

Can Ictal F18-FDG PET/CT Drawing Epileptogenic Zone in Refractory Focal Epilepsy? Histopathological and Outcome Correlation

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Abstract

Unlike interictal Positron Emission Tomography (PET), ictal PET is not regularly used in the study of refractory focal epilepsy, and its usefulness in presurgical evaluations, and prognosis value have not been established. The aim is to present six patients with epilepsy whose PET/CT brain scans showed focal hypermetabolism, and analyze their correlation with the histopathological findings and clinical results. We reviewed 146 18F-FDG PET/CT scans performed on patients with refractory focal epilepsy. Only those cases with hypermetabolic foci which were subsequently surgically resected were selected. The epidemiological and clinical data were reviewed in addition to the brain MRI, Electroencephalography (EEG), video-EEG monitoring, intraoperative Electrocorticography (ECoG), histopathology, and postsurgical outcome. The PET findings were correlated with the clinical characteristics of the seizures, the EEG, brain MRI, ECoG, and histopathology. Seven PET/CT scans carried out on six patients showed well-defined hypermetabolic foci (three temporal, four extratemporal). There was a high correlation between the clinical lateralization, EEG/ECoG findings, and hypermetabolic foci located by PET. An MRI correctly identified the resected histopathological lesion in five cases and it was negative in two. Three patients had Focal Cortical Dysplasia (FCD), one had FCD with areas of polymicrogyria, one had temporal lobe cavernoma associated with hippocampal sclerosis, and one had a focal subcortical heterotopia. Mean postsurgical follow-up was 29.1 months (range: 16-24 months) and all patients were seizure free during this period. This small series of patients who underwent surgery for intractable focal epilepsy have shown good correlation between the ictal F18-FDG PET/CT scan and the electroclinical and pathological findings. These results suggest that hypermetabolic foci showed in PET/CT provides a reliable estimation of epileptogenic zone. Focus size underestimation in one case suggest the need of doing an interictal PET before surgery.

Keywords: 18F-FDG; PET; Ictal; Hypermetabolic; Histopathology; Epileptogenic zone

Introduction

Positron Emission Tomography (PET) of the brain plays an important role in the study of patients with drug-resistant focal epilepsy since it helps identify epileptogenic foci in non-lesional cases. The most frequently used PET radiotracer in epilepsy is [18F]fluoro-D-glucose (18F-FDG) which is avidly uptaken by the cerebral cortex. The study is normally carried out during the interictal phase (without clinical seizures) when a cortical area with a reduced glucose uptake can be observed. The sensitivity of interictal PET with 18F-FDG for lateralization of focus is 80-90% in temporal epilepsy and 50-70% in extratemporal epilepsy, higher than a MRI in cases of cortical dysplasia [1-3].

Several authors have reported the occurrence of clinical or electrographic seizures while the PET is being performed, associated with hypermetabolic areas of the brain (meaning, a higher uptake of glucose) and this has been given the name of ictal PET [4,5]. However, the clinical importance of a hypermetabolic focus obtained in an ictal PET, its relationship with the electroclinical and anatomopathological findings, and its prognosis value after surgery have not yet been

established. The purpose of this study is to report seven ictal 18F-FDG PET/CT studies performed on six patients with refractory focal epilepsy that presented focal brain glucose hypermetabolism, and analyze their correlation with the histopathological findings and clinical results.

Patients and Methods

A total of 146 PET/CT scans with F18-FDG performed on patients who were referred due to refractory focal epilepsy between December 2008 and June 2012 were reviewed. All patients had been previously subjected to a high quality brain MRI with epilepsy protocol, and at least one surface EEG recording or prolonged video-EEG monitoring. PET/CT F18-FDG scans were visually reviewed, selecting those that showed focal cerebral increased uptake. Only those patients who underwent surgery and had a complete histological analysis were included in the study. All but one patient with hypermetabolic foci were monitored with scalp EEG during PET.

The PET was performed using a 16 channel-GE Discovery STE PET/CT equipment. Images were acquired 45 minutes after intravenous administration of 18F-FDG (injected dose: 3.7 MBq/kg). Three-dimensional (3D) acquisition of the brain was done for 15 minutes. The PET-CT hybrid images were read by an expert nuclear

medicine physician (DLdeG) and by an experienced neuroradiologist (MG), with a consensus report. The PET/CT images were fused with contemporary MRI using proper software (Fusion GE).

Patient preparation before screening consisted of a 4 hour fast, and a 24-hour period of abstinence from tobacco, alcohol, cola drinks, tea and coffee. Prior to injection, the patient was subjected to one hour of sensory deprivation in a semi-dark and quiet room. Patients were monitored with a scalp EEG before and during the PET. EEG electrodes were placed before entering the special room, in accordance with the International 10-20 system of Electrode Placement. EEG recording was started 30 minutes before the injection and extended until acquisition time (approximately 65-75 minutes of monitoring). The test was analysed by an expert neurophysiologist and the EEG findings were included in the PET/CT report. Younger pediatric patients were studied under anaesthesia using profound sedation during PET acquisition (approximately 20 minutes sedation).

PET images were evaluated visually and semi-quantitatively comparing Regions Of Interest (ROIs) with analogous contralateral cerebral cortex and contralateral frontal, temporal, and parietal (non-analogous) cortex which were used as references in a similar manner as Phi et al. [6]. Lesion-to-Gray matter Ratio (LGR) was calculated for analogous contralateral and non-analogous contralateral cortex in accordance with this method. A T-test was used for the statistical analysis. Surgery was performed on average 57 days after the PET/CT scan (range: 10-178 days). Presurgical planning included identification of primarily hypermetabolic area guided by a PET/MRI imaging fusion. The hypermetabolic area was fully included in the planned resection based on a system of neuronavigation (BrainLAB®). An intraoperative ECoG was performed in six surgeries and an intraoperative Ultrasound (US) in three surgeries.

