Hiroshima J. Med. Sci.
Vol. 64, No. 4, 51~57, December, 2015
HIJM 64−9

Diagnostic Performance of Positron Emission Tomography for the Presurgical Evaluation of Patients with Non-lesional Intractable Partial Epilepsy: Comparison among ^{18}F-FDG, ^{11}C-Flumazenil, and ^{11}C-Flumazenil Binding Potential Imaging Using Statistical Imaging Analysis

Daisuke KOMOTO[1,2,*], Koji IIDA[3,4], Toru HIGAKI[1], Yoko KAICHI[1], Komei TAKAUCHI[5], Koji ARIHIRO[6], Akiyoshi KAKITA[7], Yutaka HIROKAWA[8] and Kazuo AWAI[1]

1) *Department of Diagnostic Radiology, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan*
2) *Department of Diagnostic Radiology, Hiroshima City Asa Hospital, 2-1-1 Kabeminami, Asakita-ku, Hiroshima 731-0293, Japan*
3) *Department of Neurosurgery, Hiroshima University, Hiroshima 734-8551, Japan*
4) *Epilepsy Center, Hiroshima University Hospital, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-8551, Japan*
5) *Department of Radiology, Hiroshima University Hospital, Hiroshima 734-8551, Japan*
6) *Department of Anatomical Pathology, Hiroshima University Hospital, Hiroshima 734-8551, Japan*
7) *Department of Pathology, Brain Research Institute, Niigata University, 1 Asahimachi, Chuo-ku, Niigata 951-8585, Japan*
8) *Hiroshima Heiwa Clinic, 1-31 Kawara-machi, Naka-ku, Hiroshima 730-0856, Japan*

ABSTRACT

To compare the diagnostic performance of ^{18}F-FDG PET, ^{11}C-FMZ PET, and ^{11}C-FMZ BP imaging for the evaluation of patients with intractable partial epilepsy whose MRI findings are normal by using statistical imaging analysis. Ten patients underwent comprehensive presurgical evaluation, including PET studies, to assess the epileptic foci. The extent of cortical resection was based on the results of intracranial video-electroencephalography (IVEEG) monitoring and brain mapping under stimulation. The images of 10 patients and 30 controls were spatially normalized to templates generated in-house by non-rigid registration and the standardized images of the patients and controls were statistically compared. Epileptic focus candidates were visualized on a color map of axial images of each template and the focus site was identified in candidates for lobar location. In patients with Engel I postoperative seizure outcomes we assessed the sensitivity and specificity of the imaging methods for lobar focus localization. We also compared the concordance scores of patients with Engel I and Engel II-IV postoperative seizures. The sensitivity and specificity for lobar focus localization on ^{18}F-FDG PET scans was 90.0% and 84.8%, respectively; it was 30.0% and 81.4% for ^{11}C-FMZ PET, 40.0% and 66.7% for ^{11}C-FMZ BP images, and 100.0% and 51.4% for ^{18}F-FDG PET/^{11}C-FMZ PET/^{11}C-FMZ BP images. In one patient the epileptic focus not detected on ^{18}F-FDG PET scans was shown on ^{11}C-FMZ BP images. In patients with Engel I post-treatment seizures the concordance scores were significantly higher for ^{18}F-FDG PET than ^{11}C-FMZ PET and ^{11}C-FMZ BP images ($p < 0.05$). With respect to sensitivity and specificity, ^{18}F-FDG PET was superior to ^{11}C-FMZ PET and ^{11}C-FMZ BP imaging. However, in some patients with normal MRI results, ^{11}C-FMZ BP studies may complement ^{18}F-FDG PET findings in efforts to identify the epileptogenic lobar regions.

Key words: *Positron emission tomography, ^{18}F-FDG, ^{11}C-FMZ, Epilepsy*

Epilepsy is one of the most common chronic neurologic conditions in the world; it affects approximately 1% of the population[17] and in about 30% epilepsy is medically intractable[1,5,6,12]. The success of epilepsy

* Corresponding author: Daisuke KOMOTO, M.D., Department of Diagnostic Radiology, Hiroshima City Asa Hospital 2-1-1 Kabeminami, Asakita-ku, Hiroshima 731-0293, Japan
Tel: +81-82-815-5211, Fax: +81-82-814-1791, E-mail: komotorad@gmail.com

surgery is partly dependent on the identification of the lesions on magnetic resonance images (MRI) and patients in whom no lesions are detected by MRI have poor surgical outcomes[2,22]. At present there is no standard for the diagnosis and treatment of non-lesional epilepsy.

