

# Biphasic neurovascular changes in prolonged migraine aura in familial hemiplegic migraine type 2

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Received 28 January 2014

Revised 26 April 2014

Accepted 27 May 2014

Published Online First

30 June 2014

## ABSTRACT

**Objective** To report biphasic changes in cerebral blood flow (CBF) in the acute phase of hemiplegic migraine with prolonged aura (HMPA), in which aura symptoms lasted longer than 24 h, in three patients with familial hemiplegic migraine (FHM) carrying a p.H916L mutation in ATP1A2 gene.

**Methods** We assessed neurovascular changes with time in the affected cerebral hemisphere corresponding to aura symptoms during the acute phase of HMPA. Arterial spin labelling MRI, SPECT for CBF measurement and EEG in three attacks, in one attack FDG-PET measurement for cerebral metabolism was performed. We evaluated CBF at different phases of aura symptoms in 11 attacks of HMPA.

**Results** In two attacks, we found biphasic CBF changes beginning with hyperperfusion followed by persistent hyperperfusion. FDG-PET revealed increased cerebral glucose metabolism in the regions corresponding to hyperperfusion on day 4 when aura symptoms still persisted. In four attacks, Z-score-based CBF mapping revealed multifocal hypoperfusion in the early phase. Hypoperfusion in our study was seen within 19 h of the onset of the symptoms in five of seven attacks, while hyperperfusion was seen 18 h or later in eight of nine attacks. EEG showed attenuated alpha activity without paroxysmal discharge.

**Conclusions** This is the first report showing biphasic CBF changes during the prolonged aura of FHM2. This study suggested that the results of cross-sectional CBF studies should be interpreted carefully. Initial multifocal hypoperfusion is likely due to functional depression of multifocal origin in the affected hemisphere, but the mechanism of persistent hyperperfusion requires further investigation.

## INTRODUCTION

The International Classification of Headache Disorders (ICHD)-3  $\beta$  has revised the criteria for hemiplegic migraine, in which it defines that each individual non-motor aura symptom lasts 5–60 min while motor symptoms lasts <72 h.<sup>1</sup> However, in severe attacks, even non-motor symptoms occasionally last more than a few days or even weeks.<sup>2–3</sup> Spreading depression (SD), which is a short-lasting slowly propagating wave of neuronal and glial depolarisation, is widely accepted as mechanism underlying visual aura,<sup>4–5</sup> but the mechanism underlying prolonged aura symptoms remains unknown. Three genes responsible for familial hemiplegic migraine (FHM) have been identified.<sup>6–8</sup> These mutations are considered to increase susceptibility

to cortical SD.<sup>9</sup> Enhanced subcortical SD has recently been proposed as mechanism underlying prolonged motor deficits or coma.<sup>10</sup> Cortical SD causes transient hyperaemia followed by a prolonged decrease in cerebral blood flow (CBF).<sup>4–5</sup> However, both hypoperfusion<sup>11–13</sup> and hyperperfusion<sup>14–21</sup> in the affected cerebral hemisphere corresponding to prolonged aura symptoms have been documented in patients with hemiplegic migraine.

We recently reported neurovascular changes during the attack of prolonged aura symptoms in patients with FHM2, in which hyperperfusion developed in the affected hemisphere in five of eight attacks but hypoperfusion in the remaining three.<sup>22</sup> The reasons for the reversed blood flow pattern during the similar attacks of prolonged aura were not elucidated. To address the issue, we evaluated temporal neurovascular changes in additional three attacks and re-evaluated CBF data obtained from three patients of this family.

## PATIENTS AND METHODS

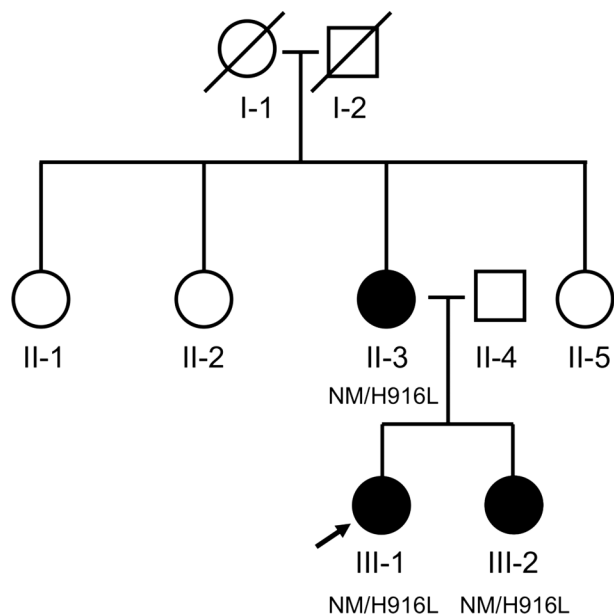
### Subjects

Three patients, including the proband, her mother and her younger sister, were previously reported elsewhere (figure 1)<sup>22</sup>; all patients were confirmed to carry a heterozygous p.H916L mutation in ATP1A2, the gene encoding the ATPase, Na<sup>+</sup>/K<sup>+</sup>-transporting, alpha 2(+) polypeptide. As previously reported, we defined “hemiplegic migraine with prolonged aura (HMPA)” as hemiplegic migraine attack, in which motor and/or non-motor aura symptoms that occurred simultaneously or in succession lasted longer than 24 h, and the ‘affected hemisphere’ as clinically affected cerebral hemisphere contralateral to hemiplegia or corresponding to aura symptoms. These patients were repeatedly admitted to Kitasato University Hospital with HMPA but neurologically intact during interictal period. We briefly describe these patients.

The proband (*patient 1*), a 45-year-old right-handed woman, had migraine without aura since 12 years of age. Since 20 years of age she began to have typical visual aura prior to onset of headache, which was occasionally accompanied by right arm weakness, aphasia, confusion and right visual field defect, but rarely accompanied by left-sided weakness. Since 31 years of age she had nine attacks of HMPA that required hospitalisation; she was twice admitted to other hospitals (at age 31 and 32 years) and seven times admitted to this hospital. Her mother (*patient 2*), a 72-year-old right-handed woman, had mild headache without aura since 38 years of age. Since 58 years of age she had four



**To cite:** Iizuka T, Tominaga N, Kaneko J, et al. *J Neurol Neurosurg Psychiatry* 2015;**86**:344–353.



**Figure 1** Pedigree of the family. Symbols represent the following: circle, female; square, male; black, hemiplegic migraine; white circles or squares, individuals without migraine; NM, no mutation. The arrow indicates the proband. All three patients (III-1: *patient 1*, II-3: *patient 2* and III-2: *patient 3*) have a heterozygous p.H916L mutation in ATP1A2 gene.

attacks of HMPA presenting as left hemiparesis; she was twice admitted to another hospital (at age 58 and 64 years) and twice admitted to this hospital. Her younger sister (*patient 3*), a 42-year-old right-handed woman, had migraine headache without aura since 12 years of age. At 39 years of age, she had migraine headache accompanied by mild right leg weakness. At 41 years of age, she was twice admitted to this hospital with HMPA ([table 1](#)).

