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Clinical Notes

Acute Striatal Necrosis in Hemiplegic Migraine With *de Novo CACNA1A* Mutation

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We report the case of a 9-year-old girl with early-onset developmental delay, chronic ataxia and prolonged hemiplegic migraine episodes bringing about progressive deterioration. Two days into one episode, diffusion-weighted magnetic resonance imaging disclosed unilateral striatal abnormal signal consistent with cytotoxic edema, which evolved into atrophy on follow-up scans. Mutational screen of *CACNA1A* gene identified a *de novo* p.Tyr1387Cys mutation.

Key words: hemiplegic migraine, striatal necrosis, CACNA1A, migraine genetics

Abbreviations: ADC apparent diffusion coefficient, DW diffusion-weighted, ESCEATHT early seizures and cerebral edema after trivial head trauma, FHM familial hemiplegic migraine, HM hemiplegic migraine, MRI magnetic resonance imaging, PCR polymerase chain reaction, SHM sporadic hemiplegic migraine

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Familial hemiplegic migraine (FHM; *International Classification of Headache Disorders*-II 1.2.4) is a rare, dominantly inherited variant of migraine with aura featuring motor weakness during the attacks. Additional paroxysmal features include epileptic seizures, dysphasia, and variable impairment of consciousness, whereas chronic neurological dysfunction occurs as a result of progressive cerebellar atrophy. FHM has been linked to mutations in any of 3 genes, *CACNA1A*, *ATP1A2*, and *SCN1A* (reviewed in Pietrobon[1]). Recently, homozygous mutations in *SLC4A4*, encoding a electrogenic Na^+-HCO_3^- cotransporter, were reported to cause hemiplegic migraine (HM) in addition to proximal renal tubular acidosis.[2] Sporadic hemiplegic migraine (SHM; *International Classification of Headache Disorders*-II 1.2.5), in turn, has been associated with *de novo* mutations in either *CACNA1A* or *ATP1A2*, the former producing the most severe phenotypes,[3] although prolonged hemiplegia may also occur with the latter.[4,5]

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In SHM, gain-of-function mutations in *CACNA1A* may produce attacks triggered by fever or mild head trauma. For one of them, p.Ser218Leu, the label "early seizures and cerebral edema after trivial head trauma (ESCEATHT)" has been used to designate an early-onset and particularly severe phenotype.[6] Similar phenotypes have been rarely reported with the p.Arg1347Glu[7] and p.Tyr1384Cys[8] *CACNA1A* mutations and at least for 1 mutation, p.Gly615Arg, in the ATP1A2 gene.[9] In these severe HM forms, magnetic resonance imaging (MRI) at the time of the attack may document cerebral cortical edema contralateral to the hemiplegia, in keeping with the presumed cortical spreading depression mechanism that is hypothesized to underlie the aura.

We describe a novel FHM neuroradiological pattern, featuring acute unilateral involvement of the striatum, in a patient with developmental delay and progressive neurological deterioration, who harbored a *de novo* p.Tyr1387Cys *CACNA1A* mutation.

CASE REPORT

The patient is the only daughter of healthy, unrelated parents. Gestation and delivery were unremarkable. The mother and maternal grandmother suffered migraineous headaches in their youth, but direct interview did not disclose any aura symptoms.

At age 3, the patient was referred for an assessment for global developmental delay and occasional episodes during which she remained lethargic and hypotonic. At that time, examination showed mild ataxia, clumsiness, and poor language skills. A brain MRI, including spectroscopy, was normal. However, a cranial computerized tomography scan at age 5, following minor head trauma with impaired consciousness, revealed cerebellar atrophy. After a viral infection at age 6, the patient became stuporous and developed acute left hemianopsia and prolonged left hemiparesis. After the episode, her cognitive and motor status had deteriorated. She showed dysarthric speech, nystagmus, central visual impairment, and global weakness with both ataxic and pyramidal signs of crural predominance. The patient could walk if aided or holding onto parallel bars.

At age 9, the patient developed fever, throbbing headache, obtundation, aphasia and right hemiparesis. Diffusion-weighted-MRI on day 2 disclosed changes suggesting cytotoxic edema in the left neostriatum and a swollen overlying cortex (Fig. 1A–C). The striatal involvement prompted a metabolic screen, including serum amino acids, lactate and biotinidase, urine organic acids, purines and pyrimidines, and cerebrospinal investigations, including lactate, all with normal results. A muscle biopsy revealed normal histochemistry and respiratory chain enzyme activities.

