Title
Migraine with prolonged aphasic aura associated with a CACNA1A mutation: A case report and narrative review

Journal
Headache The Journal of Head and Face Pain, 63(7)

ISSN
0017-8748

Authors
Jicha, Crystal J
Alex, Ashley
Herskovitz, Steven
et al.

Publication Date
2023-07-01

DOI
10.1111/head.14594

Migraine with Prolonged Aphasic Aura Associated with a CACNA1A Mutation: A Case Report and Narrative Review

Authors:

Crystal J Jicha, MD

Department of Neurology, University of California, Irvine, Irvine, CA, USA.

No conflicts of interest.

Ashley Alex

Department of Neurology, Jacobs School of Medicine/University at Buffalo, The State University of New York, Buffalo, NY, USA.

No conflicts of interest.

Steven Herskovitz

Department of Neurology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA.

No conflicts of interest.

Sheryl R Haut, MD

Department of Neurology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA.

Conflicts: Consultant: Nile - AI, UCB Pharma; Scientific Advisory Board: IQVIA

Richard Lipton, MD

Department of Neurology, Montefiore Medical Center/Albert Einstein College of Medicine, Bronx, NY, USA.

Conflicts: He receives research support from the NIH, the FDA, the National Headache Foundation and research grants from TEVA, Satsuma and Amgen. He serves on the editorial board of Neurology, senior

advisor to Headache, and associate editor to Cephalalgia. He has reviewed for the NIA and NINDS, holds in Biohaven Holdings as well as stock options in Manistee; serves as consultant, advisory board member, or has received honoraria from: Abbvie (Allergan), American Academy of Neurology, American Headache Society, Amgen, Avanir, Axsome, Biohaven, Biovision, Boston Scientific, Dr. Reddy's (Promius), Electrocore, Eli Lilly, eNeura Therapeutics, Equinox, GlaxoSmithKline, Grifols, Lundbeck (Alder), Merck, Pernix, Pfizer, Satsuma, Supernus, Teva, Trigemina, Vector, Vedanta. He receives royalties from Wolff's Headache 7th and 8th Edition, Oxford Press University, 2009, Wiley and Informa.

Keywords: migraine aura, aphasic aura, Familial hemiplegic migraine, CACNA1A, case report

Financial support: none

Abbreviations:

SPECT - single photon emission computerized tomography

FHM – familial hemiplegic migraine

IV - intravenous

CT – computed tomography

CSF – cerebrospinal fluid

EEG – electroencephalogram

MRI – magnetic resonance imaging

FLAIR - fluid attenuated inversion recovery sequence

CSD – cortical spreading depression

Abstract:

Objective

To demonstrate that a known CACNA1A variant is associated with a phenotype of prolonged aphasic aura without hemiparesis.

Background

The usual differential diagnosis of prolonged aphasia without hemiparesis includes vascular disease, seizure, metabolic derangements, and migraine. Genetic mutations in the CACNA1A gene can lead to a myriad of phenotypes, including familial hemiplegic migraine type 1, an autosomal dominant disorder characterized by an aura of unilateral, sometimes prolonged weakness. Though aphasia is a common feature of migraine aura, with or without hemiparesis, aphasia without hemiparesis has not been reported with CACNA1A mutations.

Methods

We report the case of a 51-year-old male who presented with a history of recurrent episodes of aphasia without hemiparesis lasting days to weeks. His headache was left sided and was heralded by what his family described as “confusion”. On examination, he had global aphasia without other focal findings. Family history revealed several relatives with a history of severe headaches with neurologic deficits including aphasia and/or weakness. Imaging revealed T2 hyperintensities in the left parietal/temporal/occipital regions on MRI scan with corresponding hyperperfusion on SPECT. Genetic testing revealed a missense mutation in the CACNA1A gene.

Conclusions

This case expands the phenotypic spectrum of the CACNA1A mutation and familial hemiplegic migraine to include prolonged aphasic aura without hemiparesis. Our patient’s SPECT imaging demonstrated hyperperfusion in areas correlating with aura symptoms which can occur in prolonged aura.