All three patients fulfil the ICHD-3  $\beta$  criteria for FHM2, although HMPA itself is not defined in ICHD-3  $\beta$ . Each patient had a history of febrile convulsion until 5 years of age but no ataxia. A maternal family history of the proband, including her grandfather, grandmother and three aunts, had no headache or ataxia. In total, 11 of 15 attacks of HMPA were evaluated in this hospital ([table 1](#)).

### Neuroimaging studies

All the patients underwent studies, including CBF SPECT, three-dimensional time-of-flight MR angiography (3D-TOF MRA), MRI and EEG, in the acute phase of HMPA and after recovery of aura symptoms. In three attacks, we performed 3D arterial spin labelling (ASL)-MRI using pseudo-continuous ASL (pCASL) with postlabelling delay of 1525 ms. In one attack, we performed brain metabolism study with PET using an F-18 fluorodeoxyglucose (FDG-PET) on the same day of ASL-MRI CBF study in the acute phase and 2 months later. The first SPECT or ASL-MRI flow study was performed on days 1–4 before initiation of corticosteroid therapy. MRI was performed with a GE Signa 1.5 T Scanner.

For the CBF SPECT, we used N-isopropyl-p- $^{123}\text{I}$  iodoamphetamine (IMP) (167 MBq) as a flow tracer except in the two attacks of *patient 1*, for which  $^{99\text{m}}\text{Tc}$ -d,l-hexamethyl-propyleneamine oxime (HMPAO) (740 MBq) tracer was used. IMP-SPECT acquisitions were performed by two-head rotating gamma cameras (Siemens, Asahimedec ECAM+) equipped with  $^{123}\text{I}$ -specific

fan-beam collimators. The regional CBF was assessed using three-dimensional stereotactic surface projection (3D-SSP) technique (Z-score mapping) as previously reported.<sup>22</sup>

In this study, to clarify the cause of the reversal of CBF patterns during the course of prolonged aura in the affected hemisphere,<sup>22</sup> we first evaluated temporal neurovascular changes in the seventh attack of *patient 1* with IMP-SPECT, ASL-MRI, FDG-PET and EEG, and we also performed serial measurement with ASL-MRI in two attacks of *patient 3*. Finally, we re-evaluated all the data obtained from three patients during 10 years based on the intervals between the onset of aura symptoms (symptom onset) and CBF measurement. The interval was determined and expressed in hours based on the medical records and careful history taking. A total of 17 CBF studies obtained within 96 h of symptom onset were carefully evaluated. Data obtained after 96 h were excluded from evaluation because aura symptoms and headache had improved in most attacks of HMPA. Perfusion pattern in the affected hemisphere was visually divided into either hypoperfusion or hyperperfusion, and we assessed a relationship between perfusion pattern and the intervals from symptom onset.

This study is an observational study without intervention. Genetic analysis, which was performed at the University of Tokyo, was approved by the Institutional Review Boards of both Kitasato University and the University of Tokyo. A written informed consent was obtained from all patients.

## RESULTS

### Clinical features

Clinical data of 11 attacks of HMPA are shown ([table 1](#)). The temperature on admission always elevated (median 38.4°C, range 37.0–39.1) but HMPA was not preceded by flu-like illness. Routine blood test was unremarkable. Cerebrospinal fluid examination was normal (performed at the second, third and sixth attacks of *patient 1*). Each patient reported work-related mental stress as a major factor provoking HMPA. Two patients (*patients 1 and 2*) reported the premonitory symptoms including daytime sleepiness, fatigue or increased appetite craving for sweets a few weeks before the onset of HMPA. Each patient had individual ‘predominantly or exclusively affected hemisphere’ that is susceptible to hemiplegia. *Patient 1* was admitted with left hemiplegia in 2 of 9 attacks of HMPA; however, the patient reported that right-sided weakness predominantly developed in most of hemiplegic migraine attacks. In contrast, *patient 2* developed exclusively left-sided weakness in all four attacks. *Patient 3* was twice admitted with HMPA; in both attacks the left cerebral hemisphere was responsible for the aura symptoms.

Clinical features of 11 attacks were similar to those of previously reported 8 attacks.<sup>22</sup> Headache usually began unilaterally, contralateral to hemiplegia, but it was difficult to assess detailed characteristics of headache due to concomitant aphasia, confusional state or poor responsiveness. Headache was intermingled with motor or non-motor aura symptoms, and fluctuated during the course of HMPA. Hemiplegia was usually mild or moderate, and fluctuated. Other focal signs included aphasia, agnosia, apraxia and homonymous hemianopsia. Emotional symptoms including fear, anxiety and psychiatric symptoms of disinhibition or visual hallucination were often prominent and occasionally required administration of sedatives or antipsychotic drugs, but no seizure developed. No ocular movement abnormalities or cerebellar ataxia were seen during the attacks.

In 9 of 11 attacks, each patient received corticosteroids in the acute phase after the first CBF study; either prednisone (40–60 mg/

