CASE REPORT

Thalamic and cerebellar hypermetabolism and cortical hypometabolism during absence status epilepticus

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SUMMARY

We report on a 17-year-old girl with absence status epilepticus who developed recurrent motionless confusional state and continuous generalised 3–4 Hz rhythmic delta waves on electroencephalogram (EEG). The patient had no history of absence, myoclonus or generalised convulsion. Her seizure was resistant to a combination of antiepileptic drugs including carbamazepine. Ictal positron emission tomography using [¹⁸F]fluorodeoxyglucose ([¹⁸F]FDG-PET) revealed hypermetabolism of the bilateral thalamus and cerebellum and hypometabolism of the frontal, parietal and posterior cingulate cortices. We diagnosed her seizure as absence status and obtained remission by changing medication. The findings of ictal metabolic alteration in previous studies and in our case confirm the pathogenic importance of the thalamus in absence status and that associated cortical deactivation and cerebellar activation may be related to the generation or maintenance of epileptic EEG discharges.

BACKGROUND

Absence status epilepticus (ASE) is defined as a prolonged, generalised non-convulsive seizure with impairment of the content of consciousness and electroencephalogram (EEG) generalised spike/polyspike-wave discharges at 2–4 Hz.^{1–4} The epileptogenic mechanism underlying ASE is poorly understood. A previous ictal functional MRI (fMRI) study during interictal generalised spike-and-wave or polyspike-and-wave bursts in patients with idiopathic generalised epilepsy (IGE) reported predominantly cortical deactivation and thalamic activation, which occurred symmetrically.⁵ A similar activation pattern was demonstrated in ASE by fMRI⁶ or [¹⁸F]FDG-PET.⁷ These findings support bilateral corticothalamic circuitry involvement in the pathophysiology of ASE. We report a young woman who showed a recurrent ASE as the only seizure pattern. The [¹⁸F]FDG-PET examination during ASE demonstrated symmetrical hypermetabolism of the thalamus and cerebellum and hypometabolism of the cerebral cortex.

CASE PRESENTATION

A 17-year-old girl with a history of febrile seizure at the age of 3 years presented with impairment of consciousness. Her family history was unremarkable. She had noticed a short lapse of attention several times during the 2–3 years before onset, but she had not noticed any myoclonic jerk. On the

day of admission, her mother found her to be in a state of clouding of consciousness at breakfast. She also showed mild weakness of the right hand. She was taken to the emergency department of Aizawa Hospital by ambulance. Neurological examination on arrival revealed a paucity of expression, limited spontaneous motion and small tremulous myoclonic jerks in the hand and the perioral region on the right side. She could reply to simple questions, but she did not initiate conversation. Blood test results showed no abnormality including glucose and electrolytes. Brain 1.5 T MRI was unremarkable. She was diagnosed as having epilepsy, and diazepam 10 mg was intravenously injected; she then recovered. Interictal EEG showed sporadic spike-and-waves dominantly in the left frontal areas. Based on her symptoms and EEG findings, the initial diagnosis was suspected as left frontal seizure, and treatment was initiated with oral CBZ 100 mg per day. When CBZ was increased up to 300 mg per day 3 months after the initial episode, the same seizure and confusional state recurred. The seizure continued for more than several hours, and continuous intravenous infusion of midazolam was necessary to resolve it. Then CBZ was further increased and other antiepileptic drugs (AED) were added to it, but the intervals of recurrence gradually shortened. Her seizures tended to occur in the morning and during the perimenstruation period. One year following the first episode, she was hospitalised due to recurrence of the same epileptic seizure while taking CBZ 500 mg, levetiracetam 1000 mg and phenobarbital 100 mg per day. The ictal EEG showed generalised high amplitude rhythmic delta waves at 3–4 Hz (figure 1), and the diagnosis of ASE was suspected.