Functional neuroimaging techniques such as positron emission tomography (PET) are employed when no lesions are seen on MRI scans. [18F]Fluoro-2-deoxy-D-glucose PET (^{18}F-FDG-PET) measures the glucose metabolism related to the synaptic and neuronal activity in brain tissue[16]; it is commonly used in patients scheduled for epilepsy surgery[8]. ^{11}C-Flumazenil (^{11}C-FMZ) is a selective $GABA_A$-benzodiazepine receptor antagonist. Reduced FMZ binding, as is observed in patients with partial epilepsies, is thought to reflect underlying neuronal loss. The binding potential (BP) is the ratio of B_{max}, the total density of receptors, to K_D, the radioligand equilibrium-dissociation constant[15]. ^{11}C-FMZ BP is correlated with histologically assessed neuronal loss and astrogliosis[14]. In patients with frontal lobe epilepsy, the cortical focus of decreased FMZ binding corresponded well with the location of seizure onset identified with subdural electrodes; on FDG PET images the hypometabolic zone shown on FDG PET scans appeared larger than the FMZ focus[19]. There are few reports about the comparison of ^{18}F-FDG PET, ^{11}C-FMZ PET and ^{11}C-FMZ BP imaging among the same patients in localization of the epileptic focus. As most earlier studies involved patients with abnormal MRI findings, the relationship between ^{18}F-FDG PET and ^{11}C-FMZ PET findings with respect to the localization of the epileptic focus is less well understood in patients with normal MRI findings.

We investigated the diagnostic performance of different PET imaging techniques for the presurgical evaluation of patients with non-lesional intractable focal epilepsy by subjecting ^{18}F-FDG PET, ^{11}C-FMZ PET, and ^{11}C-FMZ BP findings to statistical imaging analysis.

MATERIALS AND METHODS

Patients

We reviewed the clinical records of 16 consecutive epilepsy patients seen at the Department of Neurosurgery of Hiroshima University Hospital between December 2010 and April 2013. In all, scalp video-EEG (SVEEG) suggested localization-related epilepsy despite normal MRI findings and all underwent comprehensive presurgical evaluation including SVEEG, magnetoencephalography (MEG), ^{123}I-iomzenil (IMZ) single-photon emission computed tomography (SPECT), PET, and neuropsychological examinations. PET studies were performed at the Hiroshima Heiwa Clinic. As we excluded 6 patients because resective surgery, i.e, lobectomy, corticectomy, and amygdalohippocampectomy was not indicated, the study population was comprised of 10 patients who underwent resective surgery guided by intracranial video-EEG monitoring (IVEEG).

Evaluation of surgical outcomes

The postoperative outcome was evaluated based on the seizure classification of Engel et al[4] where class I = no disabling seizures, class II = rare disabling seizures, class III = improvement, and class IV = no improvement. The postoperative follow-up period was at least 1 year.

MRI imaging

For evaluation of the whole brain and hippocampal structures, all patients underwent MRI on a GE 3T- (GE Medical Systems, Milwaukee, WI, USA) and a TOSHIBA 1.5T scanner (Toshiba Medical Systems, Otawara, Japan). The parameters for the GE scanner were axial and coronal fluid-attenuated inversion recovery (FLAIR) (repetition time/echo time [TR/TE] = 10,002/146.3 msec, slice thickness = 6 mm, field of view [FOV] = 22 cm, matrix = 288 × 160), axial T2 weighted image (TR/TE = 4,800/99.8 msec, slice thickness = 6 mm, FOV = 22 cm, matrix = 512 × 320), volumetric three-dimensional (3D) T1-weighted (T1W) images (TR/TE = 5.8/1.9 msec, slice thickness = 1.0 mm, FOV = 22 cm, matrix = 320 × 192). For the TOSHIBA scanner they were oblique axial and coronal FLAIR (TR/TE = 6,200/10.5 msec, slice thickness = 3 mm, FOV = 22 cm, matrix = 320 × 224), oblique axial and coronal T1W images acquired by fast spin-echo-based three-dimensional real inversion recovery (3D-Real IR) (TR/TE = 1,800/10.0 msec, slice thickness = 2 mm, FOV = 20 cm, matrix = 256 × 256). In all patients these studies returned normal findings.

MEG recording

MEG recordings were digitized at 600.615 Hz using the Neuromag System (whole-head 306-channel type, Elekta-Neuromag O.Y., Helsinki, Finland). We simultaneously recorded the EEG using 19 scalp electrodes, electrocardiograms, and electrooculograms. MEG recording was in 3 - 6 blocks lasting 20 - 30 min with the patients awake or in spontaneous sleep states. We classified the distribution of an equivalent current dipole (ECD) into clusters and scatters[9].

PET imaging

^{18}F-FDG PET and ^{11}C-FMZ PET scans of all 10 patients were performed on a Discovery ST Elite PET/CT scanner (GE Medical Systems, Milwaukee, WI, USA). The patients fasted for at least 4 hr before ^{18}F-FDG PET. Image acquisition was started 50 min after the intravenous (iv) injection of ^{18}F-FDG (2.8 MBq/kg). Emission PET data were acquired for 7 min in 3D mode after brain CT scanning for attenuation correction. The PET images were reconstructed using a 3D-ordered subsets

expectation maximization algorithm in a 128 × 128 matrix with a FOV of 256 mm × 256 mm and a slice thickness of 3.27 mm.