**Table 1** Clinical features during the attack of HMPA

Patient, current age (years)	Patient 1 (III-1), 45							Patient 2 (II-3), 72		Patient 3 (III-2), 42	
Serial no of HMPA, age (years)	1st, 33	2nd, 35	3rd, 36	4th, 40	5th, 42	6th, 42	7th, 44	1st, 66	2nd, 68	1st, 41	2nd, 41
BT at admission (°C)	38.5	37.8	38.2	38.5	38.1	39.1	38.1	38.9	39.0	37.0	38.5
Side of affected hemisphere	R	L	L	L	R	L	L	R	R	L	L
Neurological manifestations	Confusion, L HP, VH, Psy	Confusion, R HP, aphasia, R VFD, VH, Psy	Confusion, R HP, aphasia, R VFD, Psy	Confusion, R HP, aphasia, R VFD, VH, Psy	Confusion, L HP, L VFD, VH, Psy	Delirium, R HP, aphasia, R VFD, VH, AH, Psy	Confusion, R HP, aphasia, R VFD, VH, Psy	Confusion, L HP, L VFD, VH, Psy	Confusion, L HP, L VFD, VH, Psy	Confusion, R HP, R HSD, aphasia, R VFD	Confusion, aphasia, R VFD
Aura duration (days)	5	10	4	8	7	7	8	12	11	4	4
CBF-SPECT (day, tracer)	Decreased in R F, T, P with CCD (2, HMPAO), normal (8, HMPAO)	Increased in L F, T, P, O with CCD (2, 4, HMPAO), normal (23, HMPAO)	Increased in L F, T (2, IMP)	Increased in L F (2, IMP), increased in L P (8, IMP)	Decreased in R F, T (1, IMP)	Decreased in L F, T, P with CCD (1, IMP), normal (13, IMP)	Decreased in L F, T, P, O with CCD (1, IMP), mildly increased in L O, T (9, IMP)	Increased in R T, P, O with CCD (2, IMP), normal (10, IMP)	Increased in R T, P, O (3, IMP), normal (10, IMP)	Increased in L F, T, P, O with CCA (3, IMP)	Decreased in L F, T, P, O with CCD (1, IMP), mildly increased in L T (7, IMP)
ASL-MRI (day)	NA	NA	NA	NA	NA	NA	Increased in L F, T, P, O with CCA (3), increased in L T, P, O with CCA (4), no laterality (9)	NA	NA	Increased in L F, T, P, O (2), no laterality (6)	Decreased in L F, T, P, O with CCD (1), increased in L F, T, P, O (2), no laterality (10)
Demonstration of MCA branches on MRA (day)	Prominently increased (3)	Prominently increased (3)	Mildly increased (2)	Mildly decreased (1)	Normal (1)	Normal (1)	Normal (1), mildly increased (3, 4, 9)	Mildly increased (2)	Mildly increased (2)	Normal (2, 6)	Mildly decreased (1), mildly increased (2), normal (10)
DWI (day)	Normal (3)	Normal (2)	Normal (2)	Normal (1)	Normal (1)	Normal (1)	Normal (1, 3, 4, 9)	Normal (2)	Normal (2)	Normal (2, 6)	Normal (1, 2, 10)
EEG (day)	LVA in R hemisphere (4)	LVA in L hemisphere (3)	LVA in L hemisphere (2)	LVA in L hemisphere (3)	NA	LVA in L hemisphere and delta slowing in R hemisphere (1)*, LVA in L hemisphere (3)	LVA in L hemisphere with slowing in R hemisphere (2)*, LVA in L hemisphere (9)	LVA in R hemisphere (2)	LVA in R hemisphere (3)	No laterality, small spike in T (2)	LVA in L hemisphere (1)
Abortive therapy (day of initiation)	None	IV furosemide 20 mg (2), acetazolamide 750 mg/day (2), PSL 60 mg/day (4)	None	IVMP 1000 mg, 3 days (1), followed by short taper-off	IVMP 1000 mg, 3 days (1), followed by short taper-off	PSL 60 mg/day (1), followed by short taper-off	PSL 60 mg/day (1), followed by short taper-off	IVMP 1000 mg, 3 days (2)	PSL 60 mg/day (2), followed by short taper-off	PSL 40 mg/day (2), followed by short taper-off	PSL 50 mg/day (1), followed by short taper-off

\*EEG recorded after IV infusion of propofol to suppress psychiatric symptoms. Both crossed cerebellar hypoperfusion and hypermetabolism are shown as CCA. Day 1 is the first day of the onset of aura symptoms.

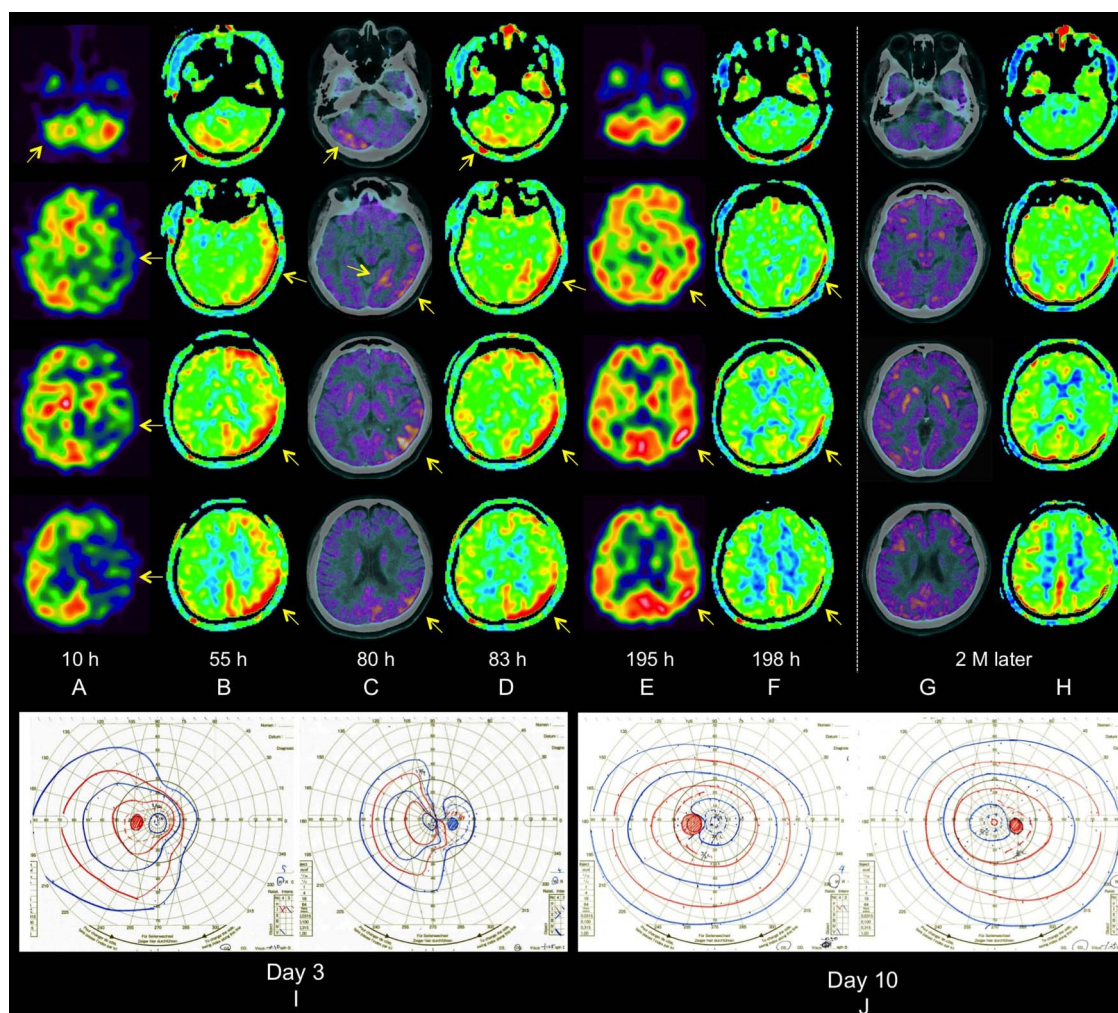
AH, auditory hallucination; BT, body temperature; CBF, cerebral blood flow; CCA, crossed cerebellar activation; CCD, crossed cerebellar diaschisis; DWI, diffusion-weighted MRI, F, frontal; HMPA, hemiplegic migraine with prolonged aura; HMPAO, 99mTc-d, I-hexamethyl-propyleneamine oxime; HP, hemiparesis; HSD, hemisensory deficit; IMP, N-isoprpyl-p-1231 iodoamphetamine; IVMP, intravenous high-dose methylprednisolone; L, left; LVA, low-voltage activity; MCA, middle cerebral artery; NA, not available; O, occipital; P, parietal; PSL, prednisone; Psy; psychiatric symptoms; R, right; T, temporal; VFD, visual field defect; VH, visual hallucination.