Background:

Familial hemiplegic migraine (FHM), a typically autosomal dominant subtype of migraine with aura, is characterized by prominent unilateral motor weakness during the aura phase. Weakness usually occurs in association with two or more other features of aura such as visual, sensory, aphasic, or brainstem symptoms.[1] The auras are often prolonged, lasting hours or days, and rarely weeks, though deficits usually resolve completely.[2,3] The genetic underpinning of FHM are predominately mutations in ion channel genes, the CACNA1A (FHM1), ATP1A2 (FHM2) and SCN1A (FHM3) genes.[4] These variants are each associated with elevated synaptic glutamate.[5,6] Glutamate elevation is thought to produce a state of brain hyperexcitability and increased susceptibility to cortical spreading depression (CSD), the presumed substrate of migraine aura.[6-8]

Though the clinical spectrum of aura related to variants in FHM genes is broad, isolated global aphasia without hemiparesis is rare and typically suggestive of other diagnoses. We report such a patient with prolonged aphasia with deficits resolving over months associated with hyperperfusion of the involved hemisphere on neuroimaging and genetic testing revealing a CACNA1A mutation.

Case Report:

The patient consented to the publication of this case report.

A 51-year-old male with a past medical history of hyperlipidemia was admitted to an outside hospital with a severe, left-sided headache and “confusion” since the previous evening. He also had nausea, photophobia, phonophobia and one episode of vomiting. He had a 20-year history of migraine with aura, with infrequent attacks averaging once yearly. Auras included difficulty speaking, along with sensory (right numbness/paresthesia) and visual (photopsia, visual obscuration) symptoms but not weakness. He had been admitted elsewhere for similar deficits 6 years prior to current presentation for

about 3 days. At that time, he was treated with butalbital/acetaminophen/caffeine. He had not had prior preventative therapy.

At the outside hospital, his examination revealed global aphasia, without hemiparesis or other findings. He was treated with acetaminophen, diphenhydramine, ketorolac, and metoclopramide in the emergency department, and subsequently with IV valproate and solumedrol with some improvement in pain but persistent aphasia. Studies included a non-contrast CT head, a CT angiography, an MRI with and without gadolinium, all of which were normal. CSF examination revealed WBC 4, protein 33 mg/dL, and HSV was negative. EEG showed left hemisphere slowing.

One week later he was transferred to our center with persistent severe left-sided headache and language disturbance. He was alert, attentive and globally aphasic. Speech was non-fluent, with very poor comprehension, poor naming, and repetition, along with alexia, agraphia, paraphasic errors and neologisms. There was no visual field cut, weakness, reflex asymmetry, dysmetria or gait dysfunction. Sensory exam was unreliable.

MRI of the brain (one week after symptom onset) showed asymmetric cortical fluid attenuated inversion recovery sequence (FLAIR) signal with swelling, including local diffusion hyperintensity involving portions of the left parietal, occipital and posterior temporal cortex (see figure 1). There was an additional small area of FLAIR signal hyperintensity within the right occipital lobe, within the deep subcortical white matter. Following contrast administration there was subtle enhancement involving the left parahippocampal gyrus and posterior perihippocampal tissues. One week later, a follow-up MRI without contrast was unchanged. Nuclear medicine brain scan with single photon emission computerized tomography (SPECT) showed increased radiotracer (Tc-99m ECD) uptake within the gray matter of the left temporal, parietal, and occipital lobes (see figure 2) corresponding to the abnormality seen on MRI, consistent with hyperperfusion to these areas. Routine and continuous EEGs showed

continuous polymorphic and rhythmic delta, attenuation of faster activities and of the posterior dominant rhythm in the left hemisphere, along with frontal intermittent rhythmic delta activity; there were no epileptiform discharges.