For ^{11}C-FMZ PET, image acquisition was started immediately after the iv injection of ^{11}C-FMZ (400 MBq/body). Emission PET data were acquired for 60 min in 3D mode (dynamic acquisition at 40 sec × 1 frame (Fr), 20 sec × 10 Fr, 60 sec × 4 Fr, 180 sec × 4 Fr, and 300 sec × 8 Fr). The PET images were reconstructed using a filtered back projection algorithm in a 256 × 256 matrix with a FOV of 307 mm × 307 mm and a slice thickness of 3.27 mm. We produced ^{11}C-FMZ static images and ^{11}C-FMZ BP images from ^{11}C-FMZ PET data. ^{11}C-FMZ static images were obtained from 40 - 60-min dynamic acquisition data. ^{11}C-FMZ BP images were prepared by using a simplified reference tissue model (SRTM) that facilitates quantitative receptor imaging without the need for arterial blood samples[13].

To obtain data on normal individuals we enlisted 30 healthy volunteers (15 males, 15 females, age 22 - 42 years, mean 32.5 years) with normal MRI results and no prior history of any medical, developmental, or psychiatric disorders; 15 volunteers each underwent ^{11}C-FMZ PET- and ^{18}F-FDG PET studies.

All ^{18}F-FDG PET, ^{11}C-FMZ PET, and ^{11}C-FMZ BP images from the 10 patients and 30 controls were spatially normalized to each template, created in-house, by non-rigid registration and standardized images were obtained.

Statistical image analysis

We compared the standardized images of the patients and controls. Statistical significance was set at a Z-score ≦ –2 by voxel-based analysis. The Z-score was obtained with the formula:

$$\text{Z-Score} = \frac{\text{Voxel value of individual patient-Mean voxel value of volunteers}}{\text{Standard deviation of volunteer's voxel value}}$$

The rank order of epileptic focus candidates was determined on the basis of the value of R. R was obtained with the formula:
R = the mean Z-score of contiguous voxels with a Z-score ≦ –2 × the number of contiguous voxels. R was shown as negative value.
Epileptic focus candidates were visualized on a color map on standardized axial ^{18}F-FDG PET, ^{11}C-FMZ PET, and ^{11}C-FMZ BP images.

The color map images of epileptic focus candidates were automatically displayed on a computer screen. The candidate regions for epileptic foci were colored in 10 steps (e.g. white = first candidate; region with a lowest R value, purple, red, orange color, yellow, yellow green, green, sky blue, blue, dark blue = region with a highest R value) (See colored bar on the left side of Fig. 1A and B). One neuroradiologist with 11 years of experience evaluated the candidate regions on color map images and estimated the registration errors. Candidate regions in cerebrospinal fluid (CSF) or white matter were considered registration errors and disregarded. The reader selected first and second candidates from which registration errors were removed.

Data analysis for localization ability

Lobar concordance was presented if the PET localization indicated the same lobar region as surgical site. Lobar concordance was evaluated in 8 regions (4 cerebral regions of each hemisphere). When the results of one or more test of ^{18}F-FDG PET, ^{11}C-FMZ PET and ^{11}C-FMZ BP were concordant for the lobar location of the epileptic foci, it was defined as concordant in ^{18}F-FDG /^{11}C-FMZ /^{11}C-FMZ BP.

In patients with postoperative Engel I seizure outcome, we assessed the sensitivity and specificity of lobar concordance using the first and second candidates on ^{18}F-FDG PET, ^{11}C-FMZ PET, ^{11}C-FMZ BP image, and ^{18}F-FDG /^{11}C-FMZ /^{11}C-FMZ BP.

Data analysis of the localization in patients with postoperative Engel I and Engel II-IV seizures

The localization indicated by the different tests was compared based on an earlier study[20]; the concordance scores were 2 = lobar concordance; 1 = hemispheric concordance; 0 = discordance or no localization. We assessed the concordance scores by using the first candidates in our statistical image analysis. Lobar concordance was presented if the PET localization indicated the same lobar region as the surgical site, hemispheric concordance if the hemisphere was the same. Otherwise, the findings were considered discordant or non-localizing. The total concordance score for each patient was determined by summing the concordance scores of all 3 tests. We compared the concordance scores in patients with post-treatment Engel I and Engel II-IV seizures. In both groups we used the Shirley-Williams multiple comparison test to evaluate the concordance scores among F-FDG PET, ^{11}C-FMZ PET, and ^{11}C-FMZ BP images.

