Carbon-11-Methionine PET in Focal Cortical Dysplasia: A Comparison with Fluorine-18-FDG PET and Technetium-99m-ECD SPECT

Masayuki Sasaki, Yasuo Kuwabara, Tsuyoshi Yoshida, Toshimitsu Fukumura, Takato Morioka, Shunji Nishio, Masashi Fukui and Kouji Masuda

Departments of Radiology and Neurosurgery, Faculty of Medicine, Kyushu University, Fukuoka, Japan

Focal cortical dysplasia is one of the known neuronal migration disorders and has recently been recognized as a cause of intractable epilepsy. In this study, we assessed the ^{11}C-methionine (MET) uptake in focal cortical dysplasia by PET, and then compared the results with that of ^{18}F-fluoro-2-deoxy-D-glucose (FDG) PET and ^{99m}Tc-ethyl cysteinate dimer (ECD) SPECT. **Methods:** Four patients (3 men, 1 woman; age range 16–68 yr) were examined by PET and SPECT for a presurgical examination of medically intractable seizures. In all 4 patients, ^{11}C-MET PET was performed for 15 min, started 15 min after the administration of 511–662 MBq MET. In 3 of 4 patients, FDG PET was performed for 15 min, and started 20 min after the administration of 185–370 MBq FDG. In all 4 patients, the cerebral blood flow was also evaluated by ^{99m}Tc-ECD SPECT for 15 min after the administration of 600 MBq ECD. **Results:** In MET PET, all 4 lesions were visually recognized to have high MET uptake areas. The MET uptake of the lesions was 1.44 ± 0.30 for the standardized uptake value (SUV) (ranging from 0.99–1.61). In FDG PET, 2 lesions were demonstrated to have low uptake areas (3.82 in SUV) while 1 had an ictal high uptake (4.74 in SUV). In ECD SPECT, 1 lesion demonstrated hypoperfusion and 1 ictal hyperperfusion while 2 showed no abnormalities. All 4 patients underwent a cortical resection and the microscopic examinations were consistent with those of focal cortical dysplasia but no evidence of a tumor was found. **Conclusion:** MET PET is useful for identifying focal cortical dysplasia as a high uptake area.

Key Words: epilepsy; focal cortical dysplasia; carbon-11-methionine; fluorine-18-fluorodeoxyglucose; PET

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Focal cortical dysplasia is one of the neuronal migration disorders characterized by the disruption of cortical lamination and the abnormal differentiation of neuroglial cells. In addition, focal cortical dysplasia has been recently recognized as a cause of intractable epilepsy (*1,2*). Although the extent of the surgical resection is determined by an intraoperative electrocorticogram (ECoG), the presurgical evaluation of epileptic foci is performed by noninvasive methods, including physiological examinations and imaging studies. SPECT using ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) demonstrated abnormal areas as hypoperfusion in an interictal state (*3*) and as hyperperfusion in an ictal state (*4*). In addition, PET using ^{18}F-fluoro-2-deoxy-D-glucose (FDG) also demonstrated hypometabolism in focal cortical dysplasia (*5,6*).

Carbon-11-L-methionine (MET) PET has been reported to be useful in detecting brain tumors (*7,8*). Recently, a high MET uptake also has been reported in nonneoplastic tissue, such as brain abscesses (*9*), brain hematomas (*10*) and cerebral ischemia (*11*). We previously reported a case demonstrating a high MET uptake in brain radiation necrosis, which thus suggested the possibility of a high MET uptake in epileptic foci (*12*).

In this study, we assessed the MET PET findings of patients with medically intractable epilepsy who were found to have focal cortical dysplasia by a histopathological examination after surgery. The results were then compared with those of both FDG PET and ^{99m}Tc-ECD SPECT.

MATERIALS AND METHODS

Patients

Four patients with medically intractable seizures were admitted to undergo examinations to determine the indications for surgical treatment. Patient characteristics are summarized in Table 1. Their ages at the time of their examinations ranged from 16–68 yr, while their ages at the time of seizure onset ranged from 7 mo to 20 yr. All PET and SPECT examinations were performed within 22 days (range 3–22 days, mean 9 days).

MRI Protocol

A 1.5-T superconducting unit (Signa, General Electric Medical Systems, Milwaukee, WI) was used for the MR imaging. T1-weighted spin-echo images were obtained with sequences of 500/18/1 (TR/TE/excitations). The T2-weighted fast spin-echo images were obtained with 2500/110/1. The imaging parameters included a 256 × 192 matrix, 23 × 17-cm field of view and 5-mm slice thickness with 2.5-mm slice gap. In Patients 1 and 2, the 0.1 mmol/kg of gadolinium-diethylenetriaminepentaacetic acid (DTPA) was administered for a postcontrast study.