The possibility of prolonged localization-related seizure was considered based on the EEG findings and levetiracetam and lamotrigine were initiated. Given symptom persistence despite treatment with multiple anti-seizure agents, he was additionally treated with magnesium, rapid infusion valproate, dexamethasone/prednisone, and verapamil over a 3-week course, along with speech therapy for a presumptive diagnosis of persistent aura without infarction. Additional negative/normal testing included an autoimmune encephalitis panel, HIV and NOTCH3 (CADASIL) studies. Genetic testing revealed a likely pathogenic heterozygous missense mutation in the CACNA1A gene (c.4999 (Isoform 1)C>T; p.Arg1667TRP; ATHENA Diagnostics), previously described in association with FHM1.[9] The patient reported a strong family history of migraine with auraand hemiplegic migraine including aphasic aura without hemiparesis.A family study is underway to better characterize migraine features among his relatives and their genetic underpinnings.

Over a 3-week hospitalization, his headache and speech gradually improved. He reported occasional visual aura (fortification spectra) and auditory hallucinations. At discharge, his spontaneous speech reemerged and word retrieval normalized but he continued to have difficulty naming low-frequency items. He was discharged on verapamil and levetiracetam for migraine prevention as well as butalbital/acetaminophen/caffeine for acute treatment of migraine attacks. On follow-up one month later, he still had a mild daily headache and delay in naming. Three months after hospital discharge, his speech was normal, and he was headache free. He continued to have repeat episodes of aura, although less prolonged, following this hospitalization with some mild word finding difficulty noted interictally on subsequent follow-ups. Repeat imaging done 1 year later showed resolution of left sided

hyperintensities and contrast enhancement. More recently, the patient experienced an aura event consisting of aphasia with left sided hemiparesis, now meeting the formal criteria for familial hemiplegic migraine. **Discussion:**

To our knowledge, this is the first case of migraine with prolonged aphasic migraine without hemiparesis attributed to a CACNA1A mutation. The CACNA1A gene is located on chromosome 19p13 and encodes for a pore forming protein on neuronal P/Q voltage gated calcium channels.[10] In FHM1 cases, CACNA1A mutations are largely due to a missense gain of function mutation which leads to increased calcium influx and increased neurotransmitter release.[2,4,6] In vitro and animal models have shown that this mutation increases neuronal excitability.[1,4] A hyperexcitable state lowers the threshold for cortical spreading depression creating a prolonged state of neuronal depolarization, possibly explaining the extended duration of these auras.[2,4,6]

CACNA1A mutations are known to have diverse phenotypic presentation including episodic ataxia type 2, spinocerebellar ataxia type 6, epileptic encephalopathy, developmental delay, autism-spectrum disorders, and early onset paroxysmal dystonia.[1,4] Multiple aura symptoms and longer duration of aura are more commonly seen in those with hemiplegic migraine.[3] This case expands on the phenotypes associated with familial hemiplegic migraine and CACNA1A mutations to include prolonged aphasic aura without hemiparesis.

Though the clinical spectrum of aura related to variants in FHM genes is broad, isolated aphasia without hemiparesis initially suggested other diagnoses such as seizure or vascular events, including TIA or stroke. While epilepsy can be associated with hyperperfusion on SPECT[11] and CACNA1A mutations[1], no epileptiform discharges or seizure events were seen on extended EEG recording while patient was symptomatic. Although stroke is easily ruled out by imaging, TIA was a possible diagnosis made less probable by the extended duration of symptoms, atypical findings on imaging including hyperperfusion

on SPECT, lack of risk factors, and recurrent attacks. Features such as the strong relationship of focal symptoms to headache, concurrent presence of visual fortification spectra commonly seen in migraine aura, and family history make the diagnosis of migraine most likely. The demonstration of a CACNA1A variant associated with FHM lends further support to the diagnosis of persistent aura without infarction.