INVESTIGATIONS

As her seizure was drug-resistant, [¹⁸F]FDG-PET was examined during the seizure in order to investigate whether her seizure was focal or generalised. Brain perfusion SPECT was not available in our hospital. The patient was treated with an intravenous infusion of midazolam 50 mg/hour during the PET examination, and EEG spike-and-wave bursts were observed before and after the examination. The local glucose uptake levels of the patient were statistically compared with the activity levels of age-matched controls (six females with somatic symptom disorder without brain injury and epilepsy, mean age and SD, 16.5 ± 1.9 years). The cerebral glucose metabolism revealed relative hypermetabolism in the thalamus, caudate nucleus and dentate

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Figure 1 Electroencephalogram recorded during the epileptic state. Generalised rhythmic delta waves continued.

nucleus and vermis of the cerebellum, and the involved areas were bilaterally and symmetrically distributed. Relative hypometabolism was observed in the bilateral frontal, parietal and posterior cingulate cortices and in the right temporal cortex (figure 2).

OUTCOME AND FOLLOW-UP

Based on confirmation of generalised seizure by PET examination, we finally diagnosed this case as ASE. We had changed to appropriate AEDs, a combination of lamotrigine and clonazepam, then her seizure was well controlled.

DISCUSSION

The following criteria of ASE were proposed: recurrent episodes of unprovoked ASE, onset of ASE in adolescence or adulthood, ASE being the main seizure type and clinical and laboratory findings consistent with a diagnosis of IGE but not suggesting one of the recognised IGE.⁴ Our case fulfilled these criteria. Myoclonus

Figure 2 Changes in glucose uptake levels measured by [18F]FDG-PET as compared with those of the controls, using statistical parametric mapping (SPM12: Wellcome Trust Centre for Neuroimaging, University College London, London, UK). Relative hypermetabolism (yellow) and hypometabolism (red) are shown in (A) and (B), respectively ($p < 0.001$), superimposed on Montreal Neurological Institute space T1-weighted MR axial images. =O4467

in the perioral region and in the hand during status periods, the age of onset, precipitating factors and exacerbation with CBZ in our patient implicated juvenile myoclonic epilepsy (JME) as a background disorder, but she had no myoclonic jerks before the onset of absence status, nor typical EEG findings, which are the core criteria for diagnosis of JME.⁸ Consequently, we diagnosed her as having IGE with absence status as the sole phenotype and obtained remission of the seizure by discontinuation of CBZ.

As the absence status of our case sustained for a relatively long period, ictal [18F]FDG-PET was available in our patient, though some interictal periods may have been interposed during the PET examination. There are several previous studies which reported changes in ictal brain metabolism in patients with absence (table 1).^{6 7 9–13} Engel *et al*⁹ measured brain metabolic changes using [18F]FDG-PET in four patients with absence and found increase in global metabolism. Theodore *et al*¹⁰ investigated two patients using [18F]FDG-PET during ictal and interictal periods and found decrease of metabolism in frontal, temporal and thalamic cortices in one patient and increase of metabolism in the caudate nucleus and the frontal cortex in another. Ochs *et al*¹¹ investigated two patients using [18F]FDG-PET and found metabolic increase of the overall brain in one and no change in the other. These inconsistent results in the initial studies may have been derived from differences in the patient's conditions at the time of the scan and limited resolution of PET. The studies after the 2000s have shown fairly consistent results, that is, hypermetabolism of the thalamus and hypometabolism of the cerebral cortex, especially frontal, parietal and posterior cingulate cortices. These changes were bilateral and symmetrical in all reports. The pattern of hypermetabolism and hypometabolism in our case is similar to that reported by Gotman *et al*⁶ and Bilo *et al*,⁷ depicting thalamic and cerebellar hypermetabolism and cortical hypometabolism, except for some asymmetrical distribution of hypometabolism. Although comparison between ictal and interictal PET findings was not attained in our study, common findings of PET activation and deactivation with the previous reports support our PET findings to be ictal changes.