PET Protocol

PET studies were performed with a HEADTOME III (Shimadzu Corp., Kyoto, Japan), and 5 contiguous slices, each 15 mm apart, were obtained. The spatial resolution was 8.2 mm with FWHM. Transmission scanning using a ^{68}Ge/^{68}Ga ring source was performed for attenuation correction. The data acquisition for MET PET for 15 min was started 15 min after the administration of 511–662 MBq MET. The data acquisition for FDG PET for 15 min was started 20 min after the administration of 185–370 MBq FDG. Although no electroencephalogram (EEG) monitoring was performed during the examinations, PET studies of Patients 1–3 were performed in an interictal state, while those of Patient 4 were performed in an ictal state because the myoclonic seizure (epilepsia partialis continua) was continuously observed during examinations. This study was approved by the Committee for the Clinical Application of Cyclotron Producing Radionuclides in Kyushu University Hospital, Fukuoka, Japan, and informed consent was obtained from all patients before starting the PET study.

The regions of interest (ROIs) of the lesions were placed carefully in visual comparison with MRI, because no coregistration of the PET images and MRI could be performed. Either square or rectangular ROIs measuring 14 × 14 mm or 14 × 18 mm in size were placed on the lesions. When the lesion showed a high activity

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For correspondence or reprints contact: Masayuki Sasaki, MD, PhD, Department of Radiology, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.

TABLE 1
Patient Characteristics

Patient no.	Age (yr)	Sex	Clinical information				MRI	Intraoperative ECoG	MET PET	FDG PET	ECD SPECT
			Onset	Size	Frequency	Drug					
1	16	M	13 yr	Partial seizure	3–4 times/mo	Carbamazepine	Right temporal T2-prolonged T1-isointense Enhanced (−)	Right temporal spike	Right temporal high, interictal (SUV = 1.58) (L/C = 1.37)	Right temporal low, interictal (SUV = 2.37) (L/C = 0.79)	Right temporal low, interictal (L/C = 0.93)
2	18	M	1 yr, 11 mo	Generalized convulsion	10–15 times/day	Phenytoin, carbamazepine, sodium valproate	Left frontal T2-prolonged T1-prolonged Enhanced (−)	Left frontal spike	Left frontal high, interictal (SUV = 0.99) (L/C = 1.17)	Left frontal low, interictal (SUV = 5.27) (L/C = 0.70)	No abnor interictal (L/C = 1.03)
3	23	F	7 mo	Partial seizure or generalized tonic-clonic seizure	2–3 times/day	Phenytoin, carbamazepine, zonisamide	Left occipital T2-prolonged T1-isointense Enhance: n.d.	Left occipital spike	Left occipital high, interictal (SUV = 1.61) (L/C = 1.10)	n.d.	No abnor interictal (L/C = 0.96)
4	68	M	20 yr	Myoclonic seizure in right hand and mouth	Continuous	Phenytoin, carbamazepine	Left frontal T2-prolonged T1-prolonged Enhance: n.d.	Left frontal spike	Left frontal high, ictal (SUV = 1.59) (L/C = 1.19)	Left frontal high, ictal (SUV = 4.74) (L/C = 1.25)	Left frontal high, ictal (L/C = 1.06)

ECoG = electrocorticogram; n.d. = not done; No abnor = No abnormalities; SUV = standardized uptake value; L/C = lesion-to-contralateral normal region ratio.

area, the ROI was placed on the highest activity area but did not cover the entire lesion. Homologous ROIs were also drawn over the contralateral analogous normal cerebral cortex. The uptake of the radiopharmaceuticals in the lesion was evaluated based on the standardized uptake value (SUV) as calculated by the radioactivity of the tumor divided by the injected radioactivity per body weight. The uptake of the radiopharmaceuticals in the lesion was also evaluated by the lesion-to-normal ratio (L/C ratio) determined as the ratio of the average counts in the lesion to those in the contralateral normal region.

