedly had normal results on brain MRI.[17] Thus, subclinical involvement is common, but is not necessarily associated with abnormal MRI findings.

The disruption of gap junction communication between oligodendrocytes and astrocytes may be the cellular mechanism by which *GJB1* mutations cause a "CNS phenotype." Certain Cx32 mutants may have dominant-negative effects on other connexins expressed in oligodendrocytes—Cx29 and Cx47[18-20]—thereby decreasing their expression. Astrocytes express different connexins than do oligodendrocytes, so that Cx32 and/or Cx47 would likely interact with Cx26, Cx30, and/or Cx43 on the astrocytic cell membrane.[21] Interestingly, dominant mutations of *GJA1/Cx43* are also associated with abnormal white matter signal on MRI.[22] The physiologic consequences of disrupting the gap junction–mediated coupling between oligodendrocytes and astrocytes likely lead to an inability of these cells to regulate fluid exchange. This could explain the restricted dif-

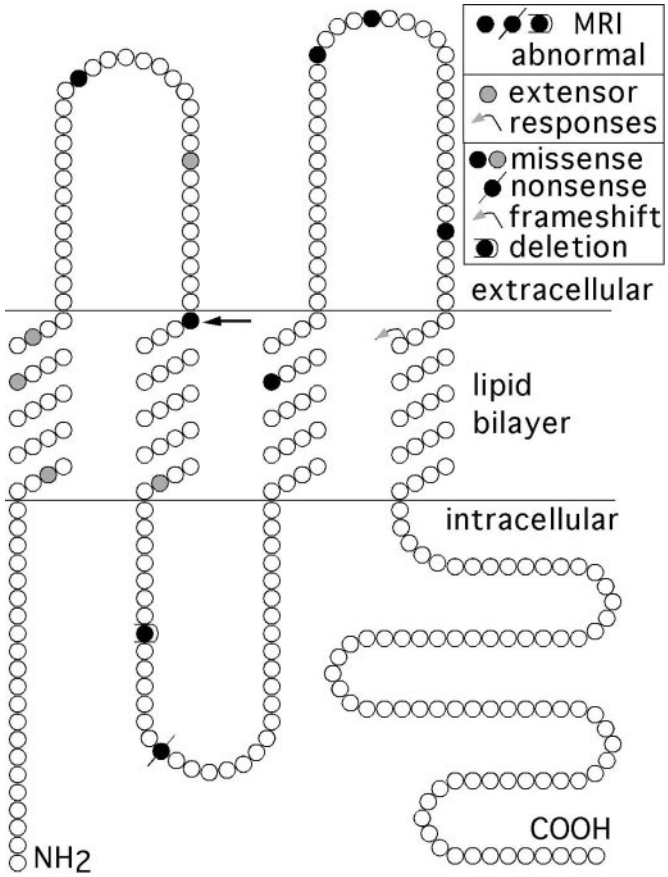

Figure 2. CMTX mutations and their associated CNS phenotypes. This is a schematic drawing of connexin32. It illustrates the positions of the CNS mutants, the nature of the mutants (missense, nonsense, frameshift, deletion), and their associated findings. The arrow marks the R75W mutation.

fusion seen on MRI of patients with CMTX in the acute phase of their ADEM-like illnesses. The resulting pathology may resemble that of Cx32/Cx47 double deficient mice, which includes features of demyelination (thin or absent myelin sheaths and axonal loss); apoptotic oligodendrocyte cell death, a finding occasionally seen in inherited dysmyelinating disorders; and vacuolation of nerve fibers, a rare finding among dysmyelinating diseases.[23,24] Regionally specific pathology is seen on MRI of patients with CMTX with ADEM-like illnesses and the Cx32/Cx47 double deficient mice for reasons yet to be determined, but may lie in the expression pattern of the different connexin proteins.[24]

The R75W mutation in the patient reported here affects an amino acid residue that is invariant among all known connexins. Mutations of the corresponding arginine in Cx26 (http://www.crg.es/deafness/) and Cx43[25] also cause dominant phenotypes. How such dominant phenotypes arise remains to be determined, but the R75W, R75Q, and R75P Cx32 mutants are all retained in the Golgi,[5,18] indicating that they do not form functional gap junctions in oligodendrocytes. Similarly, some of the Cx32 mutants associated with ADEM-like presentations (T55I, R142W, R164W), abnormal MRI (R164Q, R183H), or extensor plantar responses (M34V, A39V, M93V) also exhibit abnormal trafficking (see the table). Not all Cx32 mutants traffic abnormally, however, and the relationship of these mutations to the clinical and subclinical phenotypes will be interesting to determine. Mutants that traffic normally, which includes many carboxy-terminus mutants, have yet to be reported to cause CNS involvement.[5] The available evidence indicates a tantalizing correlation between the expression of a CNS phenotype and the trafficking of the mutant protein (figure 2). To date, none of the mutants that are associated with a CNS phenotype, including slowing of central conduction, traffic like wild type Cx32.

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