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Late Cytotoxic Edema in 2 Children With Hemiplegia: Hemiplegic Migraine or Stroke?

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Abstract

Hemiplegic migraine (HM) is a rare variant of migraine with aura, characterized by migrainous headache and fully reversible motor deficit within 24 hours. Both sporadic and familial forms of HMs are genetically heterogeneous with little information on neuroimaging during and after acute attacks. We report 2 cases of children with presumed HM and late cytotoxic edema.

Keywords

pediatric headache; hemiplegic migraine; stroke; imaging

Hemiplegic migraine (HM) is a rare variant of migraine with aura characterized by focal motor weakness. The International Classification of Headache Disorders-II (IHCID-II) classifies HM as a migrainous headache with aura features including motor weakness.¹ Unlike migraine with aura, aura symptoms in HM can last up to 24 hours. Prolonged aura symptoms (greater than 24 hours) have been reported with HM and may occur in up to 8% of cases.² The 2 subtypes – sporadic (SHM) and familial (FHM) – are genetically heterogeneous, with the following identified genes: (1) CACNA1A, a voltage-gated P/Q type

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calcium channel on chromosome 19; (2) ATP1A2, a sodium-potassium ATPase on chromosome 1; and (3) SCN1A, a voltage-gated sodium channel on chromosome 2.

Neuroimaging changes have been reported in several pediatric cases with HM (Table 1a). All cases were prolonged; however, the degree of neuroimaging changes varied. We report here the clinical features and neuroimaging of 2 children with prolonged HM with parent consent (approved by the Colorado Multi-Institutional Review Board).

CASE 1

A 9-year-old right-handed girl presented to the emergency department with acute onset of headache, right-sided weakness, vomiting, altered mental status (AMS), and aphasia. There were no recent illnesses, fevers, or head injuries. She had no previous history of migraine; however, she had a family history of migraines. Both computed tomography (CT) head and magnetic resonance imaging (MRI) brain with diffusion weighted imaging (DWI) performed 6 hours after symptom onset were normal. She was admitted to the pediatric intensive care unit (PICU). Over the first 96 hours, there was a waxing and waning clinical exam with continued lethargy, AMS, profound right-sided weakness, right neglect, and visual field deficit. Given persistent symptoms, MRI/MR angiogram brain was repeated at 93 hours (Fig. 1a, b). Repeat MRI demonstrated subtle restricted diffusion on DWI with correlating apparent diffusion coefficient (ADC) parietal cortex. Fluid attenuated inversion recovery (FLAIR) images showed very subtle swelling and cortical hyperintensity in the same location. Cerebral spinal fluid (CSF) did not indicate infection (WBC 2, RBC 0, glucose 61 mg/dL, protein 61 mg/dL) and was negative for infectious etiologies (herpes simplex, enterovirus, varicella zoster, mycoplasma). Hypercoagulability testing revealed a heterozygous mutation for factor V leiden, and elevated factor VIII (233.7%) and lipoprotein(a) (62 mg/dL). FHM sequencing panel demonstrated an unreported mutation in a highly conserved location for the ATP1A2 gene at nucleotide position 719, creating an amino acid change of isoleucine to asparagine at codon 240. The patient required inpatient rehabilitation for 18 days. Repeat MRI at 63 days was normal (Fig. 1c, d). At 1 year follow-up, she continued to have difficulties with expressive language, processing speed, and academic work and required continued speech therapy.

CASE 2

A 9-year-old right-handed girl with history of migraines and a family history of HM presented with 12 hours of headache, right-hand sensory changes, AMS, and aphasia. She became febrile several hours into her headache; however, there were no recent illness or head injuries. CT head was normal, and MRI brain with DWI was normal at 20 hours. Electroencephalogram (EEG) showed significant left sided slowing with occasional left hemispheric sharps. Lumbar puncture revealed WBC 1, RBC 8, glucose 72 mg/dL, and protein 34 mg/dL. Secondary to persistent symptoms, an MRI brain was repeated at 97 hours. The repeat exam revealed subtle small foci of mildly restricted diffusion in the left posterior frontal and parietal regions. FLAIR imaging demonstrated subtle swelling and cortical hyperintensity in the same areas. Hypercoagulability work up was unrevealing. Infectious workup for herpes simplex, enterovirus, Epstein-Barr virus, and bartonella were all negative. MRI at 101 days was normal. FHM sequencing panel revealed an unreported indeterminate mutation in a highly conserved location for the CACNA1A gene at nucleotide positions 7258 and 7289, creating an amino acid change of proline to valine at codon 2420. At 2-year follow-up, the patient had no neurological or neuropsychological deficits.