The patient's condition has remained unchanged and her current neurological status at age 12 continues to show mental retardation, visual deficit, ataxia, and spastic tetraparesis. Less severe attacks, with headache and brief hemiplegia, have recurred despite therapeutic trials with acetazolamide, topiramate or flunarizine. Follow-up MRI at age 11 revealed atrophy of the left caudate and putamen (Fig. 1D) and cerebellar atrophy.

Genomic DNA was isolated from peripheral blood and the 47 exons of the *CACNA1A* gene and their corresponding exon/intron junctions, including splice sites and branch points, were polymerase chain reaction-amplified and sequenced as we previously described.[10] The c.4160A>G variant (RefSeq NM_023035.2) in exon 26 of the gene, leading to a p.Tyr1387Cys amino acid substitution (RefSeq NP_075461.2), was identified in the probandus but not in her parents (Fig. 2A,B). False paternity was excluded by genotyping 16 polymorphic microsatellite markers, confirming that the mutation occurred *de novo* (Fig. 2C). The change was absent in 200 chromosomes from unrelated, healthy Spanish subjects.

DISCUSSION

This is the third instance where a devastating phenotype is described in association with the *de novo* p.Tyr1387Cys mutation. The previous cases (with mutation designated p.Tyr1385Cys or p.Tyr1384Cys) were a young woman with SHM, chronic ataxia, and mental retardation, who showed unilateral cerebral cortical edema on day 7 of an episode[8] and a 17-year-old man with cognitive and motor delay, chronic ataxia, and loss of consciousness during the migraine attacks, whose postictal neuroimaging was not reported (case 18 in Riant et al[3]). Our patient showed, in addition to subtle changes in the ipsilateral cortex,

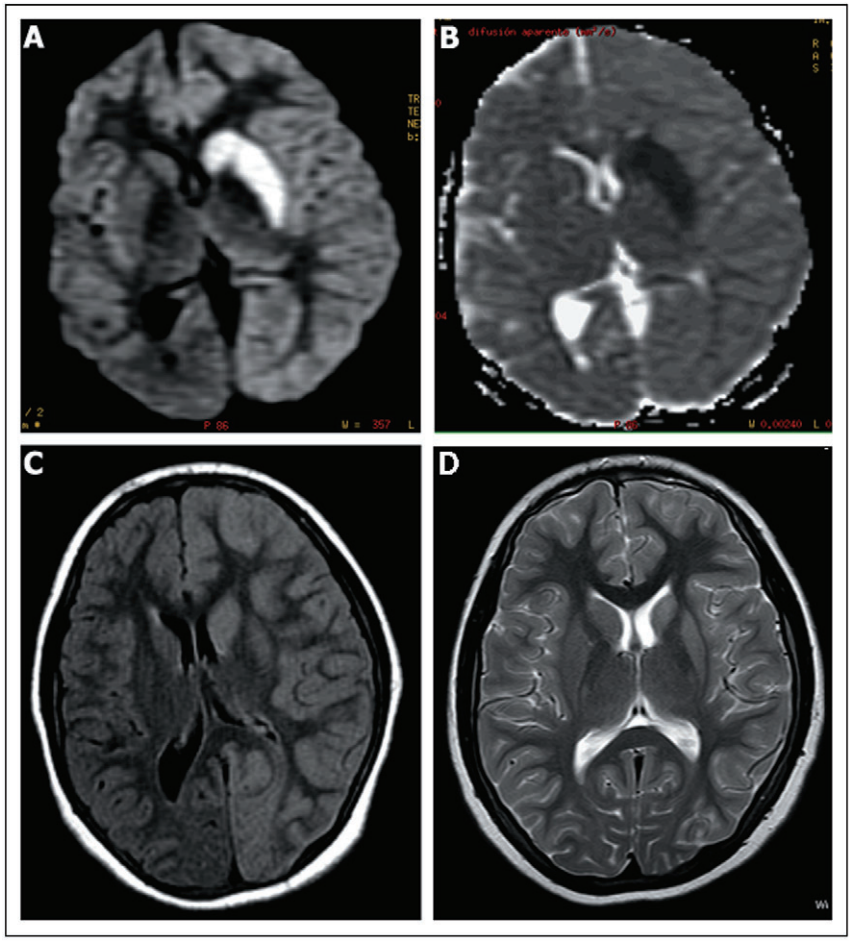

Fig 1.—Neostriatal involvement in hemiplegic migraine. On day 2 of the attack, DW-MRI showing restricted water mobility (A) and corresponding low signal on apparent diffusion coefficient (ADC) map (B) in the left striatum, plus ipsilateral gyral hyperintensity on FLAIR-T2 sequence (C). T2-weighted image 2 years later, showing left neostriatal atrophy (D).