SPECT Protocol

To obtain ECD SPECT images, data acquisition was performed for 15 min, beginning 5 min after the administration of 600 MBq ECD, using a three-detector system (GCA9300A/HG; Toshiba Corp., Tokyo, Japan) with a fanbeam collimator (128 × 128 matrix). Each detector was set to rotate continuously through 120° in 3 min, alternating in both clockwise and counterclockwise directions. A Butterworth filter, cutoff 0.24 cycle/cm and order 8, and a ramp filter were used for image reconstruction. Attenuation correction was performed using an attenuation coefficient of 0.12 cm^{-1}. The spatial resolution in plane was 7.4 mm of FWHM. Although no EEG monitoring was performed during the examinations, SPECT studies of Patients 1–3 were performed in an interictal state, while those of Patient 4 were performed in an ictal state. The ECD uptake in the lesion was evaluated by the L/C ratio by placing the ROIs measuring 15 × 15 mm or 15 × 17 mm in size in the same manner as for the PET studies as described above. As with the PET images and MRI, coregistration of the SPECT images and MRI could not be performed.

RESULTS

MRI demonstrated a focal T2-prolonged lesion in all patients (Figs. 1A, 2A and 3A). The T1-prolongation was also demonstrated in Patients 2 and 4. The gadolinium-enhanced MR studies were performed in Patients 1 and 2, but they did not demonstrate any abnormal enhancements on the lesions.

In MET PET, all 4 lesions were visually recognized as high MET uptake areas. The mean MET uptake of lesions was 1.44 ± 0.30 SUV (range 0.99–1.61). The MET uptake of the lesions were higher than those of the contralateral cerebral cortices and the L/C ratio was 1.21 ± 0.12 (range 1.10–1.37). In Patients 1 and 4, the extent of the high MET uptake areas was equal to that of the lesions shown by MRI (Figs. 1B, 3B). In Patients 2 and 3, the high MET uptake areas were smaller than the lesions shown by MRI (Fig. 2B).

In Patients 1 and 2, FDG PET demonstrated a decreased FDG uptake in the lesions (Figs. 1C, 2C). The FDG uptake of the lesion was 2.37 and 5.27 in SUV (the L/C ratio; 0.79 and 0.70), respectively. In Patient 4, FDG PET demonstrated a high FDG uptake in the lesion (Fig. 3C).

In ECD SPECT, hypoperfusion was observed in Patient 1 (Fig. 1D) while increased perfusion was seen in Patient 4 (Fig. 3D). In Patients 2 and 3, no abnormalities were observed (Fig. 2D).

All four patients underwent a resection of the focal cortical dysplasia lesion. An intraoperative ECoG with subdural grid electrodes showed epileptic spikes on the lesions. After surgery, Patients 1, 2 and 4 no longer had seizures. In Patient 3, the seizures continued but with a marked decrease in frequency. The microscopic examinations of the resected lesions were consistent with those of focal cortical dysplasia. No evidence of a tumor was found.

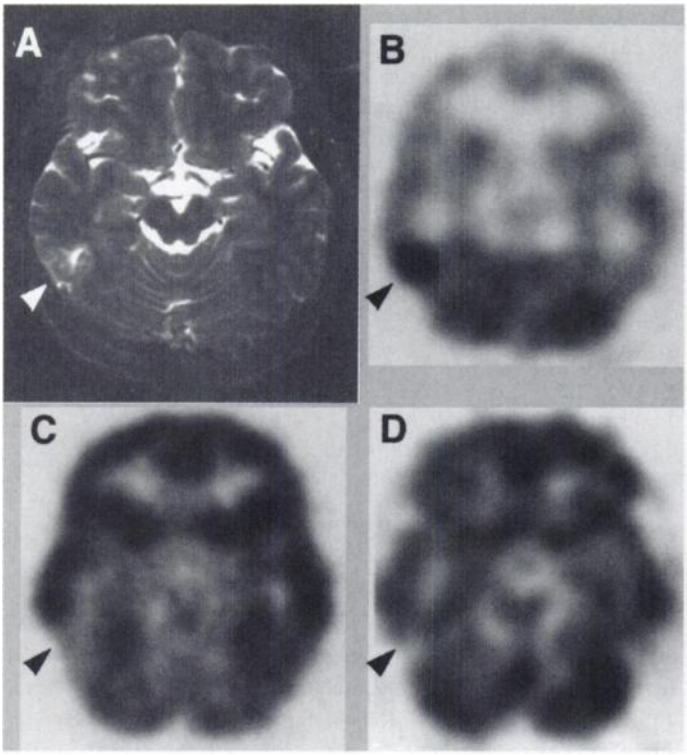

FIGURE 1. MRI, MET PET, FDG PET and ECD SPECT images of Patient 1. (A) The T2-weighted MR image (TR2500/TE110) demonstrates a T2-prolonged lesion in the posterior part of the right temporal lobe. (B) MET PET demonstrates a high MET uptake in the lesion. Both decreased FDG uptake (C) and decreased perfusion (D) are shown in the lesion.

