

Sporadic Hemiplegic Migraine with *CACNA1A* Mutation Masquerading as Acute Meningoencephalitis

Hemiplegic migraine (HM) is usually seen in developmentally normal children with a prevalence of 0.01%.^[1] Genes implicated are *CACNA1A*, *ATP1A2*, *ATP1A3*, *SCN1A*, *PRRT2*, and *SLC2A1*.^[2,3] *CACNA1A* mutations have associated features like global developmental delay and cerebellar atrophy with prodromal features like fever and encephalopathy.^[2,4]

A 5-year-old girl with global developmental delay, hypotonia, and ataxia presented with incessant cry, vomiting, and decreased responsiveness. There was a similar episode at 3 years of age after which she recovered in 2 days with symptomatic management. She was born to a nonconsanguineous couple with an uneventful perinatal history. At 5 years, she could sit unsupported, babble, and recognize parents. There was no similar history in her first and second degree relatives.

She was noted to have high-grade fever and altered sensorium and was started on intravenous ceftriaxone, acyclovir, levetiracetam and anti-edema measures. Blood investigations and cerebrospinal fluid (CSF) examination were normal. Magnetic resonance imaging (MRI) brain showed cerebellar atrophy. On day 3, left hemiparesis was noted and repeat MRI showed hyperintensity and diffusion restriction in the right parietooccipital region [Figure 1] with narrowing of the supraclinoid portion of the right internal carotid artery and M1 segment of the right middle cerebral artery on magnetic resonance angiography. Electroencephalogram showed asymmetric background slowing, more on the right side, with no epileptiform discharges. Fever resolved on day 5, power and sensorium returned to baseline by day 8. Whole exome sequencing detected a heterozygous missense variation in exon 26 of the *CACNA1A* gene (chr19:13372366T>C) that results in the amino acid substitution of cysteine for tyrosine at codon 1383 (p.Tyr1383Cys) reported as a variant of unknown significance. However, parents were negative for the same mutation by Sanger sequencing. Considering acute attack of sporadic hemiplegic migraine (SHM) due to de novo *CACNA1A* mutation, she was started on incremental doses of verapamil.

Three months later, she had a similar episode of decreased

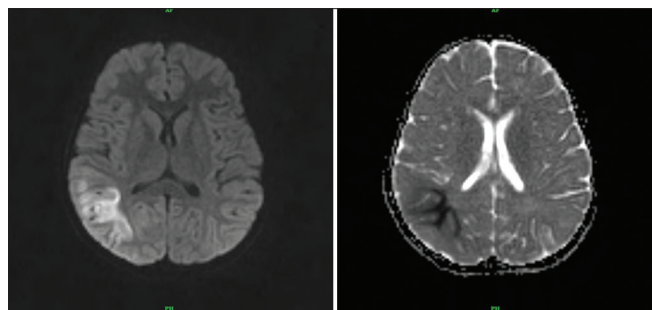


Figure 1: DWI and ADC images showing diffusion restriction in the right parieto-occipital region

responsiveness with right sided hemiparesis. Intravenous verapamil (0.1 mg/kg) resulted in early and complete recovery along with exquisite response to prophylactic acetazolamide (30 mg/kg/day) over a 2-year follow-up.

HM is a type of migraine with motor weakness and features of aura, which are fully reversible. Usually, two or more auras like visual field defects, aphasia, numbness, tingling, and ataxia are present, associated with headache during or after the aura. Motor weakness usually starts in the arm, which can be bilateral or unilateral, alternating between or during the attacks. This may be precipitated by acute stress, emotions, head injury, and lack of sleep. HM with at least one first or second degree relative with identical attacks is familial hemiplegic migraine, whereas with no similar family history is SHM.^[1,5]

Fever, meningismus, and encephalopathy can be seen in HM caused by *CACNA1A* mutations due to abnormalities in microcirculation in meningeal venous sinuses, elevations in serum and CSF interleukin 6, disruption of blood-brain barrier, and hemispheric cytotoxic edema.^[6] Thus, HM may often be misdiagnosed as encephalopathy of infectious origin.

CACNA1A gene encodes alpha_{1A} subunit of neuronal P/Q type calcium channel and its mutations result in increased calcium influx and glutamate release, leading to increased susceptibility to cortical spreading depression.^[6] Spectrum of *CACNA1A* gene mutations also includes cerebellar atrophy, early onset epileptic encephalopathy, intellectual disability, episodic ataxia, and spinocerebellar ataxia type 6.^[7] Our case had a variant Tyr1383Cys in *CACNA1A* that has not been reported in literature so far. A similar variant Tyr1385Cys with a similar presentation was reported in a patient with early onset mental retardation, episodes of HM with fever, altered sensorium, focal seizures, and cerebellar atrophy.^[4]

Differential diagnosis for HM includes alternating hemiplegia of childhood (AHC), transient ischemic attacks, Todd's palsy, meningoencephalitis, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes, homocystinuria, and ornithine transcarbamylase deficiency.^[1]

HM and AHC share common features such as repeated attacks of hemiplegia lasting for few minutes to several days, developmental delay, epilepsy, autonomic symptoms, abnormalities of ocular movements, and ataxia. *ATP1A2*, *SLC2A1*, and *CACNA1A* mutations are implicated in both the conditions. AHC usually has features such as nystagmus, choreoathetosis, and dystonia, episodes of hemiplegia or quadriplegia before 18 months, resolution of weakness by sleep, and a progressive course with mental deterioration.^[3]

The MRI findings in HM are a spectrum ranging from a completely normal study to cortical swelling, diffusion restriction, prominent intracerebral veins, and cerebellar atrophy. Perfusion studies may show transient hypoperfusion followed by hyperperfusion. Follow-up MRI usually shows complete resolution of acute radiological findings.^[1,2] In AHC with cognitive decline, the radiological findings mainly consist of cerebellar and cerebral atrophy.^[8]

In the acute phase of HM, intravenous verapamil, intranasal ketamine, triptans, frusemide, and magnesium sulphate are useful. Steroids and hypertonic saline reduce cerebral edema. Prophylactic management includes oral verapamil, acetazolamide, flunarizine, and lamotrigine.^[2] In AHC, induction of sleep in the acute stage and flunarizine as prophylaxis are common management strategies.^[8] Triggers should be identified and prevented in both the conditions.

CACNA1A mutation can lead to early onset severe developmental delay with recurrent hemiplegic attacks. It can be a great mimicker of febrile encephalopathy with noninfective/inflammatory CSF. An alternating hemiplegia or recurrent hemiplegic attacks may alert physician to hemiplegic migraine often due to channelopathies.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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