The patient's imaging demonstrated focal FLAIR hyperintensity with swelling that correlated with the hyperperfusion seen on SPECT imaging, a nonspecific finding that can be seen in multiple neurologic conditions. Previous case reports of hemiplegic migraine have shown conflicting results regarding cerebral blood flow findings. Multiple case reports and small case series have shown hyperperfusion in areas corresponding to neurologic deficits on perfusion-weighted imaging and SPECT imaging.[12-17] However, hypoperfusion has also been noted on perfusion scans done in cases of migraine with aphasic aura and prolonged aura.[18,19]

Cortical spreading depression (CSD) has long been theorized to be the underpinning of the aura phase of migraine. Initial neuronal hyperexcitability and release of neuroactive peptides leads to focal hyperemia, lasting minutes, and is followed by a wave of neuronal depolarization and marked oligemia.[20,21] Our patient with localized hyperperfusion during prolonged aphasic aura is consistent with the growing number of reports of this phenomenon in people with prolonged aura and familial hemiplegic migraine.[12-17] During prolonged aura, CSD may generate high metabolic demand leading to increased perfusion through cerebral autoregulation. The cortical swelling and contrast enhancement seen in our patient may arise from dysregulation of the blood-brain barrier through this process. Hemispheric swelling and enhancement have been noted in other case reports of hemiplegic migraine and prolonged aura.[15,16,21]

Our patient has shown improvement in headache and aura severity since his discharge on verapamil and levetiracetam, although he has noted some mild interictal word finding difficulty. There is evidence that

patients with FHM1 can develop persistent deficits outside of migraine episodes.[2] Management of FHM1 is directed at the avoidance of migraine triggers as well as medical treatments that alter cortical spreading depression dynamics.[1] Case reports and small case series have shown efficacy with medications such as verapamil, ketamine, and acetazolamide for the treatment of both headache pain and aura.[1,17] Flunarizine, a long-acting calcium channel blocker not available in the US, has been shown to be effective in the treatment of hemiplegic migraine in a pediatric study.[22]

Conclusions:

This patient had persistent aphasic aura without infarction and corresponding left hemispheric FLAIR hyperintensities with hyperperfusion seen on SPECT, a finding that has been seen in hemiplegic migraine. The presence of a missense CACNA1A mutation in this case of prolonged aphasic aura illustrates the phenotypic spectrum that can be seen in familial hemiplegic migraine type 1.

References:

1. Indelicato E, Boesch S. From Genotype to Phenotype: Expanding the Clinical Spectrum of *CACNA1A* Variants in the Era of Next Generation Sequencing. *Front Neurol.* 2021; 12: 639994.
2. Ducros A, Denier C, Joutel A, Cecillon M, Lescoat C, Vahedi K, Darcel F, Vicaut E, Bousser M, Tournier-Lasserve E. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. *N Engl J Med* 2001; 345:17-24.
3. Eriksen MK, Thomsen, LL, Olesen J. Implications of Clinical Subtypes of Migraine With Aura. *Headache*, 2006; 46(2): 286–297.
4. Russell MB, Ducros A. Sporadic and familial hemiplegic migraine: pathophysiological mechanisms, clinical characteristics, diagnosis, and management. *Lancet Neurol,* 2011; 10: 457-70. 7
5. Di Stefano V, Rispoli M, Pellegrino N, Graziosi A, Rotondo E, Napoli C, Pietrobon D, Brighina F, Parisi P. Diagnostic and therapeutic aspects of hemiplegic migraine. *J Neurol Neurosurg Psychiatry*. 2020;91(7):764-771.
6. Moskowitz MA, Bolay H, Dalkara T. Deciphering migraine mechanisms: clues from familial hemiplegic migraine genotypes. Ann Neurol. 2004; 55(2):276-80.
7. Eikermann-Haerter K, Dileköz E, Kudo C, Savitz SI, Waeber C, Baum MJ, Ferrari MD, van den Maagdenberg AM, Moskowitz MA, Ayata C. Genetic and hormonal factors modulate spreading depression and transient hemiparesis in mouse models of familial hemiplegic migraine type 1. *J Clin Invest. 2009* Jan;119(1):99-109.
8. Eikermann-Haerter K, Yuzawa I, Qin T, Wang Y, Baek K, Kim YR, Hoffmann U, Dilekoz E, Waeber C, Ferrari MD, van den Maagdenberg AM, Moskowitz MA, Ayata C. Enhanced subcortical spreading depression in familial hemiplegic migraine type 1 mutant mice. *J Neurosci.* 2011;31(15):5755-63.

