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Clinical Observations

Possible Effect of Corticoids on Hemiplegic Attacks in Severe Hemiplegic Migraine

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ABSTRACT

BACKGROUND: Sporadic and familial hemiplegic migraines are rare paroxysmal disorders characterized by transient hemiparesis and headache. The distinction is based on whether other family members are affected. In 50% of cases, these migraines are caused by CACNA1 A missense mutations. **PATIENTS:** We describe a boy with a particularly severe phenotype and a *de novo* R1349Q mutation of the CACNA1 A gene. **RESULTS:** The patient suffered from early-onset profound mental retardation, epileptic seizures, cerebellar ataxia, and progressive cerebellar atrophy. He experienced prolonged attacks of migraine with hemiparesis, seizures, altered consciousness, and fever resulting from minor head traumas. A prolonged hemiplegic attack improved following a 5-day treatment of 100 mg/d methylprednisolone. **CONCLUSION:** R1349Q mutation of the CACN1 A gene may be associated with a severe phenotype. Corticoids might be beneficial in prolonged hemiplegic attacks.

Introduction

Sporadic hemiplegic migraine (SHM) and familial hemiplegic migraine (FHM) are rare subtypes of migraine with aura. The distinction is based on whether at least one first- or second-degree relative is also affected. According to the International Headache Society, the aura is characterized by motor weakness. At least visual, sensory, and/or aphasic (dysphasic) aura is required along with motor aura for the diagnosis of FHM and SHM.[1] Attacks of FHM and SHM can be triggered by minor head trauma[2] and may be associated with loss of consciousness, fever, and epileptic seizures.[3] Permanent cerebellar signs, such as nystagmus and ataxia, occur in about 20% of FHM families.[4] In some cases, magnetic resonance imaging (MRI) reveals cerebellar atrophy.[5]

FHM is an autosomal-dominant inherited disorder and genetically heterogeneous. Mutations have been reported in three genes: CACNA1 A (19p13 - FHM1),[3] coding for the α_{1A} subunit of a calcium channel[2]; ATP1A2 (1q23 - FHM2), coding for the Na^+/K^+-ATPase subunit; and SCN1 A (2q24 - FHM3),[6] coding for the pore-forming subunit of neuronal $Na_v1.1$.channels. At least 30 mutations have been reported in a total of 100 to 200 families with FHM and in sporadic cases.[7-9] Sporadic cases of hemiplegic migraine can be caused by a *de novo* mutation in a gene that causes the familial form or by inheritance of a gene mutation from an asymptomatic parent with FHM. In still others, the disease is neither linked to CACNA1 A nor to the locus on chromosome.[1] The three main genes causing FHM seem to have minor roles in pure SHM because no SCN1 A mutation has been found and only few CACNA1 A and ATP1A2 mutations have been reported in patients with the sporadic form.[9]

We report a boy with recurrent, severe, and prolonged attacks of hemiplegic migraine. In addition, he had an early-onset profound mental retardation, epilepsy, and ataxia with cerebellar atrophy. Genetic investigations led to the identification of a novel *de novo* missense mutation in the CACNA1 A gene.

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Case Report

The patient, age 17 years, had a normal birth. He had an early-onset profound mental retardation: at age 8 months he gazed for very short periods, he was not able to sit until 2.5 years of age, and yet does not walk independently. Held at the shoulders, he had a slow, ataxic, and wide-based gait. He was able to drive his wheelchair on flat ground by himself. His speech consisted of slow, dysarthric four- to five-word sentences. He used about 100 recognizable words and understood many more. He made slow progress. On examination, he had limb and trunk hypotonia and a slightly increased resistance on flexion of the ankle. Physical examination was also notable for dysarthria, tremor, dysmetria, dyspraxia, ataxia, positive Babinski response, and ocular apraxia. Nystagmus was present in infancy and early childhood but was not noticed at age 8 years and later. Optokinetic nystagmus was reduced.

He experienced several focal seizures beginning at 8 months of age. At age 2 years, he had a grand mal attack provoked by a head trauma. He had frequent febrile seizures as well.