day, 3–5 days) or intravenous high-dose methylprednisolone (1000 mg/day, 3 days) followed by short taper-off (table 1). The rationale of corticosteroid therapy was based on our experience on dramatic response of symptoms to corticosteroids at the second attack of *patient 1* when brain MRI showed augmented vasogenic leakage in the sulci of the affected cortex with minimum oedema on day 4.<sup>19</sup> Headache and associated symptoms resolved spontaneously or following corticosteroid therapy. Aura symptoms persisted for 4–12 days (median 7 days) and were fully reversible. Once the symptoms improved, each patient began to receive lomerizine (10 mg/day), topiramate (100 mg/day), lamotrigine (25–100 mg/day), amitriptyrine (10 mg/day) or combinations of these drugs. Amitriptyrine and topiramate, which were given in *patients 1 and 2*, were not tolerated and discontinued. All patients received lomerizine and lamotrigine as prophylactic treatment. Prophylactic treatment started after resolution of aura symptoms (not before CBF studies).

### Neuroimaging findings

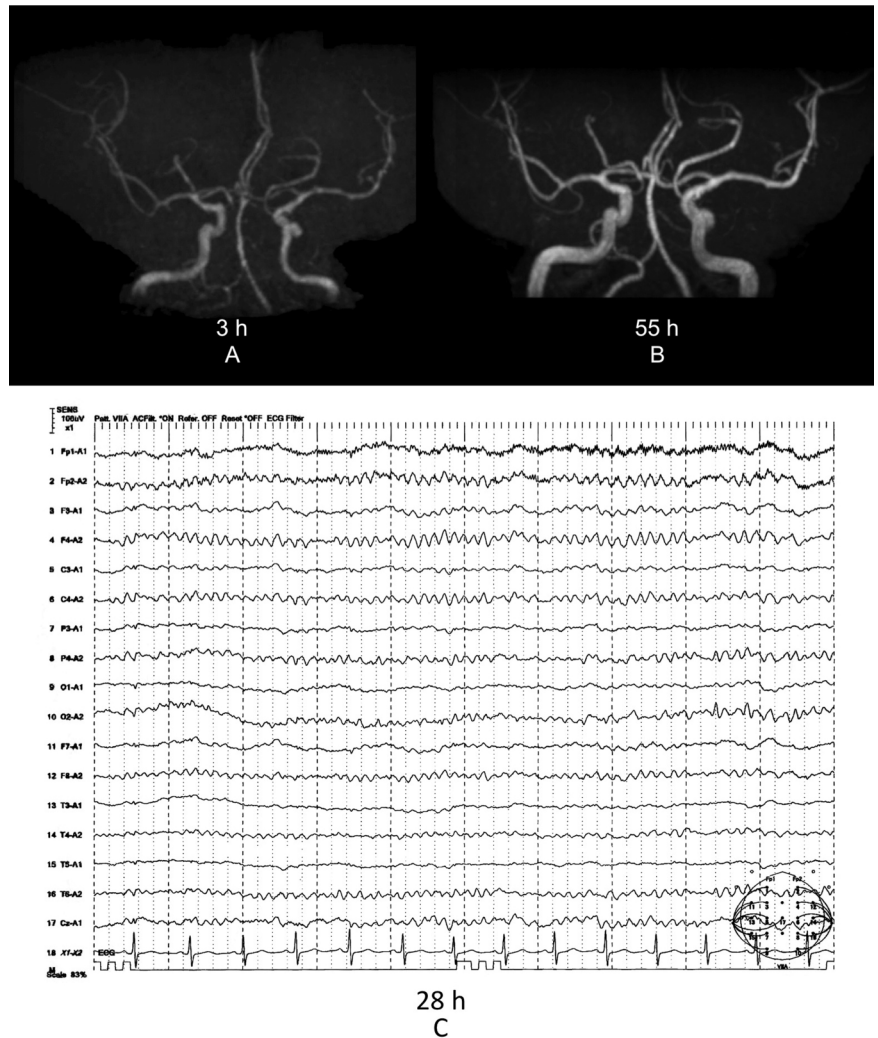
#### *Biphasic CBF changes in the acute phase of HMPA (patient 1)*

We confirmed biphasic neurovascular changes in the acute phase of the seventh attack of HMPA (figures 2 and 3). Approximately 2 weeks before admission, the patient began to have increasing appetite for chocolate, daytime sleepiness and work-related stress. On the day of admission, at 6:00 she began to have vomiting and headache followed by confusion, difficulty talking and right arm weakness. She was brought to the emergency room. On examination the temperature was 38.1°C; she was in delirious state with global aphasia, right visual field defect and right arm weakness. Initial MRI and MRA were unremarkable. After IMP-SPECT, she began to receive corticosteroids (60 mg/day). The next day, headache and aphasia markedly improved but right visual field defect and mild right arm weakness persisted. EEG on day 2 revealed attenuated alpha activity in the left cerebral hemisphere (figure 3C). Goldmann perimetry on



**Figure 2** Serial neurovascular changes and Goldmann perimetry in the acute phase of the seventh attack of hemiplegic migraine with prolonged aura (*patient 1*). IMP-SPECT shows marked reduction in blood flow in the affected left cerebral hemisphere with crossed cerebellar diaschisis (A). Arterial spin labelling-MRI (ASL-MRI) shows hyperperfusion in the affected left cerebral hemisphere with crossed cerebellar hyperperfusion (B, D). FDG-PET shows increased glucose metabolism in the affected hemisphere with crossed cerebellar hypermetabolism (C). Focal hyperperfusion is still seen in the left temporal cortex (E, F). Follow-up studies obtained 2 months later show no abnormal finding (G, H). Goldmann perimetry on day 3 reveals a right homonymous hemianopsia with macular sparing (I), but the visual field is normal on day 10 (J). A and E are IMP-SPECT, B, D, F and H were ASL-MRI, and C and G are FDG-PET, respectively. The yellow arrows show the affected cerebral hemisphere. A timing of each study from symptom onset is shown below each brain imaging.