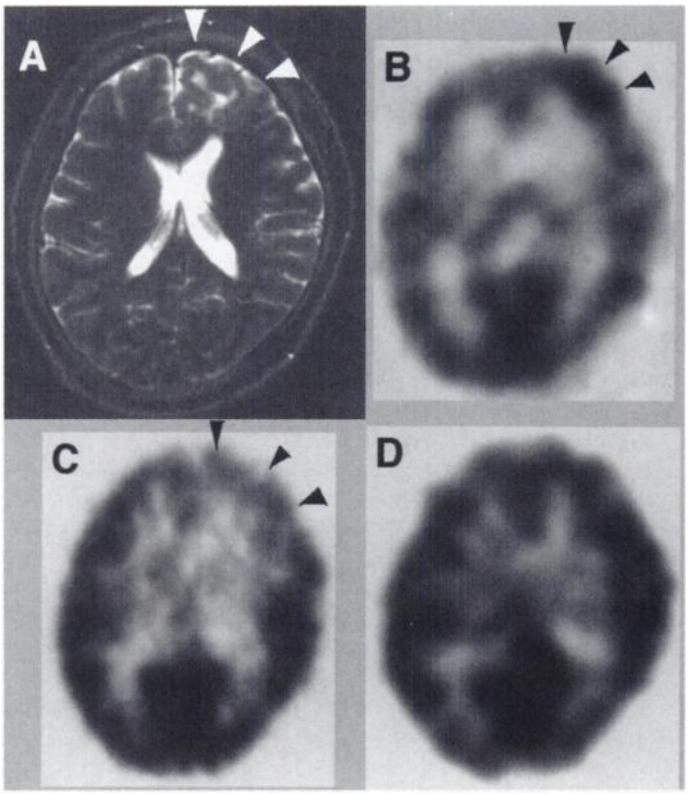

FIGURE 2. MRI, MET PET, FDG PET and ECD SPECT images of Patient 2. (A) The T2-weighted MR image (TR2500/TE110) demonstrates a T2-prolonged lesion in the left frontal lobe. (B) MET PET demonstrates a high MET uptake in the lesion. (C) Decreased FDG uptake is shown in the lesion. (D) ECD SPECT did not show any abnormalities.

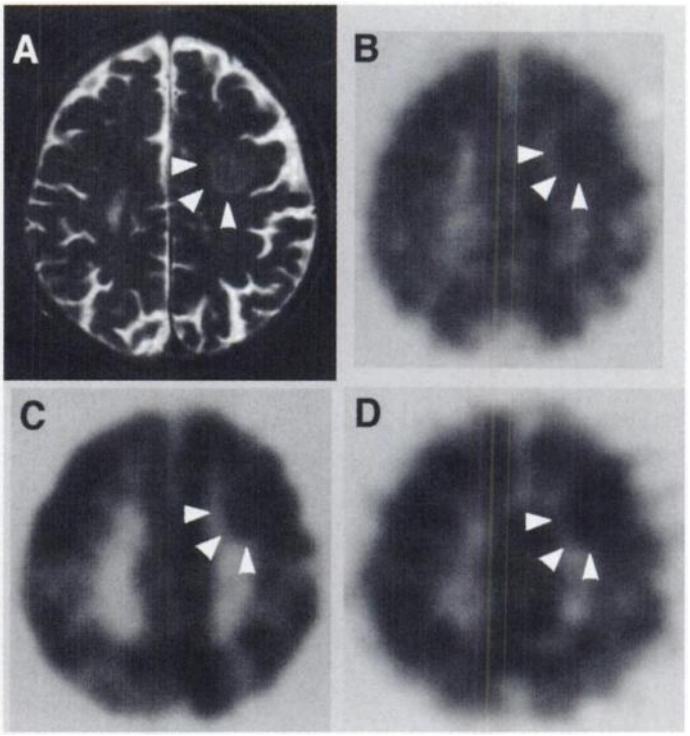

FIGURE 3. MRI, MET PET, FDG PET and ECD SPECT images of Patient 4. (A) The T2-weighted MR image (TR2500/TE110) demonstrates a T2-prolonged lesion in the left frontal lobe. MET PET (B), FDG PET (C) and ECD SPECT (D) images show an abnormally high uptake in the lesion. Clinically apparent seizures were continuously observed during all examinations.

