abstract

X-linked Charcot-Marie-Tooth disease (CMTX1) is a clinically heterogeneous hereditary motor and sensory neuropathy with X-linked transmission. Common clinical manifestations of CMTX1 disease, as in other forms of Charcot-Marie-Tooth (CMT) disease, are distal muscle wasting and weakness, hyporeflexia, distal sensory disturbance, and foot deformities. Mutations in the connexin-32 gene (gap junction protein β1 [GJB1]) are responsible for CMTX1 disease. In this report, we describe a patient with CMTX1 disease presenting with recurrent attacks of transient and episodic acute demyelinating encephalomyelitis (ADEM)-like symptoms without previous signs of lower extremity weakness or foot deformities; the patient, as well as his asymptomatic mother, exhibited a novel GJB1 mutation (p.Met1Ile). Differential diagnosis of recurrent and transient ADEM-like illness, if unexplained, should include the possibility of CMTX1 disease. Pediatrics 2014;134:e270–e273

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KEY WORDS
Charcot-Marie-Tooth disease, connexin 32, encephalomyelitis, acute disseminated, peripheral nervous system diseases

ABBREVIATIONS
ADEM—acute demyelinating encephalomyelitis
CMT—Charcot-Marie-Tooth (disease)
CMTX—X-linked Charcot-Marie-Tooth (disease)
CNS—central nervous system
EMG—electromyelogram
GJB1—Gap junction protein β1
NCS—nerve conduction study/studies

Dr Eun conceptualized this report and revised the manuscript; Dr G.-H. Kim reviewed the references and drafted the initial manuscript; Dr Ki performed genetic diagnosis, guided us through the interpretation of genetic analysis, and revised the manuscript critically; Dr K.M. Kim conceptualized the report, collected the figures, and critically reviewed the manuscript; Dr Suh commented on the imaging studies, revised the figures, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Charcot-Marie-Tooth (CMT) disease is a clinically and genetically heterogeneous hereditary motor and sensory neuropathy characterized by distal muscle wasting and weakness, sensory disturbance, hyporeflexia, and pes cavus foot deformity. It is a common disorder with a population frequency of ~1:2500. CMT1A is the most common CMT disease type, accounting for 40% to 50% of all cases, and is caused by the overexpression of the peripheral myelin protein 22 gene (PMP22). X-linked Charcot-Marie-Tooth (CMTX) disease (CMTX1) is the second most common type of CMT disease (7% to 12% of all patients) and is associated with mutations in the gap junction protein β1 gene (GJB1), which encodes connexin-32. In this report, we describe the case of a patient presenting with recurrent attacks of transient and episodic acute demyelinating encephalomyelitis (ADEM)—like illness without apparent signs of lower extremity weakness or foot deformities, in whom we identified a novel GJB1 mutation.

**PATIENT PRESENTATION**

In November 2007, a 14-year-old boy presented with right-side motor weakness and aphasia. MRI (3.0T, Magnetom Skyra; Siemens, Erlangen, Germany) revealed abnormally increased T2 signal and diffusion restriction in the splenium of the corpus callosum and centrum semiovale (Fig 1A, B, C, and D). These lesions spared the subcortical U fibers, which showed no signal enhancement. Brain magnetic resonance angiography, EEG, and cerebrospinal fluid examination revealed normal findings, including a normal lactate level (1.2 mmol/L) and absence of oligoclonal bands. Laboratory tests, including a complete blood count, electrolytes, renal function test, urinalysis, and coagulation parameters, were negative. Enterovirus, herpes virus, varicella-zoster virus, and Japanese encephalitis virus were not detected in the cerebrospinal fluid samples tested by polymerase chain reaction. Arylsulfatase A and very long chain fatty acid levels were normal. The patient had neither past illness nor a family history of any inheritable neurologic illnesses. Symptoms were completely absent on day 2 without any treatment. Follow-up MRI performed after 1 month showed marked improvement of the abnormal T2 signal hyperintensity in the corpus callosum and centrum semiovale (not shown). However, 4 years later, the patient returned after the onset of a second attack of episodic right-side hemiparesis and dysarthria. During episodes, deep tendon reflexes were normal. Brain MRI revealed approximately the same distribution of hyperintense foci as those found during the first attack (Fig 1E and F). We searched the literature to look for...
any possible differential diagnosis mainly based on MRI findings and performed electrophysiological testing and genetic analysis after finding similar case reports of CMTX disease. An electromyogram (EMG) was normal, and a nerve conduction study (NCS) of the legs revealed slightly delayed conduction velocities, but was assumed to be not conclusive (Table 1). Hemiparesis and dysarthria were shown, but completely disappeared within a few hours. These episodes occurred, sometimes 2 or 3 times in a single day. Although the radiologic findings were somewhat incompatible, we suspected a demyelinating illness such as ADEM, and the patient was treated with immunoglobulin (0.4 g/kg per day for 5 days) and intravenous methylprednisolone (30 mg/kg per day for 3 days). The patient’s symptoms suddenly disappeared on day 4. However, 2 months later, a third attack presented with episodic left-side hemiparesis lasting a few hours. Between events, deep tendon reflexes were slightly diminished at the ankles, but no obvious weakness was observed in the lower extremities. Brain MRI revealed findings similar to the previous attacks (Fig 1 G and H). EMG and NCS were repeated on both arms and legs, and EMG and NCS revealed sensorimotor polyneuropathy of the demyelinating type and decreased motor and sensory nerve conduction velocities (Table 1) with normal muscle unit potentials. We treated the patient with intravenous methylprednisolone for 3 days and then tapered to oral steroid (1 mg/kg per day, taken every other day). Brain MRI performed 1 month later revealed a return to normal diffusion; no regions showing abnormal T2 signal intensity were observed. EMG and NCS were followed up 1 month later and showed no significant changes (Table 1). When the results for genetic analysis were available, sequencing of the GJB1 gene revealed a novel G to T transversion at nucleotide position 3(c.3G>T), which has been predicted to result in an amino acid change from methionine to isoleucine at codon 1 (p.Met1Ile). The patient’s mother was also confirmed as having the same GJB1 mutation and similar results were shown on her NCS and EMG (Table 1). We performed polymerase chain reaction and restriction fragment length polymorphism analysis for the proband, the maternal grandparents, both parents, and the maternal aunt and found that the proband, the maternal grandfather, mother, and maternal aunt have the same GJB1 mutation (Fig 2). However, it is unclear whether his grandfather has a neuropathy because his limping gait may have been due to a history of car accident and there was no opportunity to confirm the mutation by using NCS. Unfortunately, we failed to obtain the patient’s uncle’s blood sample because he resided outside the country, but he did not report any symptoms by the time of this writing.

