Neurovascular changes in magnetic resonance imaging and single-photon emission computed tomography during migraine attack in patients with FHM2 mutations

Azusa Nagai1,2, Daiki Tanaka1, Kiyomi Kuroshima1, Shigehisa Ura1, Kazuto Yoshida1, Yuji Takahashi3, and Ichiro Yabe2

Abstract
The aim of this article is to provide neuroimaging data on cases with familial hemiplegic migraine (FHM). A 14-year-old male presented normal diffusion-weighted magnetic resonance imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) findings during his first hemiplegic migraine attack. However, magnetic resonance angiography (MRA) showed diffuse narrowing of the right middle cerebral artery. Cerebral blood flow–single-photon emission computed tomography showed right hypoperfusion. A follow-up study showed no abnormal findings. His mother had normal DWI, FLAIR, and MRA findings during her migraine attack. Both patients were diagnosed with FHM2 (p.R763H mutation in ATP1A2). This study highlights the importance of neurovascular examinations during the FHM2 headache phase. Further cases are required to clarify the pathophysiology of migraine.

Keywords
ATP1A2, CBF change, radiology, symptoms

Date received: 16 October 2019; Received revised February 1, 2020; accepted: 1 February 2020

Introduction
Hemiplegic migraine (HM) aura is defined as unilateral, fully reversible, visual, sensory, motor, or other central nervous symptoms. Brainstem symptoms, disturbance of consciousness, confusion, fever, and cerebrospinal fluid pleocytosis can also occur.1 Mutations in three genes have been linked to familial HM (FHM):1 CACNA1A, ATP1A2, and SCN1A, causing FHM1, FHM2, and FHM3, respectively. Since these genes control ion channel functions, the mutations cause neuronal hyperexcitability, leading to cortical spreading depression (CSD). Approximately 70 ATP1A2 mutations have been identified,2 but the clinical features and physiological mechanism underlying aura symptoms are understood poorly. Further, there is limited neuroimaging evidence of genetically identified FHM attacks. Here, we report neuroimaging findings during an attack in an FHM2 case with a known ATP1A2 mutation (p.R763H).

1 Department of Neurology, Japanese Red Cross Asahikawa Hospital, Asahikawa, Japan
2 Department of Neurology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan
3 Department of Neurology, National Center of Neurology and Psychiatry, Tokyo, Japan

Corresponding author:
Azusa Nagai, Department of Neurology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Kita14, Nishi5, Kita-Ku, Sapporo 060-8648, Sapporo, Japan.
Email: leukippus0116@gmail.com
Methods

Case reports

Patient 1, a 14-year-old male, developed sudden left-sided hemiplegia and sensory disturbance several hours before admission. He then developed nausea, vomiting, and visual disturbance of his left side. Hemiplegia and sensory disturbance improved after ~10 min, but he gradually developed a right-sided occipital headache. Neurological evaluation on admission revealed mild left-sided hemiplegia, sensory disturbance, and increased deep tendon reflex in the left arm and leg but no pathologic reflexes or cerebellar ataxia. He was unable to walk due to headache and nausea. All clinical symptoms resolved within 1 day. This was his first and only HM attack, but he had experienced occasional migraines without apparent aura. Therefore, patient 1 did not fully meet the International Classification of Headache Disorders (ICHD)-3 criteria for HM. His mother (patient 2) had been admitted with similar symptoms.

Patient 2 had no major past history but had occasionally experienced migraine with aura from a young age, accompanied by sudden syncope, transient dysarthria, and vomiting. She experienced her first HM attack at 39 years. She presented with sudden headache, dysarthria, aphasia, and left-sided hemiplegia but was misdiagnosed with hysteria. All clinical symptoms resolved within 1 day. Patient 2 fulfilled the ICHD-3 criteria for HM.

Neuroimaging

For patient 1, brain magnetic resonance imaging (MRI) was performed at 3 h after symptom onset, when hemiplegia and headache were present, using a 1.5-T scanner. Standard acute imaging for suspected stroke was performed using the following sequences: fluid-attenuated inversion recovery (FLAIR), diffusion-weighted MRI (DWI), apparent diffusion coefficient, and three-dimensional time-of-flight magnetic resonance angiography (MRA). Follow-up MRI was obtained at 24 h after onset, when hemiplegia had resolved, using a 3-T scanner.

Cerebral blood flow (CBF)–single-photon emission computed tomography (SPECT) was performed with $^{99m}$Tc-D,L-hexamethyl-propylene-amine oxide (HMPAO) (740 MBq). Initial CBF-SPECT was acquired at 4 h after onset, when left hemiplegia was resolving. Follow-up CBF-SPECT was obtained at 15 days after onset.

For patient 2, MRI was performed at about 2 h after onset when hemiplegia and headache were present, using...
Follow-up MRI after hemiplegia resolution was not obtained.

**Genetic analysis**

Mutational analysis of genomic DNA for *CACNA1A*, *ATP1A2*, and *SCN1A* was performed using direct nucleotide sequencing with specific primers. Written informed consent was obtained from both patients.

**Results**

**Genetic analysis**

Both patients had a heterozygous p.R763H (c.2288G>A) mutation in *ATP1A2*.

**Neuroimaging**

For patient 1, MRI revealed normal DWI and FLAIR findings, but MRA showed diffuse narrowing of the right middle cerebral artery (Figure 1). CBF-SPECT revealed a large area of hypoperfusion in the right cerebral hemisphere, which did not respect anatomical vascular boundaries. CBF-SPECT also revealed crossed cerebellar diachisis (CCD) in the left cerebellar region. Follow-up MRI and CBF-SPECT showed complete resolution.