DISCUSSION

Our cases demonstrate 2 prolonged HM with delayed neuroimaging changes that both resolved after the acute period (Table 1b). HM is a rare primary headache disorder normally characterized by less than 24 hours of neurological deficit.¹ These cases are similar to several previously reported (Table 1a),^{3–7} including prolonged attacks,^{3–7} hemispheric^{3–7} or diffuse cortical edema,⁴ and occasional subtle diffusion abnormalities.^{4,6} All 7 cases had MRI changes and prolonged attacks. Although it has been estimated that 8% of SHM are prolonged,² it does not appear that any particular gene is more likely to produce protracted attacks.

The mildly restricted diffusion seen in our cases and those in the literature likely corresponds to mild cytotoxic edema resulting from the HM attack.³ Although diffusion changes are commonly assumed to represent ischemic tissue, Chabriat et al propose that the subtle diffusion abnormalities in HM are the result of prolonged neuronal depolarization.⁸ Similarly, Kumar et al found no perfusion abnormalities on single-photon emission computed tomography (SPECT), but fluorine 18-labeled deoxyglucose (FDG) positron emission tomography (PET) demonstrated significant decrease in metabolic activity in the involved hemisphere, supporting the notion of neuronal depression.⁵ This could also explain why there is a lag between radiological and clinical findings that is not normally seen in ischemic events. The diffusion abnormalities in our cases were subtle, and the cortical swelling was not limited to any discrete vascular territory. The transient and late restricted diffusion changes may indicate metabolic stress where neuronal cells are unable to meet energy demands, resulting in dysfunction and mild swelling of cells without ultimate neuronal cell death.

Although most cases showed radiographic and clinical resolution, one case in the literature showed residual volume loss, and Case 1 in our series continued to have persistent neurological symptoms requiring an individualized learning plan. In addition, Dodick et al report an FHM case with acute hemispheric edema, no diffusion changes, and a persistent neurological deficit 2 years later.⁹ These cases suggest that permanent migrainous infarction occurs in a minority of patients. Hypometabolism on PET and reduced perfusion on SPECT 3 months after onset of attack suggests irreversible neuronal death without ischemia may also occur.⁹ Paradoxically, Herold et al have shown normal cerebral oxygen consumption during an episode of HM.¹⁰ Cerebellar atrophy can also be seen in adults with HM, which was not reported in any of the reviewed published pediatric cases or in our series. This could represent additional long-term sequela in HM.

Not all patients with HM are found to have a mutation in 1 of the 3 recognized genes; however, abnormalities in the identified calcium channel or Na⁺/K⁺ pump may explain the changes thought to be related in HM. A possible explanation for neuronal compromise with prolonged attacks is neuronal excitability via increased ionic flux and glutamate and decreased glutamate uptake in HM.^{8,9} These changes may lead to prolonged cortical spreading depression and neuronal injury seen in HM.

In conclusion, the pathophysiology and significance of cytotoxic edema in childhood HM remains uncertain. Imaging changes may show mild hemispheric edema with or without diffusion changes, which are often subtle if present. Sporadic cases may be more commonly associated with ATP1A2 gene⁷ as opposed to CACNA1A. Prolonged HM may produce residual symptoms and persistent MRI findings, and it is unclear if there is underlying infarction vs non-ischemic neuronal cell death. Serial imaging during and after resolution of an attack may help elucidate the pathophysiology and spectrum of HM, including the use of functional imaging techniques such as PET and SPECT.

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Abbreviations

ADC	apparent diffusion coefficient
AMS	altered mental status
CSF	cerebral spinal fluid
CTH	computed tomography head
DWI	diffusion weighted imaging
EEG	electroencephalogram
FDG	fluorine 18-labeled deoxyglucose
FHM	familial hemiplegic migraine
FLAIR	fluid attenuated inversion recovery
HM	hemiplegic migraine
IHCD-II	International Classification of Headache Disorders-II
MRI	magnetic resonance imaging
PET	positron emission tomography
PICU	pediatric intensive care unit
SHM	sporadic hemiplegic migraine
SPECT	single-photon emission computed tomography