**DISCUSSION**

Our patient did not complain of any difficulty in walking except during acute episodes, exhibited no foot deformity, and had no family history of CMT disease. His initial presentation with episodic hemiparesis led us to diagnose his condition as ADEM-like illness during his first attack. While searching the literature for any possible differential diagnosis mainly based on MRI findings, we subsequently noticed peripheral neuropathy after repeating electrophysiological testing during the third attack. Genetic testing later confirmed the GJB1 mutation.

To date, >400 mutations in GJB1 have been reported to cause CMTX1 disease (the Inherited Peripheral Neuropathies Mutation Database is available at http://www.molgen.ua.ac.be/CMTMutations/Mutations/MutByGene.cfm). We identified

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TABLE 1 Electrophysiological Findings

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—, not tested.
a novel mutation with a G to T change at nucleotide 3, resulting in the substitution of methionine to isoleucine (p.Met1Ile). Because this is the start codon, we suspect that one of the following can result from this change:

- complete deletion of the protein because GJB1 mutations are loss-of-function mutations in almost all patients3 (some exceptions exist4);
- an extension by activating an upstream translation initiation, which is possible for connexin-32 because 10 bases upstream of the initiation codon there is another ATG sequence;
- an N-terminal deletion by activating downstream translation initiation, which is unlikely for connexin-32 because there is no other methionine until p.34 (first transmembrane [TM] domain).

In our case, peripheral polyneuropathy was mild. A similar pattern (mild phenotype) was also noted in another case report with a codon 1 mutation of GJB1 (p.Met1Arg).5 Because most GJB1 mutations are loss-of-function mutations as mentioned previously, this mild phenotype might be a typical manifestation at an early stage of CMTX1 disease and we should follow a patient’s progress. The second result, an extension by activating an upstream translation initiation, could be another explanation for mild phenotype, which needs to be elucidated in future research.

There are several reported cases of CMTX1 disease with transient central nervous system (CNS) involvement. The attacks were provoked by illness, exposure to high altitudes,6 and hyperventilation7 but can be unprovoked as in our case. Most of these showed signs of peripheral polyneuropathy such as weakness, muscle wasting in the legs, or pes cavus.5–10 However, a case of CMTX disease who manifested transient CNS symptoms without any signs of peripheral neuropathy was reported,11 as in our patient. Five months after the transient CNS symptoms, he finally developed signs and symptoms of neuropathy in the form of absent ankle reflexes. The case also suggests that transient CNS symptoms in CMTX1 disease can occur without axonal degeneration in the peripheral nerves, masquerading as ADEM-like illness. In addition, the pathogenesis of CNS symptoms does not seem to involve axonal degeneration because the changes in brain MRI were reversible over a short time period. Many researchers now think that a decreasing number of functioning gap junctions between oligodendrocytes and astrocytes in situations of metabolic stress may affect the CNS phenotype, making both cell types vulnerable to impairment of intercellular exchange of ions and small molecules.12 This possibility could explain the restricted diffusion noted on MRI of patients with CMTX1 disease during their ADEM-like illness. However, there are still no clear mechanisms linking the impairment of intercellular transport of molecules to the diminished integrity of myelin and the axon.

CONCLUSIONS

We describe a novel GJB1 mutation in a patient with CMTX1 disease masquerading as ADEM-like illness who did not have symptoms of peripheral polyneuropathy or a known family history. This finding is particularly important for pediatricians who are not familiar with CMTX1 disease with a CNS phenotype. Differential diagnosis of recurrent and transient ADEM-like illness, if unexplained, should include X-linked peripheral polyneuropathy (CMTX1).

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REFERENCES

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