RESULTS

Seizure profiles

Table 1 shows the clinical profiles, the results of presurgical imaging studies, and the resection area of the 10 patients, 4 of whom were males. Their ages ranged from 14 to 46 years (mean 28.8 years). Five patients had partial seizures alone. The other 5 manifested ictal symptoms on SVEEG of partial seizures with secondary generalization. There were 5 patients with complex partial and one patient with simple partial seizures. The ictal onset on SVEEG was localized in 5 patients, 4 had multiple foci. MEG spikes were observed in 8 patients, 3 had single-cluster ECDs suggestive of the epileptic zone. Two independent clusters were seen in the bilateral hemispheres of 2 patients. In the other patients there were scattered or no epileptic spikes on

MEG recordings. In 5 patients ^{123}I-IMZ SPECT findings were unilaterally abnormal, in the others there were bilateral abnormal or no findings on ^{123}I-IMZ SPECT.

Surgical procedures, postoperative seizure outcome, and histological findings

The surgical procedures were single- (n=2) and multilobar corticectomy (n=4) and anterior temporal lobectomy with amygdalohippocampectomy (n=2) or hippocampal transection (n=2) (Table 2). In the course of 20 to 49-month postoperative follow-up (mean 35.8 months), 5 patients suffered no (Engel class I) and the other 5 residual seizures (Engel class II-IV). The residual seizures experienced by 2 patients (Engel class II) during a one- and two year post-operative period abated in the most recent 8 and 12 months. In the other 3 (Engel class IV) there was no improvement.

Of the 10 patients, 3 had cortical dysplasia and 2 had gliosis; in one patient it was probably accompanied by cortical dysplasia. In another patient we observed tissue-destructive lesions; the other 4 were free of significant alterations.

Localization ability

We selected 5 patients (Cases 1, 2, 3, 4, and 5) with good outcomes (Engel class I) to analyze the

Table 1. Clinical characteristics of the 10 epilepsy patients

Case	Age/Sex	Seizure semiology	SVEEG		MEG-ECD	^{123}I-IMZ SPECT	^{18}F-FDG PET	^{11}C-FMZ PET	^{11}C-FMZ BP	^{18}F-FDG/^{11}C-FMZ/ ^{11}C-FMZ BP	Sugical resection
			ictal	interictal							
1	33/M	CPS 2nd GTC	L F•T	L F•T	L P cluster	L F•T	L F•T•P	L T•P	L T, R T	L F•T•P, R T	L F•T
2	32/M	CPS	L T	L T	R T, L T scatters	L T	L F•T	L T	L T, R T•O	L F•T, R T•O	L T
3	38/F	CPS	R F•T	R F•T	R F•T cluster	R F•T	R F, L F	L F•O	R T•O, L T•O	R F•T•O, L F•T•O	R F•T
4	22/M	CPS 2nd GTC	R T, L T	R T, L T	R T, L T clusters	R T, L T	R T•P	L T	L T	R T•P, L T	R T
5	14/F	SPS CPS	Not localized	Not localized	R F•T, L F scatters	Not localized	R F, L F	L F•T	R T•O, L T•O	R F•T•O, L F•T•O	R F
6	46/F	CPS	R T	R T, L T	No spike	L F•T	L F	L P	R T, L T	R T, L F•T•P	L T
7	23/F	CPS	R F, L F	R F•T, L F•T	R T, L T clusters	Not localized	R F, L P	R O, L O	R T, L T•P	R F•T•O, L T•P•O	L F
8	28/M	CPS 2nd GTC	R F	R F, L F•T	R F cluster	L T	L F	L F	R T, L T	R T, L F•T	R F•T
9	28/F	SPS CPS 2nd GTC	R T•O, L O	R T, L T	R T•O scatter	R F•O, L F•O	R F, L F	Not localized	R T, L F	R F•T, L F	R T•O
10	24/F	CPS 2nd GTC	R T, L T	R T, L T	No spike	R T,L T	R F•T•P, L F•T•P	R F•T, L F	R F•T, L P	R F•T•P, L F•T•P	R T

Abbreviations: CPS = complex partial seizure, 2nd = secondary, GTC = generalized tonic-clonic seizure, SPS = simple partial seizure, SVEEG = scalp video-electroencephalography, L = left, R = right, F = frontal lobe, T = temporal lobe, O = occipital lobe, P = parietal lobe, MEG = magnetoencephalography, ECD = equivalent current dipole, ^{123}I-IMZ SPECT = [^{123}I]iomazenil single-photon emission computed tomography, ^{18}F-FDG PET = [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography, ^{11}C-FMZ PET = [^{11}C]flumazenil positron emission tomography, ^{11}C-FMZ BP = [^{11}C]flumazenil binding-potential imaging.