**Figure 3** MR angiography (MRA) and EEG obtained in the acute phase of the seventh attack of hemiplegic migraine with prolonged aura (*patient 1*). Initial MRA shows no apparent laterality of the middle cerebral artery (MCA) and its branches (A, 3 h after symptom onset). Follow-up MRA shows mild vasodilatation of the left MCA (B, 55 h after symptom onset). EEG on day 2 reveals low-voltage activity with attenuation of alpha rhythm in the left affected cerebral hemisphere (C, approximately 28 h after symptom onset).



day 3 revealed a right homonymous hemianopsia with macular sparing (figure 2I), but on day 10 the visual field was normal (figure 2J). Aura symptoms completely resolved on day 9 but mood change and mild headache persisted. Follow-up EEG on day 9 revealed relatively low-voltage alpha activity in the left hemisphere, but photic driving response was seen.

IMP-SPECT obtained 10 h after symptom onset showed extensive hypoperfusion in the left cerebral hemisphere with crossed cerebellar diaschisis (CCD) (figure 2A). However, subsequently performed ASL-MRI revealed hyperperfusion with crossed cerebellar hyperperfusion (figure 2B, D). The follow-up MRA revealed mild vasodilatation of the left middle cerebral artery (MCA) (figure 3B). Mild hyperperfusion also persisted on day 9 (figure 2E, F). Despite the presence of prolonged neurological deficits, FDG-PET on day 4 showed increased glucose metabolism in the area of hyperperfusion with crossed cerebellar hypermetabolism (figure 2C). Two months later, brain imaging was normal.

#### Biphasic CBF changes in the acute phase of HMPA (*patient 3*)

We also confirmed biphasic CBF changes in the second attack (figure 4). On the day of admission, at 7:40, the patient presented with difficulty talking without headache or weakness. She was brought to the emergency room. On examination the temperature was 38.5°C. Neurological examination showed aphasia, right visual field defect but no apparent weakness.

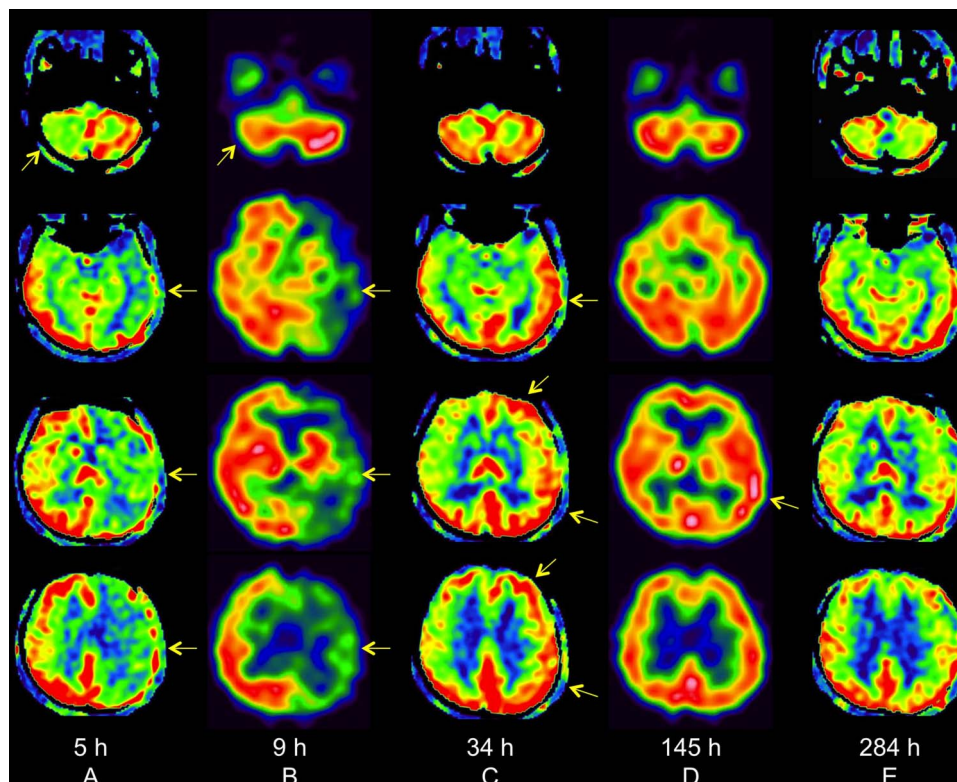
After ASL-MRI and IMP-SPECT, she began to receive corticosteroids (50 mg/day). The next day, she became able to talk slowly and reported her headache as 8/10 in intensity. All symptoms resolved on day 5 but mild headache persisted.

Initial CBF studies obtained within 9 h of symptom onset showed hypoperfusion with CCD (figure 4A, B), but the follow-up ASL-MRI obtained 34 h of symptom onset revealed hyperperfusion (figure 4C). Mild hyperperfusion still persisted on day 7 (figure 4D).

#### Relationship between CBF changes and timing of CBF measurement

Representative two axial images were plotted according to the intervals between symptom onset and CBF studies. Individual imaging of *patients 1, 2 and 3* is shown in panels A, B and C, respectively (figure 5).

In panel A, CBF data obtained from seven attacks are shown. The first four SPECT obtained within 19 h of symptom onset showed marked hypoperfusion in the affected hemisphere. In contrast, the remaining studies obtained 24 h or later showed hyperperfusion. In panel B, both SPECT showed unilateral hyperperfusion in the affected hemisphere, but both studies were performed 19 h or later after presentation. In panel C, the first two studies obtained within 9 h of symptom onset showed hypoperfusion, but other studies obtained 18 h or later showed hyperperfusion.