striking unilateral striatal high signal intensity on diffusion-weighted-MRI images and a corresponding low apparent diffusion coefficient value, consistent with cytotoxic edema. That this acute event led to focal necrosis was confirmed by the ipsilateral atrophy found in the follow-up MRI. Striatal necrosis is the hallmark of various metabolic, infectious, toxic, or vascular insults, mitochondrial encephalopathies being one of the most frequent causes in childhood. Altered calcium homeostasis caused by dysfunctional $Ca_V2.1$ channels has been shown to severely affect mitochondrial function, leading to cerebellar granule cell death in the leaner mouse model.[11] Our patient's muscle, however, did not show morphological or biochemical changes to suggest mitochondrial dysfunction.

Although acute basal ganglia involvement has not been recognized in HM, a FHM neuropathological study showed neostriatal cystic and granular infarcts with differing appearances, indicating the existence of long-standing striatal lesions.[12] Recently, a further SHM case carrying the *de novo* p.Arg349Gln *CACNA1A* mutation developed the ESCEATHT phenotype after presenting with early-onset developmental delay.[13] In this 5-year-old girl, MRI at the time of the attack revealed left-sided cerebral edema, but 7 months later T2-weighted hypersignal was noted over the left striatum. It is conceivable that excitotoxicity, resulting from FHM-increased synaptic glutamate, could target the selectively vulnerable neostriatum.

Of note, psychomotor retardation preceded the onset of migraine episodes in our patient and the others with the p.Tyr1387Cys variant[3,8] and that with the p.Arg349Gln variant,[13] thus suggesting that these

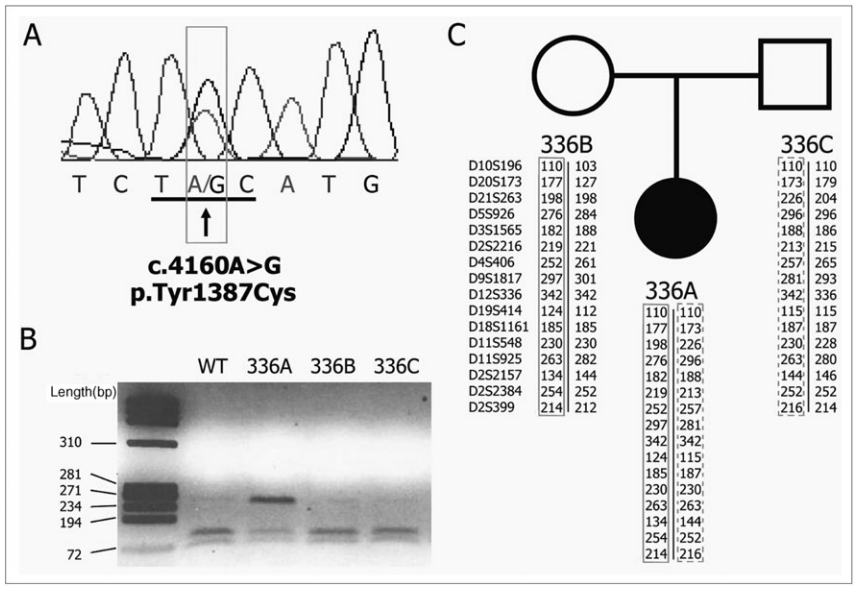

Fig 2.—Identification of the *de novo* missense mutation in the *CACNA1A* gene. (A) Sequence analysis of exon 26 in the affected sib (336A). The arrow indicates the heterozygous A-to-G transition at position 4160 of the cDNA (c.4160A>G). (B) Assessment of the presence of the mutation in all the family members by digestion with the *Acc*I restriction enzyme: the c.4160A>G mutation abolishes the restriction site in the affected sib (336A). (C) Pedigree and polymorphic microsatellite markers used to rule out false paternity: the father (336C) and the mother (336B) transmit alleles at all studied polymorphic sites (n = 16) to their daughter (336A).

de novo mutations result in dysfunctional neuronal P/Q calcium channels that may alter neurotrans mission or other critical processes during brain development. This is also reflected in the series reported by Riant et al,[3] where 3 out of 8 patients bearing *de novo CACNA1A* mutations developed severe mental retardation years before they were diagnosed with SHM.

