Ictal-Interictal Comparison of FDG-PET Findings in Sporadic Hemiplegic Migraine

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Abtract

Purpose: Sporadic hemiplegic migraine (SHM) is characterized by a prolonged motor aura that accompanies a migraine attack, and its underlying pathophysiology remains unclear. Functional image during the event can help to explore the mechanism.

Case report: We report a finding of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) in a 15-year-old female with SHM. She presented with recurrent right arm weakness and pain with migrainous headache. A video electroencephalogram showed no evidence of epilepsy during the events. Subtraction of ictal-interictal FDG-PET coregistered to magnetic resonance imaging was performed for the image analysis. In comparison with the interictal state, the FDG-PET image showed decreased glucose metabolism in the bilateral dorsal lateral frontal cortices and bilateral occipital cortices, whereas increased metabolism in the left precentral motor cortex and right premotor cortex.

Conclusion: These findings reveal an increase in metabolism in the motor cortex during general cortical dysfunction in the frontal and occipital cortices in SHM.

Key words: FDG-PET, hemiplegic migraine, migraine, positron emission tomography, SISCOM

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INTRODUCTION

Hemiplegic migraine (HM) is defined as fully reversible motor weakness that lasts less than 72 hours accompanied by headache according to the criteria of the newly revised International Classification of Headache Disorder III (ICHD-III), which was released in 2018[(1)]. "Sporadic" hemiplegic migraine (SHM) is differentiated from “familial” hemiplegic migraine (FHM) on the basis of there being no first- or second-degree relative with HM[(1)].

SHM is an etiologically heterogeneous disorder. The pathophysiology is still unclear and is probably related

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to cortical spreading depression (CSD), which indicates neuronal metabolic dysfunction[2]. Based on metabolic imaging, there was a report of 18-fluorodeoxyglucose positron emission tomography (FDG-PET) of reversible hypometabolism in the contralateral cortex compatible with the concept of CSD[3]. On the other hand, there was also a report of hypermetabolism during an SHM[4].

To clarify this issue, we report a patient with SHM whose ictal-interictal FDG-PET was substracted and coregistered with magnetic resonance imaging (MRI). Comparison maps were obtained between these FDG-PET images.

CASE REPORT

A 15-year-old girl with SHM visited Taipei Veterans General Hospital in 2017. She presented with recurrent right distal arm weakness twice a week that each time lasted for approximately 3 hours to 3 days. The HM attack started with right limb weakness and pain. A throbbing headache in the right temporal region soon developed. The headache was moderate to severe in intensity, aggravated by physical activity and accompanied by nausea, vomiting, photophobia and phonophobia. The headache disappeared before the weakness subsided. Diclofenac (75 mg) and sumatriptan (50 mg) were used during the events. Valproate (200 mg) and flunarizine (5 mg) were first prescribed once daily for preventive treatment. We shifted to verapamil (120 mg) once daily due to frequent attacks. The brain MRI was normal and without evidence of acute infarction. A video electroencephalogram (EEG) was performed over three consecutive days. Two episodes were recorded, and the EEG showed no changes compared to baseline during the events, and no focal abnormality or unequivocal epileptiform discharge was observed in the interictal stage.

FDG-PET was acquired during and after the headache (36 hours after onset and 24 hours after the headache and weakness subsided). The FDG-PET image analysis consists of 4 steps, as shown in Fig. 1. The details of each step were described as follows.

Step 1.

Registration The ictal-interictal FDG-PET was coregistered to the high-resolution structural MRI via 3D voxel registration using the normalized mutual information method to correct for differences resulting from head movement[5].