9. Albury CL. 2018, Using whole exome sequencing and genetic association studies to investigate common and complex migraine, PhD thesis, Queensland University of Technology, Brisbane, viewed 14 Sept. 2022, < https://eprints.qut.edu.au/122954/1/Cassie_Albury_Thesis.pdf>).
10. Ophoff RA, Terwindt GM, Vergouwe MN, et al. Familial hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the Ca2+ channel gene CACNL1A4. *Cell*. 1996;87(3):543-552.
11. Grünwald F, Menzel C, Pavics L, et al. Ictal and interictal brain SPECT imaging in epilepsy using technetium-99m-ECD. *J Nucl Med*. 1994;35(12):1896-1901.
12. Lindahl AJ, Allder S, Jefferson D, Allder S, Moody A, Martel A. Prolonged hemiplegic migraine associated with unilateral hyperperfusion on perfusion weighted magnetic resonance imaging. J Neurol Neurosurg Psychiatry. 2002;73(2):202-3.
13. Mourand I, Menjot de Champfleur N, Carra-Dallière C, et al. Perfusion-weighted MR imaging in persistent hemiplegic migraine. *Neuroradiology*. 2012; 54(3):255-260.
14. Oberndorfer S, Wöber C, Nasel C, et al. Familial hemiplegic migraine: follow-up findings of diffusion-weighted magnetic resonance imaging (MRI), perfusion-MRI and [99mTc] HMPAO-SPECT in a patient with prolonged hemiplegic aura. *Cephalalgia*. 2004;24(7):533-539.
15. Barbour PJ, Castaldo JE, Shoemaker EI. Hemiplegic Migraine During Pregnancy: Unusual Magnetic Resonance Appearance With SPECT Scan Correlation. *Headache*, 2001; 41, 310-316.
16. Iizuka T, Sakai F, Suzuki K, Igarashi H, Suzuki N. Implication of Augmented Vasogenic Leakage in the Mechanism of Persistent Aura in Sporadic Hemiplegic Migraine. *Cephalalgia*. 2006;26(3):332-335.
17. Hsu DA, Stafstrom CE, Rowley HA, Kiff JE, Dulli DA. Hemiplegic migraine: hyperperfusion and abortive therapy with intravenous verapamil. *Brain Dev*. 2008;30(1):86-90.
18. Relja G, Granato A, Ukmar M, Ferretti G, Antonello RM, Zorzon M. Persistent aura without infarction: description of the first case studied with both brain SPECT and perfusion MRI. *Cephalalgia*. 2005;25(1):56-59.

19. Linn J, Freilinger T, Morhard D, Bruckmann H, Straube A. Aphasic migraineous aura with left parietal hypoperfusion: a case report. *Cephalalgia*, 2007; *27*(7), 850–853.
20. Eikermann-Haerter K, Ayata C. Cortical spreading depression and migraine. *Curr Neurol Neurosci Rep*. 2010;10(3):167-173.
21. Roth C, Ferbert A, Huegens-Penzel M, Siekmann R, Freilinger T. Multimodal imaging findings during severe attacks of familial hemiplegic migraine type 2. *J Neurol Sci*. 2018; 392, 22-27.
22. Peer Mohamed B, Goadsby PJ, Prabhakar P. Safety and efficacy of flunarizine in childhood migraine: 11 years' experience, with emphasis on its effect in hemiplegic migraine. *Dev Med Child Neurol*. 2012; 54(3):274-277.