The clinical features of our patient also raise the issue of the clinical overlap between HM and alternating hemiplegia of childhood (AHC). Although in AHC the attacks of hemiplegia are the harbinger of neurological deterioration, long-term outcome is quite similar to the one seen in our SHM patient. Indeed, intermediate FHM/AHC phenotypes were associated with another *de novo CACNA1A* mutation.[14]

CONCLUSIONS

The severe end of the HM clinical spectrum is characterized by a complex, progressive syndrome featuring developmental delay, prolonged migraine attacks, and neurological deterioration. The p.Tyr1387Cys mutation at the *CACNA1A* gene appears as a recurrent cause of this devastating phenotype. The present findings suggest that HM is a diagnostic consideration when evaluating unilateral acute striatal lesions in childhood.

REFERENCES

1. Pietrobon D. Familial hemiplegic migraine. *Neurother*. 2007;4:274-284.
2. Suzuki M, Van Paesschen W, Stalmans I, et al. Defective membrane expression of the Na^+-$HCO3^-$ cotransporter NBCe1 is associated with familial migraine. *PNAS*. 2010;107:15963-15968.
3. Riant F, Ducros A, Ploton C, et al. De novo mutations in ATP1A2 and CACNA1A are frequent in early-onset sporadic hemiplegic migraine. *Neurology*. 2010;75:967-972.
4. Jen JC, Klein A, Boltshauser E, et al. Prolonged hemiplegic episodes in children due to mutations in ATP1A2. *J Neurol Neurosurg Psychiatry*. 2007; 78:523-526.
5. De Sanctis S, Grieco GS, Breda L, et al. Prolonged sporadic hemiplegic migraine associated with a novel de novo missense ATP1A2 gene mutation. *Headache*. 2011;51:447-450.

6. Stam AH, Luijckx GJ, Poll-Thé BT, et al. Early seizures and cerebral oedema after trivial head trauma associated with the CACNA1A S218L mutation. *J Neurol Neurosurg Psychiatry*. 2009;80:1125-1129.
7. Stam AH, Vanmolkot KRJ, Kremer HPH, et al. CACNA1A R1347Q: A frequent recurrent mutation in hemiplegic migraine. *Clin Genet*. 2008;74:481-485.
8. Vahedi K, Denier C, Ducros A, et al. CACNA1A gene de novo mutation causing hemiplegic migraine, coma, and cerebellar atrophy. *Neurology*. 2000;55: 1040-1042.
9. Vanmolkot KR, Stroink H, Koenderink JB, et al. Severe episodic neurological deficits and permanent mental retardation in a child with a novel FHM2 ATP1A2 mutation. *Ann Neurol*. 2006;59:310-314.
10. Cuenca-León E, Corominas R, Fernàndez-Castillo N, et al. Genetic analysis of 27 Spanish patients with hemiplegic migraine, basilar-type migraine and childhood periodic syndromes. *Cephalalgia*. 2008;28: 1039-1047.
11. Bawa B, Abbott LC. Analysis of calcium ion homeostasis and mitochondrial function in cerebellar granule cells of adult CaV 2.1 calcium ion channel mutant mice. *Neurotox Res*. 2008;13:1-18.
12. Neligan P, Harriman DG, Pearce J. Respiratory arrest in familial hemiplegic migraine: A clinical and neuropathological study. *Br Med J*. 1977;2:732-734.
13. Malpas TJ, Riant F, Tournier-Lasserve E, et al. Sporadic hemiplegic migraine and delayed cerebral oedema after minor head trauma: A novel de novo CACNA1A gene mutation. *Dev Med Child Neurol*. 2010;52:103-104.
14. de Vries B, Stam AH, Beker F, et al. CACNA1A mutation linking hemiplegic migraine and alternating hemiplegia of childhood. *Cephalalgia*. 2008; 28:887-891.

Sumatriptan in Excessive Doses Over 15 Years in a Patient With Chronic Cluster Headache

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We report the case of a 49-year-old lady with cluster headache, who had received sumatriptan s.c. treatment for 15 years with daily dosages between 12 and 222 mg (average of 150 mg during the last year). The therapy was successful in aborting CH attacks. Long-term overdosage of sumatriptan was well tolerated, without adverse events.

Key words: sumatriptan, chronic cluster headache, side effect, overdosage

Abbreviations: CH cluster headache, s.c. subcutaneously

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