**Figure 4** Serial neurovascular changes in the acute phase of the second attack of hemiplegic migraine with prolonged aura (*patient 3*). Both arterial spin labelling-MRI (ASL-MRI) and IMP-SPECT show marked reduction in blood flow in the affected left cerebral hemisphere with crossed cerebellar diaschisis (A, B). Follow-up ASL-MRI shows hyperperfusion in the affected left cerebral hemisphere (C). Focal hyperperfusion is still seen in the left temporal cortex (D). No abnormal hyperperfusion is seen (E). A, C and E are ASL-MRI, and B and D are IMP-SPECT. The yellow arrows show the affected cerebral hemisphere. A timing of each study from symptom onset is shown below each brain imaging.

As shown in [figure 5](#), it may be summarised that hypoperfusion was seen within 19 h of symptom onset in 5 of 7 attacks (71.4%) while hyperperfusion was seen 18 h or later in 8 of 9 attacks (88.9%), but data were not assessed by statistical analyses.

#### Multifocal reduction of CBF in the early phase of HMPA

We assessed surface distribution of CBF using Z-score maps in 9 of 11 attacks ([figure 6](#)). Decrease z-score map revealed multifocal reduction in the affected hemisphere when CBF was measured within 10 h of symptom onset in four attacks. In contrast, we found multifocal or widespread hyperperfusion in the affected hemisphere after 19 h or later, in some of which ipsilateral vasodilatation was seen on MRA ([table 1](#)).

#### EEG

EEG on day 1–4 showed low-voltage activity with attenuation of alpha rhythm in the affected hemisphere ([figure 3C](#)), but no apparent paroxysmal discharge was seen. Photoc driving response was also absent in the affected hemisphere when the patients had visual blurring or visual field defect. In two attacks (the sixth and seventh attacks of *patient 1*), slowing wave was more marked in the non-affected hemisphere than in the affected hemisphere when the patient had prominent psychiatric symptoms that required propofol infusion. These findings were reversible. We did not find difference in EEG pattern between day 1 and day 2 or later.

#### DISCUSSION

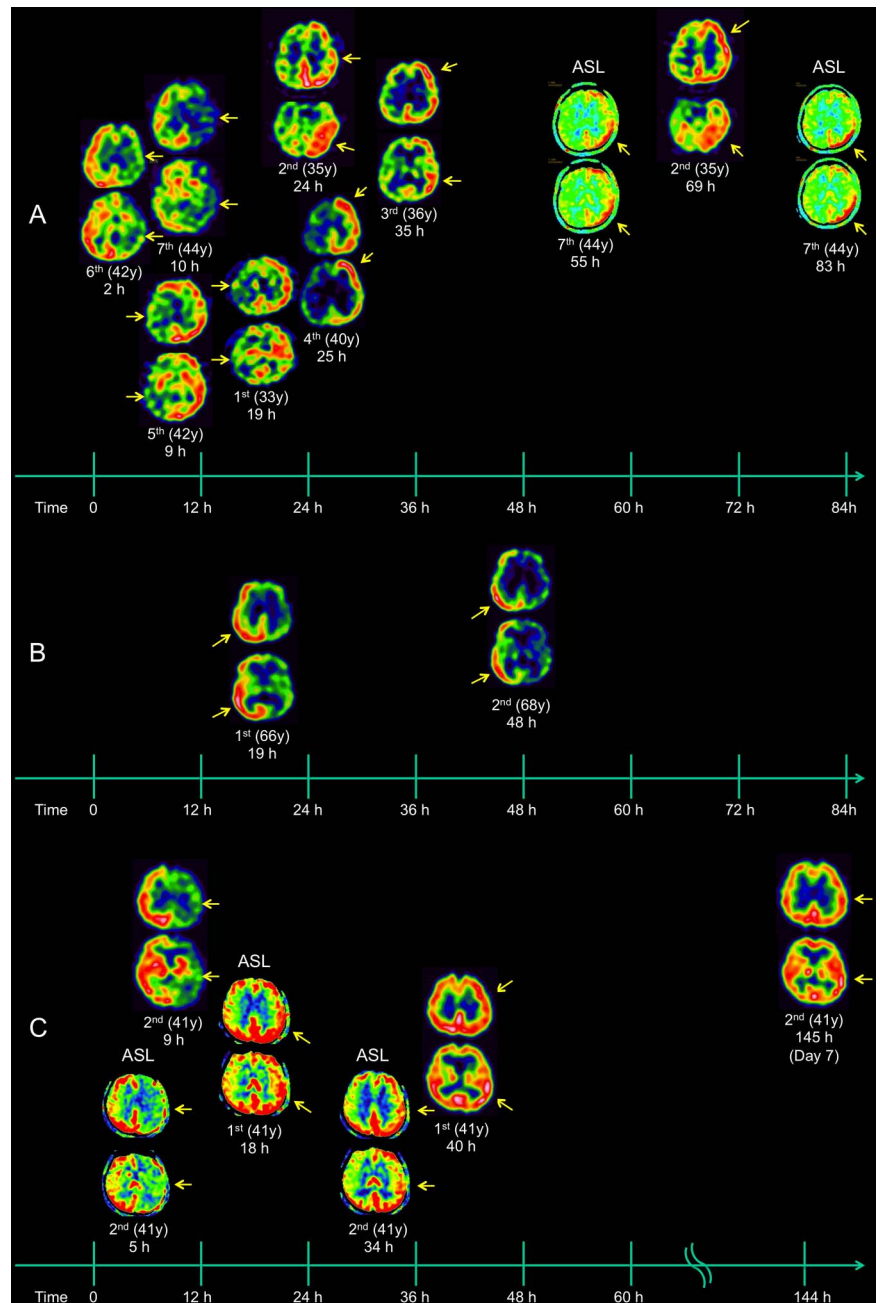
This study revealed several aspects. First, in two attacks of HMPA, we confirmed similar biphasic CBF changes in the

affected hemisphere. Second, in four attacks, Z-score maps revealed multifocal hypoperfusion in the affected hemisphere corresponding to aura symptoms in the early phase when aura symptoms were evolving. Third, in one attack, FDG-PET showed increased glucose metabolism in the affected regions with crossed cerebellar hypermetabolism when aura symptoms persisted. Finally, this study disclosed that there might be a turning point in transition from hypoperfusion to hyperperfusion approximately 18–19 h of aura symptom onset of HMPA.

This study is the second report on neurovascular changes in the acute phase of HMPA in this family. Clinical features and a possible role of the mutation were previously reported.<sup>22</sup> In this study, we focused on temporal neurovascular changes in the acute phase and re-evaluated all the data based on the intervals from symptom onset to CBF measurement in order to address the issues; why the previous studies showed a reversed CBF pattern despite clinically similar attack, and what is a major factor that affects CBF.