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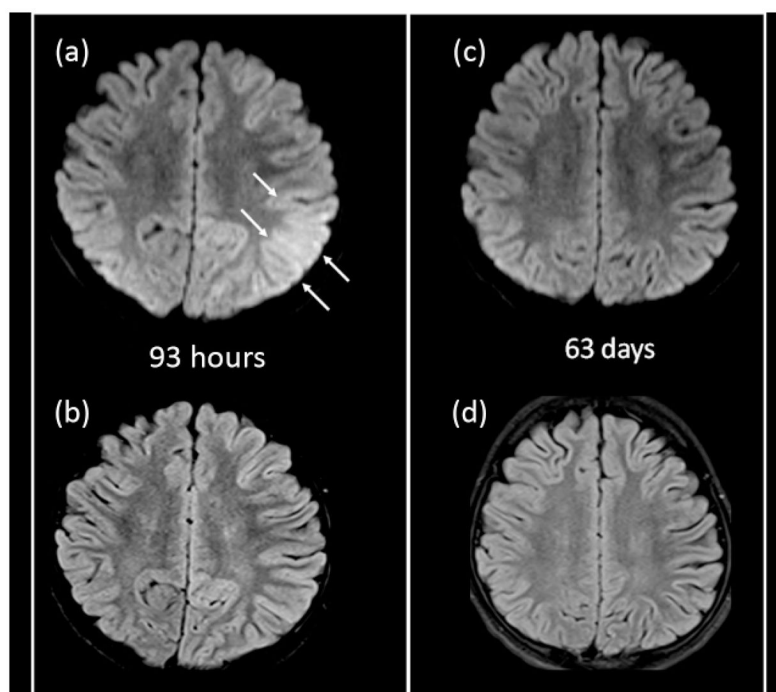


Fig 1.

Case 1 MRI at 93 hours demonstrates restricted diffusion on diffusion weighted imaging (DWI) images (a) in parietal region (ADC dark, not shown). Fluid attenuated inversion recovery (FLAIR) images at 93 hours show subtle swelling and cortical hyperintensity (b), not as conspicuous as diffusion changes. Both findings had completely resolved on MRI performed at 63 days (c) on DWI and (d) FLAIR.

Table 1

(a) Previous Pediatric Reports of Hemiplegic Migraines With Neuroimaging Changes (b) Cases 1 and 2 Reported Here

Author	Age/gender	Presentation	FHx [‡]	MRI	Repeat MRI	Genetic	Dx
(a)							
Butteriss et al. 2003 ³	14-year-old male	HA, R hemiparesis, aphasia, AMS (previous episode of L hemiparesis)	+	3 weeks-diffuse L cortical swelling (DWI+, ADC-), L MCA mildly prominent	6 months-nl	Not done	FHM
Hart et al. 2009 ⁴ (3 family members)	14-year-old male	AMS, dysphasia	+	50 hours-mild L parietal cortical swelling	4 months-nl	Not done	FHM
	12-year-old male	Minor head injury, R hemiparesis, dysphasia, fever, focal seizures	+	L diffuse cortical swelling (DWI+)	3 months- ↓ L cortical volume	CACNA1A neg	FHM
Kumar et al. 2009 ⁵	8-year-old male	Minor head injury, AMS	+	Diffuse cerebral edema	2 weeks-nl	Not done	FHM
	12-year-old female	HA, R hemiparesis, AMS, aphasia	+	Admission-nl Day 3 and 10-L cortical edema (DWI-)	1 month-nl	Not done	FHM
Toldo et al. 2010 ⁶	8-year-old female	HA, R hemiparesis, aphasia, fever, AMS	-	9 hours-nl Day 4 and 11-Diffuse L cortical swelling (DWI+, ADC+)	6 months-nl	Missense in ATP1A2	SHM
De Sanctis 2011 ⁷	6-year-old male	HA, R hemiplegia, somnolence, fever	-	L frontal and parietal leptomeningeal enhancement, DWI-, MRA- Day 10 L cortical edema (DWI-, ADC-)	2 months-nl	Missense in ATP1A2	SHM
(b)							
Case 1	9-year-old female	HA, R hemiparesis, aphasia, AMS	- [‡]	6 hours-normal 93 hours-L Cortical swelling (DWI+/ADC+)	2 months-nl	ATP1A2 pos, [§]	SHM
Case 2	9-year-old female	HA, R hemiparesis, aphasia, AMS	+	20 hours-normal 75 hours-L cortical swelling (DWI+/ADC+)	3 months-nl	CACNA1A indeterminate	FHM

[‡] FHx positive for migraine.

[‡] FHx for hemiplegic migraine.

[§] Unreported mutation in highly conserved location.

ADC = apparent diffusion coefficient; AMS = altered mental status; DWI = diffusion weighted imaging; FHx = family history; HA = headache; MRI = magnetic resonance imaging; R = right.