Table 2. Operations and surgical seizure outcomes (Engel class) in 10 patients

Case	Age/Sex	Operation	Engel class	Histology
1	33/M	L frontal corticectomy, temporal corticectomy	I	No significant alterations
2	32M	L anterior temporal lobectomy with amygdalohippocampectomy	I	Gliosis and probable focal cortical dysplasia type I
3	38/F	R frontal corticectomy, temporal corticectomy	I	No significant alterations
4	22/M	R anterior temporal lobectomy with hippocampal transection	I	No significant alterations
5	14/F	R frontal corticectomy	I	Cortical dysplasia
6	46/F	L anterior temporal lobectomy with hippocampal transection	II	No significant alterations
7	23/F	L frontal corticectomy	II	Focal cortical dysplasia type IIb
8	28/M	R frontal corticectomy, temporal corticectomy	IV	Gliosis
9	28/F	R temporal corticectomy, occipital corticectomy	IV	Tissue-destructive lesion (etiology unknown)
10	24/F	R anterior temporal lobectomy with amygdalohippocampectomy	IV	Non-hippocampal sclerosis, focal cortical dysplasia type I

Table 3. Results of statistical image analysis of the lobar location of the first and second focus candidates

Case	Age/Sex	Imaging technique				Surgical resection
		^{18}F-FDG PET	^{11}C-FMZ PET	^{11}C-FMZ BP image	^{18}F-FDG /^{11}C-FMZ /^{11}C-FMZ BP	
1	33/M	L F•T•P	L T•P	L T, R T	L F•T•P, R T	L F•T
2	32/M	L F•T	L T	L T, R T•O	L F•T, R T•O	L T
3	38/F	R F, L F	L F•O	R T•O, L T•O	R F•T•O, L F•T•O	R F•T
4	22/M	R T•P	L T	L T	R T•P, L T	R T
5	14/F	R F, L F	L F•T	R T•O, L T•O	R F•T•O, L F•T•O	R F

Abbreviations: L = left, R = right, F = frontal lobe, O = occipital lobe, P = parietal lobe, T = temporal lobe, ^{18}F-FDG PET = [^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography, ^{11}C-FMZ PET = [^{11}C]flumazenil positron emission tomography, ^{11}C-FMZ BP = [^{11}C]flumazenil binding potential imaging

diagnostic capability of the various imaging techniques (Table 3). In patients where first and second lobar focus candidates were identified, the sensitivity and specificity for lobar localization were greater for ^{18}F-FDG PET than the other imaging modalities. They were 100.0% and 51.4% for ^{18}F-FDG PET/^{11}C-FMZ PET/^{11}C-FMZ BP imaging (Table 4).

In all but Case 3 the epileptic foci were visualized on ^{18}F-FDG PET images; they were superior to ^{11}C-FMZ PET and ^{11}C-FMZ BP images. In case 3 the epileptic focus not visualized on ^{18}F-FDG PET scans was revealed on the ^{11}C-FMZ BP image (Fig. 1).

Table 4. Sensitivity and specificity for lobar focus localization on ^{18}F-FDG PET, ^{11}C-FMZ PET, and ^{11}C-FMZ BP images and ^{18}F-FDG /^{11}C-FMZ /^{11}C-FMZ BP in patients with Engel I seizure outcomes

	Sensitivity	Specificity
^{18}F-FDG PET	90.0 %	84.8 %
^{11}C-FMZ PET	30.0 %	81.4 %
^{11}C-FMZ BP image	40.0 %	66.7 %
^{18}F-FDG /^{11}C-FMZ /^{11}C-FMZ BP	100.0 %	51.4 %

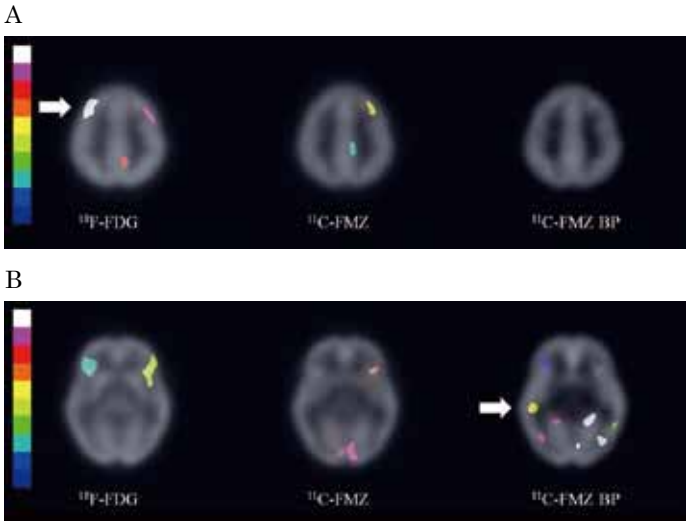

Fig. 1. Case 3. A color map of epileptic focus candidates on each template of axial ^{18}F-FDG PET, and ^{11}C-FMZ PET and ^{11}C-FMZ BP images. The patient underwent right frontal and temporal corticectomy based on the results of IVEEG monitoring and electrocortical stimulation brain mapping. The reader selected first and second candidates from which registration errors were removed. The first and second candidates were used to analyze the diagnostic capability (See Table 3).

