Biphasic neurovascular changes during prolonged hemiplegic migraine aura in FHM2

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Disclosure

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Objective

✓ To report time-dependent neurovascular changes in hemiplegic migraine with prolonged aura (HMPA) in a single Japanese family of FHM2.
This patient had migraine since 12 y of age. Since 20 y of age visual aura developed with headache, which was accompanied by right hemiparesis and aphasia. One day before admission, the patient began to have headache and vomiting, and 2 hr later she noticed stiffness in the right arm and difficulty in talking. Next day she was admitted to our hospital. On admission she had aphasia, right visual field defect and right arm weakness, and she lapsed into a delirium state.
We reported extensive hyperperfusion with augmented vasogenic leakage in the affected cortex corresponding to prolonged aura lasting more than 24 hours\textsuperscript{1}.

Case presentation

We reported extensive hyperperfusion with augmented vasogenic leakage in the affected cortex corresponding to prolonged aura lasting more than 24 hours.

HMPAO-SPECT (on admission)

DWI (on admission)

Case presentation

✓ Sustained activation of the trigeminovascular system following CSD might cause augmented vasogenic leakage and edema resulting in the delay of spontaneous recovery of brain dysfunction¹.

Four years later, her mother, who denied of having migraine, was admitted to our hosp. with hemiplegic migraine at the age of 66 years.
Gene analysis

- Mutational analysis for all exons of the CACNA1A, ATP1A2 and SCN1A genes in 3 subjects (at The University of Tokyo).

We identified a novel heterozygous p.H916L mutation in the exon 20 of the ATP1A2 gene in all 3 subjects.
We identified a novel heterozygous p.H916L mutation in the exon 20 of the ATP1A2 gene in all 3 subjects. This mutation was located at the 8th inter-membrane domain of the ATP1A2 protein, which belongs to the subfamily of Na⁺/K⁺-ATPase.
Results

- We reviewed neuroimaging studies during acute stage of 9 attacks of hemiplegic migraine with prolonged aura (HMPA) in 2 subjects.
- Each patient had an individual predominantly affected hemisphere.
- Aura symptoms lasted 4 to 12 days (median 8 days).

<table>
<thead>
<tr>
<th>Patient</th>
<th>Patient #1 (proband), 45 y</th>
<th>Patient #2 (mother), 72 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serial no.</td>
<td>1\textsuperscript{st}, 33 y</td>
<td>2\textsuperscript{nd}, 35 y</td>
</tr>
<tr>
<td>BT (°C)</td>
<td>38.5</td>
<td>37.8</td>
</tr>
<tr>
<td>Affected hemisphere</td>
<td>R</td>
<td>L</td>
</tr>
<tr>
<td>Neurologic symptoms</td>
<td>confusion, L HP, VH, Psy</td>
<td>confusion, R HP, aphasia, R VFD, VH, Psy</td>
</tr>
<tr>
<td>Aura duration (d)</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

AH: auditory hallucination, BT: body temperature, HP: hemiparesis, HSD: hemisensory deficit, L: left, Psy: psychiatric symptoms, R: right, VFD: visual field defect, VH: visual hallucination

- In 7 of 9 attacks, the patients received corticosteroids, which appeared effective.
Results

* We reviewed neuroimaging studies during acute stage of 9 attacks of hemiplegic migraine with prolonged aura (HMPA) in 2 subjects.
* Each patient had an individual predominantly affected hemisphere.
* Aura symptoms lasted 4 to 12 days (median 8 days).
* Based on the 9 attacks (Patient #1 and #2), we reported a high incidence of hyperperfusion in the affected hemisphere.
Which cerebral hemisphere is really affected?

Right arm weakness, aphasia, right VF defect, delirium

Left arm weakness, left VF defect, delirium

We determined the affected hemisphere clinically.

The cause of the reversed flow pattern was not elucidated.
To clarify the cause of the revised flow pattern, we assessed serial changes in CBF in additional 3 attacks of 2 patients (Patients #1 and #3) with IMP-SPECT, ASL-MRI*, or FDG-PET.

We re-evaluated all data obtained from 3 patients based on the intervals between the onset of aura symptoms and CBF measurement.