DISCUSSION

MET is well known to be one of the most effective radiopharmaceuticals for evaluating brain tumors (*7,8*). MET accumulation initially was thought to depend on protein synthesis, however, other metabolic processes, including transmethylation processes with MET as a methyl donor and transmembrane amino acid transport, are now also thought to take part in MET accumulation. Recent reports demonstrating a high MET uptake in nonneoplastic tissue, such as a brain abscess (*9*), intracerebral hematomas (*10*), cerebral ischemia (*11*) and brain radiation necrosis (*12*) have suggested that a high MET uptake cannot always rule out the presence of nonneoplastic lesions. In this study, all four patients with focal cortical dysplasia showed high MET uptake.

The exact mechanisms for the increased MET uptake in focal cortical dysplasia remain unclear. The disruption of the blood-brain barrier (BBB) results in leakage of MET to the extracellular space and thus enables an increased uptake in the cells (*13*). In addition to the BBB disruption, some modifications of the amino acid transport mechanism, such as the gliotic reaction, inflammatory changes or hyperperfusion, may be responsible for the increased uptake of MET in nontumorous lesions. However, there is no evidence supporting these pathomechanisms in the focal cortical dysplasia lesion.

In relation to aging, alternations of the amino acid uptake in the brain have been examined using animal models (*14–18*). A developmental decline in neutral amino acid influx into the brain is thought to primarily reflect a reduction in the capacity of the neutral amino acid carrier across the BBB and not a change in transport affinity. In maturing animals, a high degree of brain protein synthesis has also been reported (*18*). In humans, an age-related decline in the brain MET uptake was observed by O'Tuama et al. (*19*). A high MET uptake in the focal cortical dysplasia lesion observed in our preliminary study

may indicate that the focal cortical dysplasia has an immature nature. We did not calculate either the transport rate constants or the mass influx of MET, because we did not measure the plasma MET activity. Further examinations evaluating the role of both the amino acid transport mechanism and protein synthesis will provide more accurate information for pathomechanisms of high MET uptake in focal cortical dysplasia lesions.

Epileptic activities can also be another possibility of a high MET uptake in nonneoplastic lesions as shown in our previous study (*12*). Structural abnormalities, such as tumors and arteriovenous malformations, are often associated with chronic neocortical epilepsy and are usually considered to be epileptogenic due to their effect on the adjacent cortex. In contrast, several recent reports have suggested that the focal cortical dysplasia lesions themselves are the source of epileptogenicity (intrinsic epileptogenicity), independent of any effect related to the surrounding and apparently nondysplastic cortex (*20–22*). In our study, either frequent or almost continuous paroxysmal activities were recorded from the ECoG electrodes that were placed over the surface of the focal cortical dysplasia lesion intraoperatively, while few paroxysmal activities were observed on the normal appearing adjacent cortex. No EEG monitoring was performed during our PET studies. In Patient 4, who demonstrated continuous seizures throughout the examination, both increased FDG uptake and hyperperfusion were observed in the lesion. In the other three patients without any clinical seizures during the examination, neither increased FDG uptake nor hyperperfusion were observed in the lesions. Although we cannot rule out the possibility that the subclinical seizures, which may be responsible for hyperperfusion (*23*) and hypermetabolism (*24*), might have existed during the MET PET examination, it is unlikely that a high MET uptake was attributed to the ictal hypermetabolism.

Interictal FDG hypometabolism was observed in two patients, and it is consistent with the findings of the previous reports (*5,6*). Interictal hypoperfusion was observed in one patient and no abnormality was seen in two patients. These findings may be due to the limitations of the lower sensitivity for detecting the epileptic foci of the cerebral blood flow studies with interictal SPECT than that of FDG PET (*25–27*), although the ictal SPECT studies using either ^{99m}Tc-HMPAO or ^{99m}Tc-ECD have been thought to be more sensitive than FDG PET (*3,28–30*). A developmental increase in cortical glucose metabolism was reported by Chugani et al. (*31*) in the maturing brain in the neonatal period. A gradually increasing cerebral metabolism during prenatal maturation was also observed in most brain structures in an animal model (*32*). A similar pattern of developmental changes in the cerebral blood flow was also reported by using ^{123}I-IMP (*33*) and ^{99m}Tc-HMPAO (*34*). From our preliminary study, both FDG hypometabolism and hypoperfusion in focal cortical dysplasia lesions may also indicate that focal cortical dysplasia consists of immature tissue.

CONCLUSION

MET PET is considered useful for detecting focal cortical dysplasia as high uptake areas.

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