A: The right frontal lobe was identified as an epileptic focus candidate by ^{18}F-FDG PET but not by ^{11}C-FMZ PET and ^{11}C-FMZ BP imaging. The first and second candidates were right frontal lobe (white) and left frontal lobe (purple) on ^{18}F-FDG PET, respectively.

B: The right temporal lobe was identified as an epileptic focus candidate by ^{11}C-FMZ BP imaging but not on ^{18}F-FDG PET images. The first and second candidates were left temporal and occipital lobe (white) and right temporal and occipital lobe (yellow) on ^{11}C-FMZ BP imaging, respectively. Epileptic focus candidates displayed in purple, red and orange color were regarded as registration errors.

Table 5. Localization concordance among the imaging modalities and the resection site

Case	Age/Sex	^{18}F-FDG PET/ score	^{11}C-FMZ PET/ score	^{11}C-FMZ BP image/ score	Total score sum	Surgical resection	Engel class
1	33/M	L F･T / 2	L T･P / 2	L T / 2	6	L F･T	I
2	32/M	L F･T / 2	L T / 2	R T･O / 0	4	L T	I
3	38/F	R F / 2	L O / 0	L T･O / 0	2	R F･T	I
4	22/M	R T･P / 2	L T / 0	L T / 0	2	R T	I
5	14/F	R F / 2	L F / 0	L T･O / 0	2	R F	I
6	46/F	L F / 1	L P / 1	R T / 0	2	L T	II
7	23/F	R F / 0	L O / 1	R T / 0	1	L F	II
8	28/M	L F / 0	L F / 0	L T / 0	0	R F･T	IV
9	28/F	R F / 1	NA / 0	R T / 2	3	R T･O	IV
10	24/F	R F･T･P / 2	R F･T / 2	R F･T / 2	6	R T	IV

Abbreviations: F = frontal lobe; L = left; NA = not available; O = occipital lobe; P = parietal lobe; R = right; T = temporal lobe

Focus localization in patients with Engel I and Engel II-IV seizure outcomes

Table 5 shows the concordance scores for individual patients. Lobar concordance (score=2) on ^{18}F-FDG PET, ^{11}C-FMZ PET, and ^{11}C-FMZ BP image was presented in 6, 3, and 3 patients, respectively. The average total concordance score tended to be higher in Engel I- than Engel II-IV patients (3.2 vs. 2.4) but the difference was not statistically significant. Stipulating that the concordance scores of ^{18}F-FDG PET were higher than those of ^{11}C-FMZ PET and ^{11}C-FMZ BP images, multiple comparison tests showed that the ^{18}F-FDG PET scores were significantly higher ($p < 0.05$) in Engel I patients; in patients with persistent seizures (Engel II-IV), the difference was not significant.

DISCUSSION

We assessed the sensitivity and specificity for lobar localization of the epileptic focus of different imaging modalities in patients whose treatment outcome was classified as Engel I. We found that ^{18}F-FDG PET was superior to ^{11}C-FMZ PET and ^{11}C-FMZ BP imaging and that the sensitivity of ^{18}F-FDG/^{11}C-FMZ/^{11}C-FMZ BP was 100%. In Case 3, ^{11}C-FMZ BP did, while ^{18}F-FDG PET did not show the epileptic focus, suggesting that the addition of ^{11}C-FMZ PET increased the sensitivity for detecting these foci. Our reference standard was an Engel I seizure outcome after cortical resection rather than concordance with IVEEG findings that, because they may not localize the epileptogenic zone, represent a suboptimal reference standard[24].

The sensitivity of ^{18}F-FDG PET in patients with intractable epilepsy was similar in our and earlier studies. Others[7,11,18] reported that its sensitivity was 85% - 90% for the detection of epileptic foci in patients with temporal lobe epilepsy. In patients with extratemporal epilepsy ^{18}F-FDG PET performs more poorly; its sensitivity was 45% - 92% (generally ~55%) for localizing the epileptic focus in the frontal lobe[3,10,21].

The sensitivity of ^{11}C-FMZ PET and ^{11}C-FMZ BP imaging was lower in our study than in earlier studies[14,18]. The comparison of ^{18}F-FDG PET, ^{11}C-FMZ PET and ^{11}C-FMZ BP imaging in epileptic focus localization was discussed in very few reports. In addition, most earlier studies involved patients with abnormal MRI findings. This discrepancy between our and earlier studies may be attributable to their inclusion of patients with abnormal MRI findings. In patients with temporal lobe epilepsy, ^{11}C-FMZ BP was reduced in all patients with abnormal hippocampal volumetry or T2 relaxometry on MRI. ^{11}C-FMZ BP was reduced in 46% of the patients with a hippocampal volume within the normal range[14]. In 100 patients, including 66 patients with abnormal MRI findings, ^{11}C-FMZ PET showed abnormality in 73 % patients[18].