* ASL-MRI was obtained with pseudo-continuous ASL (pCASL).
This patient was brought to the emergency room 2 h after the onset of presentation. On exam., she had **aphasia, right visual field defect and right arm weakness.**
Low voltage activity with attenuation of alpha rhythm in the left cerebral hemisphere.

28 h after symptom onset (day 2)
She received prednisone (60 mg) followed by tapered off.

All symptoms resolved on day 9.
CBF changes

Turning point

Symptoms and signs

Time 0  24h  48h  72h  96h  120h  144h  168h  192h  216h

EEG 28h

10h  55h  80h  83h  195h  198h (day 9)
Both CBF and cerebral glucose metabolism were increased during acute stage but normal during interictal state.

CCA was found.

These findings cannot be explained by trigemino-vascular activation alone.

Increased synaptic activation may contribute to these neurovascular changes.
Changes in CBF during acute stage of 7 attacks of HMPA (Patient #1: a proband)

Each image is plotted according to the intervals.

A turning point in transition from reduction in flow to hyperperfusion 19-24 h after onset of HMPA
CBF changes during acute stage of 2 attacks of HMPA (Patient #2: her mother)

A turning point in transition from reduction in flow to hyperperfusion 19-24 h after onset of HMPA
CBF may increase earlier than 19 h of symptom onset.
CBF changes during acute stage of 2 attacks of HMPA (Patient #3: her younger sister)

Time

Symptoms and signs

CBF changes

1st (41y)
CBF changes during acute stage of 2 attacks of HMPA (Patient #3: her younger sister)

A turning point: 12-18 h after onset of aura symptoms
Summary of 11 attacks
A: Patient #1, 7 attacks

*Hypoperfusion, suggesting biphasic changes in CBF*

✓ Hypoperfusion was transiently seen *within 19 h of the onset of aura symptoms while hyperperfusion was seen 18 h or later.*

C: Patient #3; 2 attacks
Summary of 3D-SSP Z-score maps

A: Patient #1, 5 of 7 attacks

**Multifocal reduction in CBF in 4 attacks**

- Early multifocal reduction in CBF may reflect **CSD of multifocal origins** simultaneously arising from different parts of the affected hemisphere.

C: Patient #3; 2 attacks
This study suggests that the results of cross-sectional CBF studies should be interpreted carefully.

Initial multifocal hypoperfusion is likely due to functional depression of multifocal origins in the affected hemisphere.

Surface blood vessels and parenchymal arterioles receive different nerve innervation.

Surface blood vessels receive extrinsic nerve innervation, such as trigeminal and parasympathetic nerves.

Parenchymal arterioles receive intrinsic nerve innervation through neuron-astrocyte communication, which is dependent on synaptic activity.

Aura evolution phase: Prolonged aura phase

- Early hypoperfusion is likely to reflect spreading depression or oligemia.
- What is the mechanism underlying sustained hyperperfusion?

- Hyperperfusion with prominent vasodilatation might be in part due to sustained activation of the trigemino-vascular system, including the trigemino-parasympathetic reflexes.
- Hyperperfusion with increased glucose metabolism cannot be explained by trigeminovascular activation alone. Increased activation of synapses or astrocytes may also contribute to hyperperfusion.
- Aura symptoms and headache develop simultaneously or one after another, but these neurovascular changes are more likely associated with aura symptoms rather than headache itself.

ASL-MRI
- Patient #3 (2nd) 5 h → 34 h

FDG-PET
- Patient #1 (7th) 80 h → Patient #1 (2nd) 83 h

CBF-SPECT
- Patient #1 (2nd) 24 h

Gad-FLAIR
- Patient #1 (2nd) day 4
Neuronal Panx1 channel opening, followed by HMGB1 release….

Aura evolution phase
Multifocal hypoperfusion
Multifocal CSD

Prolonged aura phase
Sustained hyperperfusion
Trigeminovascular & astrocytic activation
Conclusion

- We reported biphasic neurovascular changes during prolonged hemiplegic migraine aura.
- Initial multifocal hypoperfusion is likely due to CSD of multifocal origin, but the mechanism of subsequent persistent hyperperfusion requires further investigation.
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