Each patient had individual ‘predominantly or exclusively affected hemisphere, as has been known in hemiplegic migraine.’<sup>23</sup> We previously reported that hyperperfusion more frequently developed than hypoperfusion in the ‘predominantly affected hemisphere’ (83% vs 17%) while only hypoperfusion developed in the ‘non-predominantly affected hemisphere’ and then speculated that a tendency of hyperperfusion in the ‘predominantly affected hemisphere’ may reflect clustering of SD in the affected hemisphere intrinsically susceptible to hemiplegia.<sup>22</sup> However, in the previous study, we did not repeat SPECT within a short period of time because of the half-life of <sup>123</sup>I (13.2 h). Therefore, we repeatedly measured CBF with non-invasive

**Figure 5** Blood flow imaging obtained from three patients in the acute phase of hemiplegic migraine with prolonged aura (HMPA). Two selected, representative axial images are plotted according to the intervals between the onset of aura symptoms and cerebral blood flow (CBF) measurement. Data of *patients 1, 2* and *3* are shown in A–C, respectively. Hypoperfusion was frequently seen within 19 h of symptom onset in 5 of 7 attacks of HMPA (71.4%) while hyperperfusion was seen 18 h or later in 8 of 9 attacks of HMPA (89%). The yellow arrows show the affected cerebral hemisphere. The serial number of HMPA and timing of each study from symptom onset are shown below each brain imaging. The age at onset of each attack of HMPA is shown in the parentheses. ASL indicates axial images of ASL-MRI.



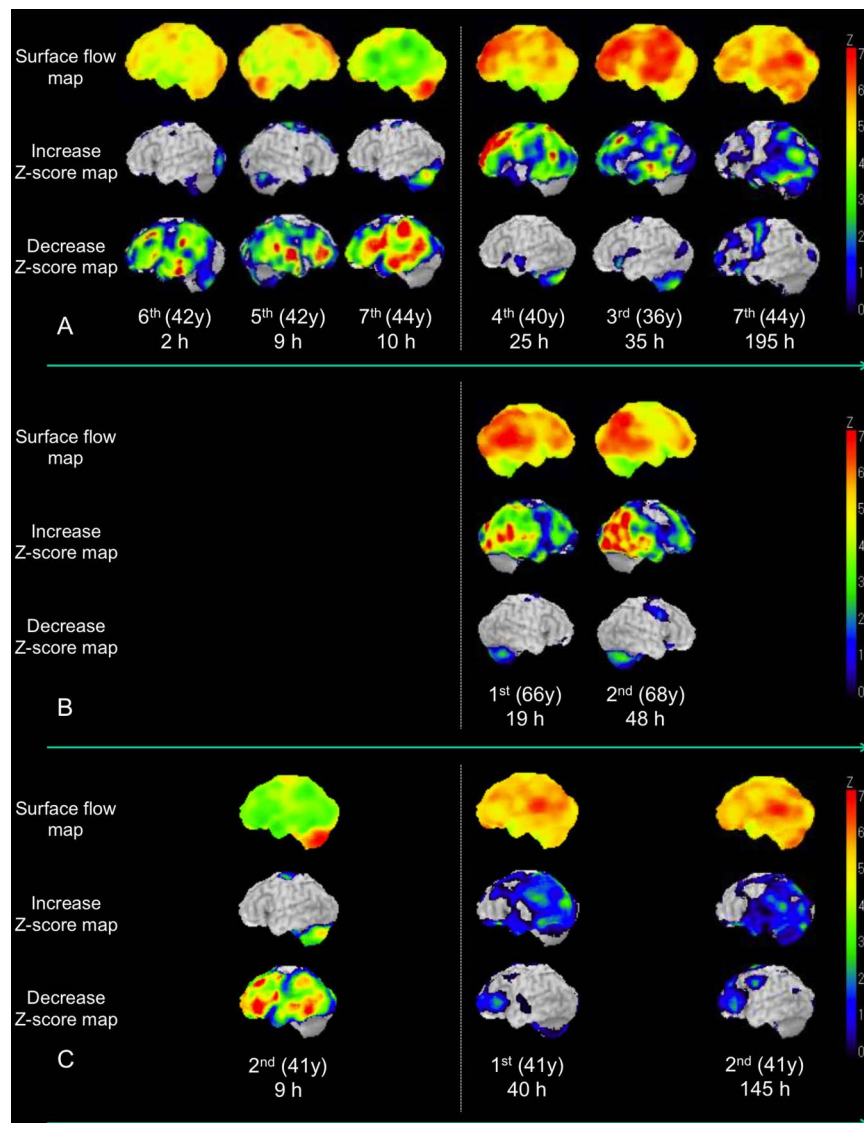
ASL-MRI. As a result, we found hyperperfusion in up to 8 of 9 attacks (89%) and hypoperfusion in 3 of 9 attacks (33%) in the ‘predominantly affected hemisphere’. But CBF was not measured earlier than 18 h of symptom onset in 6 of the 9 attacks, thus we might have missed hypoperfusion in these attacks. In contrast, in the ‘non-predominantly affected hemisphere’, only hypoperfusion was found, but no SPECT was obtained after 19 h of symptom onset; therefore, hyperperfusion might have been missed. This retrospective study indicated that perfusion pattern is more likely associated with the timing of CBF measurement.

It is of importance that biphasic CBF pattern was confirmed in two patients. This finding indicates that CBF changes quickly within a day of the onset of symptoms, and the results of cross-sectional CBF study should be interpreted cautiously. The concept of biphasic CBF changes is supported by whole data in our series. Delayed hyperperfusion following hypoperfusion has

been reported since 1988,<sup>24</sup> but the imaging resolution was poor at that time. Based on these data, CBF changes may be divided into two phases: hypoperfusion and hyperperfusion.

Based on the current understanding of the mechanism of hemiplegic migraine,<sup>2–25</sup> hypoperfusion is likely due to functional depression reflecting cortical or subcortical SD. In typical visual aura, reduction in CBF usually starts posteriorly and spreads anteriorly; however, in hemiplegic migraine, language, weakness, sensory or visual symptoms occur simultaneously or in succession. Multifocal hypoperfusion on Z-score maps closely related to rapid progression of each aura symptom implies that hemiplegic migraine aura may reflect SD of multifocal origin arising from a different part of the affected hemisphere. It is difficult to detect SD with surface EEG in human, but less-responsive attenuated EEG activity in the affected hemisphere is compatible with functional depression. There is coupling between brain function and CBF in the early hypoperfusion

**Figure 6** Z-score maps obtained in the acute phase of hemiplegic migraine with prolonged aura (HMPA) of patients 1, 2 and 3. Surface flow map, increase Z-score map and decrease Z-score map of the affected cerebral hemisphere of each attack of HMPA are shown. Z-score maps obtained from patients 1, 2 and 3 are shown in A–C, respectively. Decrease Z-score map obtained within 18 h of symptom onset shows multifocal reduction in cerebral blood flow (CBF) in the affected cerebral hemisphere corresponding to aura symptoms (A, C), whereas increase Z-score map obtained 19 h or later shows hyperperfusion. A broken vertical line separates hypoperfusion and hyperperfusion phase. The serial number of HMPA and timing of each study from symptom onset are shown below each brain imaging. The age at onset of each HMPA is shown in the parentheses.