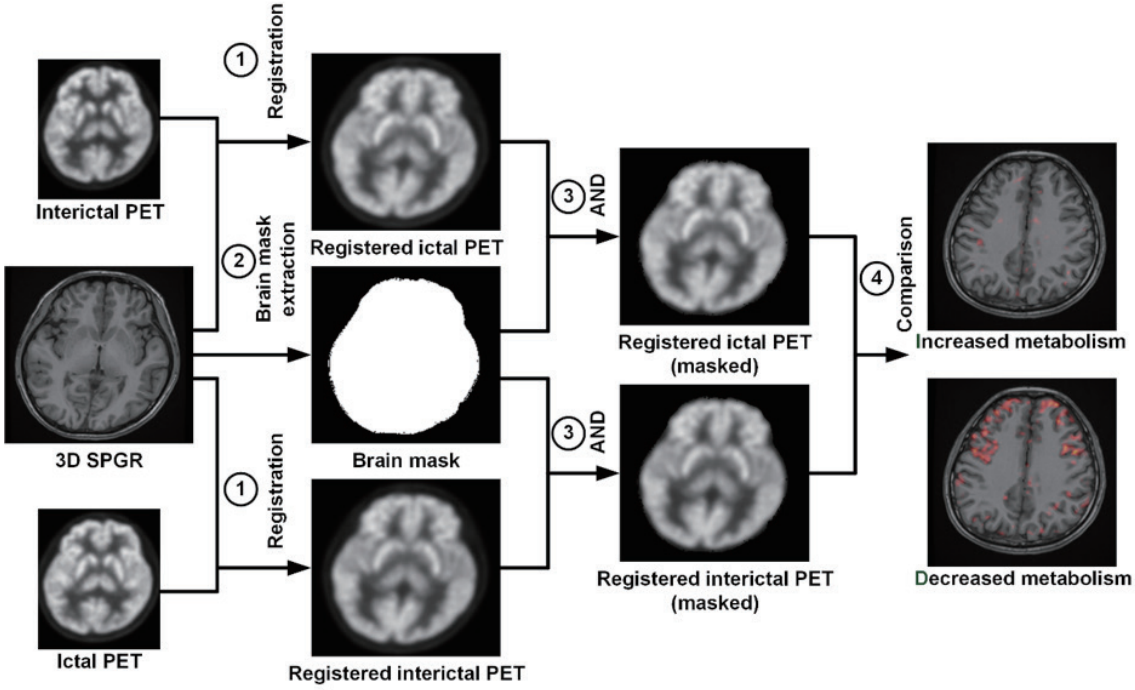

Figure 1: Schematic diagram showing the workflow employed for FDG-PET image analysis. The process included four steps: registration, brain mask extraction, ROI definition, and comparison between ictal and interictal state FDG-PET.