At age 8 years, after a minor head trauma, he experienced an attack of vomiting, fever, altered consciousness, partial tonic-clonic seizures, and right-sided hemiplegia. He remained stuporous for 8 hours and hemiplegic for 7 days and then gradually recovered over 2 weeks without sequelae. The motor deficit began to improve as fever remitted. Some episodes of head trauma without subsequent hemiplegia attacks were reported. The second attack, at age 13, consisted of a left hemiplegia with fever, headache, focal seizures, impairment of consciousness, and vomiting provoked by a mild head trauma. The third hemiplegic attack, at age 14, was associated with headache, lasted for several hours and was not provoked by a head trauma. The fourth attack, at age 15, consisted of transient hemiplegia, vomiting, impairment of consciousness, and a grand-mal seizure. In addition, he had headaches at irregular intervals with neither vomiting nor neurological deficits.

Blood and cerebrospinal fluid examinations excluded a metabolic disease or infectious encephalopathy. Echocardiography showed no evidence for patent foramen ovale. Several interictal electroencephalograms showed a normal background activity without epileptic discharges. An electroencephalogram after the right-sided attack recorded diffuse slowing over the left hemisphere. Brain MRI at age 8 months revealed no abnormalities. A second brain MRI at age 8 years showed a cerebellar atrophy, which was unchanged on follow-up at age 13 (Figs 1 and 2).

A phenobarbital therapy was instituted at age 2. Carbamazepine was added and then changed to sulthiame, which seemed to be more effective. At age 12 sulthiame was replaced by topiramate, which is licensed to prevent migraine attacks as well. After the third hemiplegic attack, low-dose aspirin was added to topiramate. Acetazolamide and verapamil were not effective in the acute management of the hemiplegic attack. During the fourth attack, the patient had not improved after 8 days. Hemiplegia and consciousness improved following the administration of 100 mg/d methylprednisolone, which was given during 5 days. Epileptic seizures were interrupted with lorazepam or clonazepam. The patient wore a helmet to try to minimize head trauma.

The proband's father experienced cluster headache beginning in the second decade of life. The paternal grandfather and aunt reported similar symptoms as the father. Four paternal relatives had migraine with vomiting. The proband's mother and maternal grandmother had a pattern of migraine with aura. There were no other cases of hemiplegic migraine among the proband's relatives.

DNA from the proband and his parents was extracted from peripheral blood using standard procedures. A R1349Q missense mutation in the CACNA1 A gene was identified. This mutation was absent in his parents.

Discussion

We describe a rare *de novo* R1349Q missense mutation in the CACNA1 A calcium channel subunit gene in a patient with severe mental retardation, progressive cerebellar atrophy and attacks of hemiplegia, and impairment of consciousness triggered by minor head trauma.

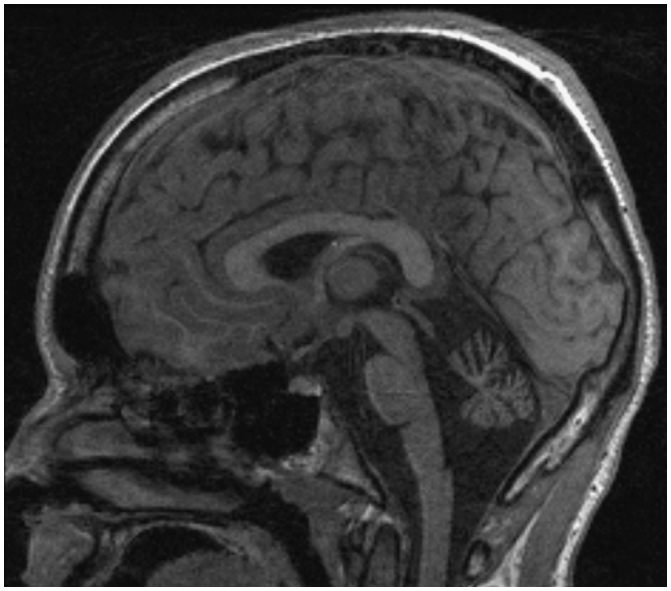

FIGURE 1.
T1 sagittal cranial magnetic resonance image at age 8 showing marked cerebellar atrophy.

The phenotype of this patient is particularly severe. The hemiplegic migraine attacks lasted up to 2 weeks and consisted of impairment of consciousness, vomiting, hemiplegia, fever, and seizures. In addition, he showed permanent neurological signs: early-onset profound mental retardation, epileptic seizures independent from FHM attacks, and cerebellar signs.