The sensitivity and specificity for lobar focus localization on ^{123}I-IMZ SPECT scan were 80.0% and 97.1%, respectively; they were 30.0% and 81.4% for ^{11}C-FMZ PET. We evaluated the images of ^{123}I-IMZ SPECT visually. We selected 5 patients (Case 1, 2, 3, 4, 5) with good outcomes (Engel class I) to analyze the diagnostic capability of ^{123}I-IMZ SPECT in the same way as PET studies. ^{123}I-IMZ SPECT was superior to ^{11}C-FMZ PET for the sensitivity especially. Earlier study demonstrated decreased IMZ uptake in ipsilateral mesial temporal region in all patients who had mesial temporal epilepsy on only one side with normal MRI findings[23].

In patient 3, the resection sites were the right frontal and temporal lobe. ^{18}F-FDG PET identified the right frontal lobe as a candidate for the epileptic focus but missed the right temporal lobe; ^{11}C-FMZ BP detected this epileptic focus. This shows that ^{11}C-FMZ BP studies can complement ^{18}F-FDG PET findings in efforts to identify the epileptogenic lobar regions in patients with normal MRI results. Ryvlin et al reported that ^{11}C-FMZ PET yielded useful information that complemented MRI- and ^{18}F-FDG PET findings in specific situations and that in 55% of their patients with unilateral cryptogenic frontal epilepsy it provided further evidence on the side and site of seizure onset[18].

The total concordance score tended to be higher in patients classified as Engel I than Engel II-IV and a high score across the PET studies appeared to be associated with favorable surgical outcomes. However, possibly due to our small sample size, the difference between patients with higher and lower scores was not statistically significant. In our Engel I patients the ^{18}F-FDG PET scores were significantly higher than the scores of ^{11}C-FMZ PET and ^{11}C-FMZ BP ($p < 0.05$). As we used the seizure-free outcome (Engel I) as the reference standard, we concluded that ^{18}F-FDG PET was significantly more useful than ^{11}C-FMZ PET and ^{11}C-FMZ BP from the perspective of the concordance score.

Our study has some limitations. Our sample size was small because we included only epilepsy patients with normal MRI findings and because we excluded patients whose preoperative studies showed that local resection was not indicated. In addition, because a seizure-free outcome was our reference standard, we included only patients that could be followed for at least one year. Second, a neuroradiologist subjectively identified the first and second candidates for epileptic foci on a color map and discounted foci on the CSF or white matter as registration errors. A larger database is needed to reduce registration errors.

In summary, overall, ^{18}F-FDG PET was superior to ^{11}C-FMZ PET and ^{11}C-FMZ BP imaging with respect to sensitivity and specificity. However, in some cases such as our Case 3, ^{11}C-FMZ BP- can complement ^{18}F-FDG PET findings in efforts to identify the epileptogenic lobar regions in patients with

normal MRI results.

ACKNOWLEDGEMENTS

The authors have no conflict of interest.

(Received August 30, 2015)
(Accepted November 11, 2015)