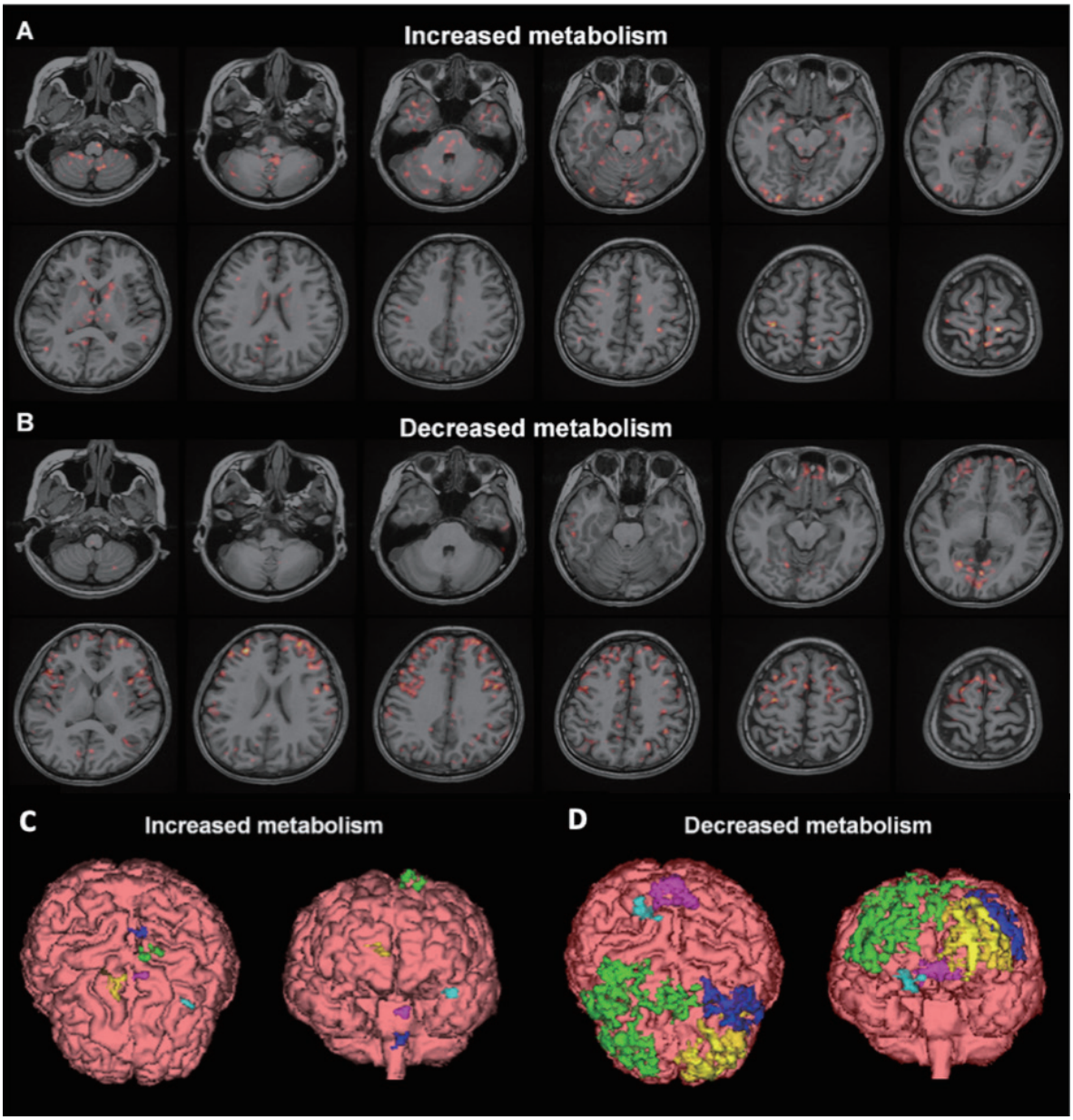

Figure 2: The ictal and interictal state FDG-PET comparison results superimposed on the high-resolution structural MR image. The red shadows showed increased metabolisms in the left pre-central region (A), and decreased metabolisms in the bilateral dorsal lateral frontal cortices and bilateral occipital cortices (B). The changes of metabolisms were shown on a 3D rendering of brain MR images using the following parameters: activation threshold (%) = 10, maximum activation objects = 5, and minimum activation size = 10 (C, D).

Step 2.

Brain mask extraction A brain mask was extracted from MRI based on estimates of the inner and outer skull surfaces using Brain Extraction Tool, a software package developed at the Center for Functional MRI of the Brain, University of Oxford, Oxford, United Kingdom[6].

Step 3.

Region of interest (ROI) definition The ROI was identified using a logical and operation that was applied to the coregistered ictal-interictal FDG-PET and brain mask, respectively.

Step 4.

Comparison The comparison between the ictal and interictal FDG-PET was performed using Subtraction Ictal Single-Photon Emission Computed Tomography (SPECT) Coregistered to MRI (SISCOM) software[7] in ANALYZE 12.0 imaging software (AnalyzeDirect, Overland Park, KS, United States) to measure the increases and decreases in metabolism. The activation level threshold was set to a standard deviation of 1.5.

The results revealed reduced metabolism in the bilateral dorsal lateral frontal cortices and bilateral occipital cortices and increased metabolism highest in the left precentral motor cortex followed by right premotor cortex during the HM attack compared to the symptom-free state (Fig. 2).

DISCUSSION

The migraine aura typically fully resolves within 60 minutes, but motor symptoms during complicated migraine can last up to 72 hours[1]. Thomsen LL et al. demonstrated that in SHM, the cortical spread of the symptoms was more extensive, and the duration was often more prolonged than during a typical migraine aura[2]. This result indicated that in SHM, once CSD started, brain regions were involved at much larger and broader scales and even extended beyond the cortices compared to those involved in a typical migraine aura[2].