In general, most published sporadic and de novo cases with CACNA1 A and ATP1A2 mutations are associated with

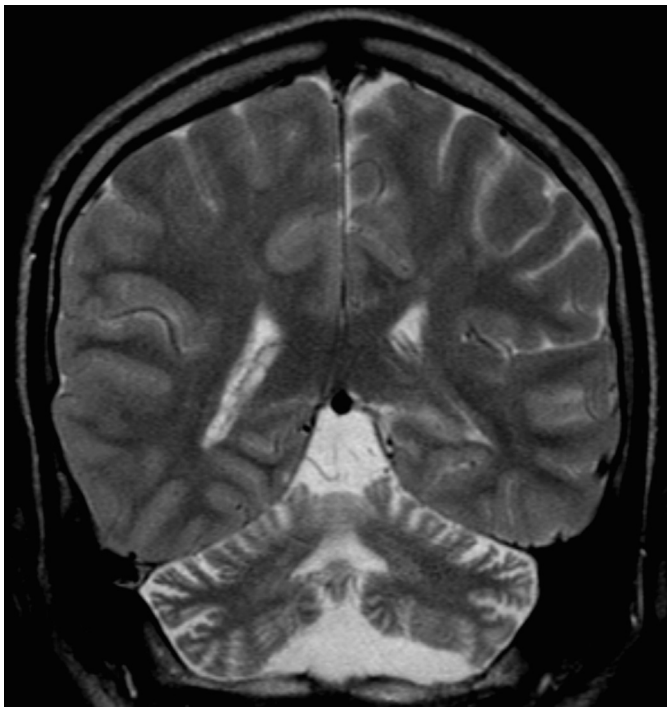

FIGURE 2.
T2 coronal cranial magnetic resonance image at age 8 showing marked cerebellar atrophy.

neurological manifestations.[9,10] Permanent cerebellar signs affect about 50% of cases with CACNA1 A mutations.[3] Seizures occurring independently from hemiplegic migraine attacks have been described in more than 60 familial and sporadic cases with mutations in CACNA1 A; ATP1A2 and SCN1 A.[9] Various degrees of mental retardation have been reported in at least 16 patients, including 15 de novo sporadic cases.

This mutation has already been described in a 6-year-old girl with prolonged attacks after minor head trauma associated with seizures, hemiparesis, fever, and altered consciousness. An MRI at age 2 detected a mild cerebellar atrophy, but no data are given about a possible presence of mental retardation or epilepsy.[11]

Management of FHM and SHM is empiric and relies primarily on the principles of the common types of migraine. Sulthiame, topiramate, and aspirin were given to prevent migraine attacks. Their efficiency cannot be demonstrated because the mean attack frequency in SHM and FHM varies from one attack per day to four or five attacks within a lifetime.[12] Sulthiame and topiramate were given to prevent seizures as well. Fever and seizures were treated symptomatically. Acetazolamide and verapamil have been postulated in the acute management of the hemiplegic attack,[12] but were not effective in our case.

The fourth attack responded well to 100 mg/d methylprednisolone, which has been reported to be useful in some cases of status migrainosus lasting longer than 72 hours.[13] The pathogenesis of migraine headaches is not well understood. In the mouse model carrying mutations in the CACNA1 A gene, mutant mice exhibit increased propensity for cortical spreading depression, a propagating wave of neuroglial depolarization implicated in migraine aura. This cortical spreading depression can be suppressed with steroids in the mouse model.[14] Reversible cerebral edema has been described in attacks of hemiplegic migraine in children.[15] Corticosteroids theoretically mitigate cortical spreading depression and edema and decrease the pain und duration of an acute attack. Iuzuka et al.[16] reported a dramatic improvement with corticoids 60 mg/d of a hemiplegic attack in a 35-year-old woman suffering from of sporadic hemiplegic migraine. But they had no effect in another case reported by Kumar et al.,[17] who gave no data on the dose.

FHM should not only be suspected in individuals with typical episodic headache and hemiparesis. Screening for a CACNA1 A mutation should also be performed in children with transient hemiparesis attacks who cannot express their headache verbally because of mental retardation, especially if they associate permanent neurological signs as ataxia. Early genetic diagnosis can avoid invasive procedures and institute preventive measures to avoid minor head trauma. More studies on the effectiveness of corticoids are needed.

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