The thalamic activation confirms the central role of the thalamus in the generation of generalised spike-and-wave discharges (SWDs) in absence, although thalamic activation does not necessarily indicate initiation of SWDs or rhythm generation mechanism. Thalamic activation is not specific for absence, but it is commonly observed in IGE of other types, and it is estimated to be a cardinal pathophysiology underlying IGE.^{14 15} Activation of thalamic subnuclei may be different in different type of IGE, but the low spatial resolution of PET makes more precise localisation difficult. Changes in local metabolism do not necessarily indicate changes in the firing rate of intrinsic nerve cell bodies, but they do reflect overall synaptic activity including activity of afferents to a nucleus, its intrinsic interneurons and recurrent collaterals.¹⁶ Therefore, the widely distributed cortical deactivation may not suggest activation of thalamocortical fibres. Raichle *et al*¹⁷ analysed the oxygen extraction fraction regionally throughout the brain in normal human subjects at resting condition with their eyes closed and found uniform deactivated cortical regions, and the authors called the condition the 'default of the brain'. Based on the similarity of the distribution of deactivation in the 'default of the brain' and absence, Gotman *et al*⁶ hypothesised that spike-and-wave bursts cause a partial suspension of the default state of the brain, leading to altered consciousness and cortical deactivation during generalised epileptic discharges. The actual mechanism underlying altered activity of the thalamus and cortex in absence remains open to future studies.

Table 1 Summary of the cases of absence in the literature in which ictal brain metabolism was investigated

Authors, year	Patient/age (years)	Methods	EEG findings	Regions of hypermetabolism	Regions of hypometabolism
Engel <i>et al</i> , 1985 ⁹	4 patients/6–12	FDG-PET	3–4 Hz GSW	Global brain	None
Theodore <i>et al</i> , 1985 ¹⁰	1 patient/22 (absence status) 1 patient/22	FDG-PET FDG-PET	2–3 Hz GSW 2 Hz GSW	None Caudate nucleus and frontal cortex	Frontal and temporal cortices and thalamus none
Ochs <i>et al</i> , 1987 ¹¹	1 patient/18 1 patient/26	FDG-PET FDG-PET	3–4 Hz GSW 2.5–3.5 Hz GSW	Overall brain	None
Prevett <i>et al</i> , 1995 ¹²	8 patients/23–63	H ₂ ¹⁵ O and PET	3–4 Hz GSW	Thalamus (CBF)	None
Salek-Haddadi <i>et al</i> , 2003 ¹³	1 patient/36	fMRI	3 Hz GSW	Thalamus	Large areas of cortex
Gotman <i>et al</i> , 2005 ⁶	11 out of 15 patients with IGE/18–66	fMRI	GSW	Thalamus, insula, mesial midfrontal region and cerebellum	Frontal and parietal regions and posterior cingulate gyrus
Bilo <i>et al</i> , 2010 ⁷	1 patient/56 (absence status)	FDG-PET	2–3 Hz GSW	Thalamus and cerebellum	Frontal, parietal and posterior cingulate cortices
Present case	1 patient/17 (absence status)	FDG-PET	3–4 Hz GSW	Thalamus, caudate nucleus and cerebellum	Frontal, parietal and posterior cingulate cortices

CBF, cerebral blood flow; fMRI, functional MRI; GSW, generalised spike-and-wave; IGE, idiopathic generalised epilepsy.

Two recent reports, Gotman *et al*⁶ and Bilo *et al*,⁷ and ours commonly showed hypermetabolism in the cerebellum, the vermis in the former two studies and the vermis and deep cerebellar nuclei in our case. As the cerebellum has a strong projection to the thalamus, thalamic activation may suggest involvement of the cerebellum as epileptogenesis or rhythm generation. On the other hand, cerebellar hypermetabolism may result from thalamic activation through connections between the thalamus, brainstem and cerebellum as suggested by Kameyama *et al*.¹⁸

In conclusion, the findings of ictal [18F]FDG-PET in our case confirm the pathogenic importance of the thalamus in absence status and associated cortical deactivation and cerebellar activation await further investigation.

Learning points

- ▶ [18F]FDG-PET was examined in a case of absence status epilepticus.
- ▶ Ictal PET revealed hypermetabolism of the bilateral thalamus and cerebellum.
- ▶ Hypometabolism was shown in the frontal, parietal and posterior cingulate cortices.
- ▶ Thalamic activation is estimated to be the pathogenic alteration in absence status.
- ▶ Cerebellar activation and cortical deactivation await further investigation.

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