Since HM is not common and the published studies of HM by using functional nuclear image are few, most of the studies are case reports and the methods and tools are not consistent (Table 1). Previous studies have shown

Table 1. The hemiplegic migraine studies by nuclear functional images

Study/reference	No. of HM case	Age of onset (years)	Comment
Barbour et al. (2001)[15]	1	31	SHM during pregnancy. SPECT scan showed hyperperfusion of affected hemisphere in ictal state.
Oberndorfer et al. (2004)[8]	1	3	Follow-up findings in FHM. SPECT scan revealed hyperperfusion of affected hemisphere on day 2, less marked on day 9, and normal findings on day 24.
Iizuka et al. (2006)[10]	1	35	SPECT scan showed hyperperfusion of affected hemisphere in ictal state.
Cha et al. (2007)[4]	2 (twins)	40	PET scan showed increased metabolism contralateral to the hemiplegic side in SHM in ictal state.
Guedj et al. (2010)[3]	1	15	PET scan showed decreased metabolism contralateral to the hemiplegic side in FHM compared to normal subjects in ictal state.
Arias-Rivas et al. (2012)[14]	1	79	SISCOM in FHM showed hyperperfusion of affected hemisphere in ictal state.
Topakian et al. (2013)[11]	1	28	PET showed decreased brain metabolism at 10-year follow-up in SHM.
Eom et al. (2013)[16]	1	13	SPECT scan showed hypoperfusion of affected hemisphere in SHM in interictal state.
Koyano et al. (2014)[17]	1	8	Sixteen hours after the onset, SPECT revealed hypoperfusion of affected hemisphere.
Iizuka et al. (2015)[9]	3	12, 8, 12	PET scan showed decreased metabolism of affected hemisphere in ictal state.

FHM: familial hemiplegic migraine, HM: hemiplegic migraine, PET: positron emission tomography, SHM: sporadic hemiplegic migraine, SISCOM: SPECT coregistered to MRI, SPECT: single-photon emission computed tomography

transient hyperperfusion contralateral to the hemiplegia in HM by perfusion MRI, MRI and SPECT[3,8]. In a report of two attacks of FHM type 2, biphasic cerebral blood flow changes began with hypoperfusion followed by persistent hyperperfusion. This finding indicated that the initial hypoperfusion was related to functional depression caused by CSD[9]. Hyperperfusion was noted in the prolonged aura phase, which suggested the underlying pathophysiology involved in hyperemia and vasogenic leakage was activated by the trigeminovascular system because of CSD[10].

In the studies using FDG-PET, decreased metabolism in the contralateral perisylvian cortex at the time of the hemiplegic attack was noted in a female patient with FHM type 2[3]. Another case that was followed for 15 years showed decreased FDG-PET uptake in the bilateral supratentorial cortices and the left cerebellum, both of which occurred in the interictal phase[11]. In a 15-year-old boy with HM, the FDG-PET showed increased activity in the right temporal, insular and occipital lobes. They interpreted the results as an increase in metabolic demand could lead to vasodilation of the blood vessels ipsilateral to the irritated cortex and cause vasogenic leakage with focal inflammation[4,10]. In our case, substantial increase in glucose metabolism in the contralateral precentral motor cortex and ipsilateral premotor cortex were the functional regions associated with the clinical manifestation of limb weakness. The increased metabolisms can be explained by "neurogenic" inflammation triggered by cortical leptomeningeal plasma extravasation induced by trigeminovascular afferents activated by CSD[4,10,11]. The time we acquired the ictal FDG-PET 36 hours after symptom onset of image might explain the disparity between our study and the other one[3,11].

Interictal FDG-PET imaging has commonly been used for the localization of epileptogenic foci during epilepsy surgery work-ups[12]. Ictal FDG-PET has limited use for the localization of epileptic seizures due to the temporal dynamic of 45 minutes during FDG-PET uptake. However, in status epilepticus, FDG-PET hypermetabolism was reported and regarded as a metabolic biomarker. This marker had 100% specificity in electrographic and electroclinical status epilepticus[12]. We believe that FDG-PET is a useful imaging tool to investigate the metabolic changes during long ictal duration events in SHM.

Ictal SPECT has long been used as a tool for localizing seizure foci[13]. SISCOM was demonstrated to increase sensitivity and obtain more reproducible results for the detection of changes compared to simple visual inspection of ictal and interictal scans[13]. One report[14] described a 79-year-old woman with FHM who showed reversible perfusion abnormalities by SISCOM. A SPECT scan was performed during and after an attack with persistent aura, which showed differential hyperperfusion in foci in the affected hemisphere that involved the precentral lateral motor cortex and parieto-temporal region. We used this method in the FDG-PET images to increase the sensitivity of the detection of metabolic changes between the interictal and ictal states in SHM. To the best of our knowledge, this is the first report that has used this method to demonstrate glucose metabolic changes in HM.

Declaration of conflicts of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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