For patient 2, MRI revealed normal DWI, FLAIR, and MRA findings. CBF-SPECT was not conducted.

**Discussion**

Here, we reported neurovascular changes in an FHM2 family. CBF-SPECT played an important diagnostic role, as the CBF changes in patient 1 were suggestive of HM, while he did not fully meet the ICHD-3 criteria for HM. Conversely, patient 2 was misdiagnosed as hysteria without CBF-SPECT, although she presented with typical HM symptoms and fulfilled the ICHD-3 criteria for HM. Another diagnostic clue in patient 1 was that the aura symptoms occurred gradually and in succession, suggesting a relationship with the propagation of CSD. Patient 1 demonstrated CCD, which is another unique aspect of our case; CCD has been reported frequently in acute stroke but rarely in migraine.

Two FHM2 patients in the same family with the p.R763H gene mutation showed similar clinical characteristics. They presented with unilateral headache and contralateral hemiplegia, which persisted for 1 day and a few hours, respectively. Although their characteristics were similar to those of our cases, MRI or CBF-SPECT findings were not presented.

CBF changes during migraine have been well studied. The first observable event in an attack of migraine with aura is a posterior decrease in regional CBF in one
hemisphere, followed by headache onset. Regional CBF then gradually changes from abnormally low to abnormally high without an apparent change in headache, which are referred to as biphasic CBF changes.

However, the neurovascular changes in genetically determined FHM remained unclear until recently, due to its low prevalence. Associations between FHM and hyperperfusion, normoperfusion, and hypoperfusion have been reported, but the timings of the scans from migraine onset varied. Iizuka et al. assessed neurovascular changes over time in the affected cerebral hemisphere corresponding to aura symptoms during the acute phase of FHM. They repeatedly measured CBF during each migraine attack in FHM patients, confirming the same biphasic CBF pattern as Olesen et al. (Figure 2). The pathological basis of biphasic CBF changes is postulated to start with the diffusion of neuronal and glial cell depolarization in the cerebral cortex during the aura phase, with subsequent inhibition of neural activity. This phenomenon is called CSD. Hypoperfusion may represent the suppression of neural activity and the concomitant decrease of CBF during CSD. Thereafter, CBF increases gradually during the headache phase. Although the mechanism underlying hyperperfusion remains unknown, it is postulated that the activation of the trigeminovascular system causes neurogenic inflammation in the affected hemisphere.

In conclusion, our cases demonstrated the value of neuroimaging to identify neurovascular changes during the early headache phase of FHM. For patient 1, CBF-SPECT was performed during the acute headache phase when left hemiplegia and right hemisphere hypoperfusion were present. Right hemisphere hypoperfusion is thought to correspond to CSD; this finding is consistent with previously reported “biphasic CBF changes.” However, our findings should be interpreted carefully due to the cross-sectional nature of this study. Observing dynamic CBF changes using functional brain imaging during a migraine attack is crucial to clarify the pathophysiology of migraine.

**Clinical implications**

1. Our cases demonstrated the value of neuroimaging to identify neurovascular changes during the early headache phase of FHM.
2. The neuroimaging finding in our cases is consistent with previously reported “biphasic CBF changes” in HM attack.
3. Patient 1 demonstrated CCD, which is another unique aspect of our case; CCD has been reported frequently in acute stroke but rarely in migraine.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) received no financial support for the research, authorship, and/or publication of this article.

**ORCID iD**

Azusa Nagai https://orcid.org/0000-0003-3333-8772

**References**

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018; 38(1): 1–211.
2. Iizuka T, Takahashi Y, Sato M, et al. Neurovascular changes in prolonged migraine aura in FHM with a novel ATP1A2 gene mutation. *J Neurol Neurosurg Psychiatry* 2012; 83: 205–212.
3. Jurkat-Rott K, Freilinger T, Dreier JP, et al. Variability of familial hemiplegic migraine with novel A1A2 Na⁺/K⁺-ATPase variants. *Neurology* 2004; 62: 1857–1861.
4. Spadaro M, Ursu S, Lehmann-Horn F, et al. A G301R Na⁺/K⁺-ATPase mutation causes familial hemiplegic migraine type 2 with cerebellar signs. *Neurogenetics* 2004; 5(3): 177–185.
5. Olesen J, Friberg L, Olsen TS, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. *Ann Neurol* 1990; 28(6): 791–798.
6. Roth C, Ferbert A, Huegens-Penzel M, et al. Multimodal imaging findings during severe attacks of familial hemiplegic migraine type 2. *J Neurol Sci* 2018; 392: 22–27.
7. Guedj E, Belenotti P, Serratrice J, et al. Partially reversible cortical metabolic dysfunction in familial hemiplegic migraine with prolonged aura. *Headache* 2010; 50: 872–877.
8. Hansen JM, Schytz HW, Larsen VA, et al. Hemiplegic migraine aura begins with cerebral hypoperfusion: imaging in the acute phase. *Headache* 2011; 51: 1289–1296.
9. Iizuka T, Tominaga N, Kaneko J, et al. Biphasic neurovascular changes in prolonged migraine aura in familial hemiplegic migraine type 2. *J Neurol Neurosurg Psychiatry* 2015; 86(3): 344–353.
10. Moskowitz MA. Neurogenic versus vascular mechanisms of sumatriptan and ergot alkaloids in migraine. *Trends Pharmacol Sci* 1992; 13: 307–311.