REFERENCES

1. **Berg, A.T., Shinnar, S., Levy, S.R., Testa, F.M., Smith-Rapaport, S. and Beckerman, B.** 2001. Early development of intractable epilepsy in children: a prospective study. Neurology **56**: 1445-1452.
2. **Bien, C.G., Szinay, M., Wagner, J., Clusmann, H., Becker, A.J. and Urbach, H.** 2009. Characteristics and surgical outcomes of patients with refractory magnetic resonance imaging-negative epilepsies. Arch. Neurol. **66**: 1491-1499.
3. **da Silva, E.A., Chugani, D.C., Muzik, O. and Chugani, H.T.** 1997. Identification of frontal lobe epileptic foci in children using positron emission tomography. Epilepsia **38**: 1198-1208.
4. **Engel, J., Jr., Rasmussen, T. and Ojemann, L.** 1993. Outcome with Respect to Epileptic Seizures, 2nd ed. Raven Press, New York.
5. **Engel, J., Jr.** 1998. Etiology as a risk factor for medically refractory epilepsy: a case for early surgical intervention. Neurology **51**: 1243-1244.
6. **Farrell, K., Wirrell, E. and Whiting, S.** 2006. The definition and prediction of intractable epilepsy in children. Adv. Neurol. **97**: 435-442.
7. **Gaillard, W.D., Bhatia, S., Bookheimer, S.Y., Fazilat, S., Sato, S. and Theodore, W.H.** 1995. FDG-PET and volumetric MRI in the evaluation of patients with partial epilepsy. Neurology **45**: 123-126.
8. **Gok, B., Jallo, G., Hayeri, R., Wahl, R. and Aygun, N.** 2013. The evaluation of FDG-PET imaging for epileptogenic focus localization in patients with MRI positive and MRI negative temporal lobe epilepsy. Neuroradiology **55**: 541-550.
9. **Iida, K., Otsubo, H., Matsumoto, Y., Ochi, A., Oishi, M., Holowka, S., et al.** 2005. Characterizing magnetic spike sources by using magnetoencephalography-guided neuronavigation in epilepsy surgery in pediatric patients. J. Neurosurg. **102**: 187-196.
10. **Kim, Y.K., Lee, D.S., Lee, S.K., Chung, C.K., Chung, J.K. and Lee, M.C.** 2002. (18)F-FDG PET in localization of frontal lobe epilepsy: comparison of visual and SPM analysis. J. Nucl. Med. **43**: 1167-1174.
11. **Knowlton, R.C., Laxer, K.D., Ende, G., Hawkins, R.A., Wong, S.T., Matson, G.B., et al.** 1997. Presurgical multimodality neuroimaging in electroencephalographic lateralized temporal lobe epilepsy. Ann. Neurol. **42**: 829-837.
12. **Kwan, P. and Brodie, M.J.** 2000. Early identification of refractory epilepsy. N. Engl. J. Med. **342**: 314-319.
13. **Lammertsma, A.A. and Hume, S.P.** 1996. Simplified reference tissue model for PET receptor studies. NeuroImage **4**: 153-158.
14. **Lamusuo, S., Pitkanen, A., Jutila, L., Ylinen, A., Partanen, K., Kalviainen, R., et al.** 2000. [11 C]Flumazenil binding in the medial temporal lobe in patients with temporal lobe epilepsy: correlation with hippocampal MR volumetry, T2 relaxometry, and neuropathology. Neurology **54**: 2252-2260.
15. **Mintun, M.A., Raichle, M.E., Kilbourn, M.R., Wooten, G.F. and Welch, M.J.** 1984. A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. Ann. Neurol. **15**: 217-227.
16. **Rocher, A.B., Chapon, F., Blaizot, X., Baron, J.C. and Chavoix, C.** 2003. Resting-state brain glucose utilization as measured by PET is directly related to regional synaptophysin levels: a study in baboons. NeuroImage **20**: 1894-1898.
17. **Romanelli, P., Striano, P., Barbarisi, M., Coppola, G. and Anschel, D.J.** 2012. Non-resective surgery and radiosurgery for treatment of drug-resistant epilepsy. Epilepsy Res. **99**: 193-201.
18. **Ryvlin, P., Bouvard, S., Le Bars, D., De Lamerie, G., Gregoire, M.C., Kahane, P., et al.** 1998. Clinical utility of flumazenil-PET versus [18F]fluorodeoxyglucose-PET and MRI in refractory partial epilepsy. A prospective study in 100 patients. Brain **121**: 2067-2081.
19. **Savic, I., Thorell, J.O. and Roland, P.** 1995. [11C] flumazenil positron emission tomography visualizes frontal epileptogenic regions. Epilepsia **36**: 1225-1232.
20. **Seo, J.H., Holland, K., Rose, D., Rozhkov, L., Fujiwara, H. and Byars, A.** 2011. Multimodality imaging in the surgical treatment of children with nonlesional epilepsy. Neurology **76**: 41-48.
21. **Swartz, B.W., Khonsari, A., Vrown, C., Mandelkern, M., Simpkins, F. and Krisdakumtorn, T.** 1995. Improved sensitivity of 18FDG-positron emission tomography scans in frontal and "frontal plus" epilepsy. Epilepsia **36**: 388-395.
22. **Tellez-Zenteno, J.F., Hernandez Ronquillo, L., Moien-Afshari, F. and Wiebe, S.** 2010. Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. Epilepsy Res. **89**: 310-318.
23. **Umeoka, S.,Matsuda, K., Baba, K., Usui, N., Tottori, T., Terada, K., et al.** 2007. Usefulness of ^{123}I-iomazenil single-photon emission computed tomography in discriminating between mesial and lateral temporal lobe epilepsy in patients in whom megnetic resonance imaging demonstrates normal findings. J. Neurosurg. **107**: 352-363.
24. **Widjaja, E., Shammas, A., Vali, R., Otsubo, H., Ochi, A., Snead, O.C., et al.** 2013. FDG-PET and magnetoencephalography in presurgical workup of children with localization-related nonlesional epilepsy. Epilepsia **54**: 691-699.

CONTENTS

Hiroshima J. Med. Sci.
December 2015 volume 64 number 4