‘aura evolution phase’. However, subsequent hyperperfusion (and/or hypermetabolism) does not seem to couple with functional depression in the late hyperperfusion ‘prolonged aura phase’. Although sustained cortical hypoperfusion has been reported in persistent visual aura without infarction,<sup>26</sup> HMPA in our patients is not identical to persistent aura without infarction.

The mechanism underlying hyperperfusion remains unknown. One might argue that late hyperperfusion is a non-specific epiphenomenon due to compensatory mechanism following hypoperfusion. However, there is no convincing evidence supporting this hypothesis. One might also concern about drug effect; topiramate is a carbonic anhydrase inhibitor,<sup>27</sup> and lomerizine has a vasodilator effect.<sup>28</sup> These drugs may have altered cerebrovascular physiology; however, hyperperfusion on days 2 to 4 in the previous study<sup>22</sup> was observed before initiation of the treatment with corticosteroids, topiramate or lomerizine. Therefore, drug effect is not likely a cause of hyperperfusion.

CBF is tightly regulated by both intrinsic neuronal activity and extrinsic nerve innervations,<sup>29</sup> the parenchymal arterioles are controlled by a local synaptic activity through neuron–astrocyte communication,<sup>30–31</sup> whereas the surface blood vessels are controlled by both trigeminal and autonomic innervations through

neuropeptides, including calcitonin gene-related peptide (CGRP), acetylcholine, neuropeptide Y, vasoactive intestinal polypeptide (VIP) and others.<sup>32</sup> Cortical SD has been shown to activate not only peripheral but also central trigeminovascular system, causing headache and associated symptoms.<sup>33–34</sup>

Based on these basic neurovascular anatomical relationships, we previously assumed that unilateral hyperperfusion with vasodilatation of the surface blood vessels in the affected hemisphere might be in part due to sustained activation of the trigeminovascular system that is driven by cortical SD.<sup>22</sup> However, extrinsic trigeminovascular activation alone cannot account for increased glucose metabolism. To explain this, intrinsic activation of neurons and/or astrocytes may be taken into account, which leads to an increase of both glucose uptake of astrocytes and release of vasodilatory substances from perivascular endfeet, such as epoxyeicosatrienoic acid, adenosine, nitric oxide and cyclooxygenase-2 metabolites, resulting in increase in blood flow.<sup>35</sup> Glucose, which is taken up by astrocytes, is converted into lactate and released for neurons as an energy substrate (astrocyte–neuron lactate shuttle hypothesis<sup>36</sup>).

Epileptic seizure may explain both hyperperfusion and hypermetabolism; however, in our series, neither epileptic seizure nor paroxysmal discharge was seen, thus the absence of epileptic



seizure does not support neuronal activation. The mechanism underlying paradoxically increased glucose metabolism despite prolonged neurological deficits remains elucidated. In the current hypothesis of FHM2, ATP1A2, which is primarily expressed in astrocytes, is essential in the clearance of released glutamate and potassium from the extracellular space during neuronal activity. FHM2 mutations that cause loss of function of ATP1A2 are considered to lead to decreased glutamate clearance and an increase of potassium in the synaptic cleft, which may increase susceptibility to cortical SD.<sup>37, 38</sup> Therefore, sustained increase of extracellular glutamate may contribute to sustained activation of astrocytes that leads to increased glucose metabolism by increasing glucose uptake from astrocytes despite prolonged neurological deficits.

Other important findings include the presence of premonitory symptoms, fever and prominent psychiatric symptoms. Two patients reported long-lasting premonitory symptoms before the onset of attacks. These symptoms are more likely associated with functional alteration of hypothalamus, but we did not have a chance to evaluate blood flow or metabolism in the premonitory phase. Fever associated with rapid evolution of aura symptoms or headache may also suggest hypothalamic dysfunction, but our studies did not show marked blood flow changes in the deep brain structure. Psychiatric symptoms are not generally considered as aura symptoms; however, increased fear or anxiety has been shown in FHM2 animal models<sup>38</sup> and psychotic aura symptoms have been described in FHM2.<sup>39</sup> Therefore, psychiatric symptoms in the acute phase might be a spectrum of aura symptoms and may have been underestimated in FHM2. Further study will be required.

There are various limitations. First, the patient's number is very small due to the rarity of the disorder. Second, attacks were recorded multiple times among the same patients. Different attacks with long interictal intervals up to years were not likely related to each other; however, we cannot completely exclude the possibility that different attacks in the same patient might be somewhat related to each other. Other issues include retrospective collection of data, necessary upgrades of the different imaging modalities with long duration of follow-up, including some biases in data collection, inconsistency of acquisitions type and timing for the different attacks. We did not assess neurovascular changes in terms of headache-related changes. The aura symptoms and headache occurred almost simultaneously or one after another, headache and mood changes often lasted longer than aura symptoms. Neurovascular changes, particularly of CBF, are more likely associated with aura symptoms rather than headache itself. Our study gives the rationale for further studies to clarify the mechanism underlying prolonged aura in hemiplegic migraine.

**Acknowledgements** We are extremely grateful to all participants for their contribution to this study and acknowledge the efforts of research staffs, who worked on the clinical, genetic and neuroimaging data collection. We particularly thank Professor Shoji Tsuji, Yuji Takahashi and Yoshio Momose in Department of Neurology, Graduate School of Medicine, University of Tokyo, for their genetic analysis in this family. This work was in part supported by Grants-in-Aid of the Research on Intractable Diseases (Mitochondrial Disorder) from the Ministry of Health, Labour and Welfare of Japan.

**Contributors** TI and FS equally contributed to drafting and revising the manuscript, data collection, study concept and interpretation of data. NT, JK, MS, TA, JH and KN equally contributed to data collection, interpretation of data and revising the manuscript.

**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** The previous genetic study as stated in the manuscript.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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