All patients were followed up after surgery and they were classified according to the Engel Scale [7], in which Class I corresponds to patients free of disabling seizures, Class II to rare disabling seizures, Class III to significant improvement, and class IV to no significant

improvement. In addition to the latter, the evaluation also used the ILAE classification system [8] in which Class 1 consists of patients who are completely seizure free and without auras, Class 2 patients who only experience auras, Class 3 patients with one to three seizure days per year, Class 4 patients with four seizure days per year to 50% reduction of baseline seizure days, Class 5 patients with less than 50% reduction of baseline seizure days, and Class 6 patients with more than 100% increase of baseline seizure days. The requirement to obtain informed consent was waived.

Results

Median age at PET study was 3 years (range 1 month-38 years). All patients suffered from frequent seizures or non-convulsive epileptic status when the PET was performed. All of them showed ictal or interictal epileptiform activity when subjected to the EEG during or after FDG injection. Only one patient lacked EEG monitoring during PET, with clinical seizure occurring after FDG injection. Seven ictal PET studies, carried out on six patients, showed well-defined hypermetabolic foci (three temporal, four extratemporal), and with histopathologic confirmation of a lesion in all of them. There was good correlation between the clinical evaluation (focalization and lateralization), EEG/ECoG findings, and hypermetabolic foci in all cases. The MRI correctly identified the histologic lesion in five cases (three cases with type II FCD, one with FCD plus areas of polymicrogyria, and one with focal subcortical heterotopia); and it was negative in two cases (one with type Ia FCD and the other with hippocampal sclerosis plus amygdala gliosis, coexisting with temporal lobe cavernoma, which was evident in the MRI). The mean post-surgical follow-up was 29.1 months (range: 16-42 months) and all patients were seizure free for this period.

The post-surgical outcome as well as a summary of the clinical, EEG, MRI, PET, intraoperative and histopathological findings are shown in Table 1. Cases 1 and 3 are shown in Figures 1 and 2.

Subject	Gender/Age at PET/CT study	Age at epilepsy onset	Seizure semiology	Interictal EEG	Ictal EEG	MRI	PET and EEG findings during PET	Type of surgery and intraoperative ECoG	Histopathological findings	Follow-up and outcome (Engel/ILAE)
1	M/10 months	2 months	Asymmetric tonic posturing of upper limbs, tonic eye version to the left, and left head version.	R fronto-central	R frontal	Possible R frontal FCD	R frontal hypermetabolism (Figure 1)	R frontal cortex resection	Type IIb FCD	42 m
							Without EEG during PET (Clinical seizures AI)	Without EA post-resection		I/1a
2 (*)	M/1 months	6 days	Ictal apnea, pallor, cyanosis, flushing, and staring.	R temporo-occipital	R temporo-occipital	Signal abnormality in R occipital white matter suggesting FCD	Intense R occipital hypermetabolism, mild R temporal hypermetabolism.	R occipital lobectomy	Type IIa FCD	37 m
							R posterior electrographic ictal events BI and AI.	ECoG Not performed		IV/5

3 (*)	M/4 months	6 days	Loss of consciousness, change in facial expression, right tonic eye version, tonic posturing of right limbs.	R temporal	R temporal	Possible FCD in R temporal pole	Intense R temporal hypermetabolism (Figure 2) R temporal electroclinical ictal events BI and AI. Interictal PET: Severe R temporal hypometabolism (**). R temporal interictal EA.	R temporal lobectomy, R hippocampectomy, R anterior frontal topectomy Without post-resection EA	Type IIa FCD and polymicrogyria	30 m I/1a
4	F/38 years	36 years	Loss of consciousness, oral and right hand automatisms.	R temporal	R temporal	Mild R hippocampal sclerosis	R hippocampal hypermetabolism. R anterior mesial temporal electrographic ictal events AI.	R temporal lobectomy Without post-resection EA	Type IIb FCD	40 m I/1a
5	F/37 years	30 years	Abdominal aura, fear and oral automatisms with or without impairment of awareness.	Normal EEG	R temporal	R temporal posterior-mesial cavernoma	R amygdala hypermetabolism, hypometabolic focus over cavernoma. Intermittent polymorphic theta over R fronto-temporal region during drowsiness BI and AI. Occasional R fronto-temporal sharp waves in somnolence BI.	Cavernoma resection, R amygdalohippocampectomy Without post-resection EA	Cavernoma, hippocampal sclerosis, and amygdala gliosis.	22 m I/1a
6	M/3 years	3 months	Loss of consciousness, eye blinking, eye version to the right, right limbs clonic activity, upper limbs tonic posturing.	L frontal	L frontal	Normal	L frontal hypermetabolism Frequent interictal EA in L fronto-temporal region BI and AI.	L frontal resection Residual EA over L primary motor cortex	Type Ia FCD	17 m II/1a
7	F/9 years	7 years	Loss of consciousness, oral and	R frontal	R frontal	R frontal cortical lesion	Hypermetabolic focus over R middle and	R frontal resection	Focal subcortical heterotopia	16 m

			hands automatisms, sudden behavior changes.			suggesting FCD	superior frontal gyri, and superior frontal sulcus.		and diffuse gliosis	I/1a
							R frontal electrographic ictal events AI.	Without post-resection EA		

Table 1: Epidemiological, electroclinical, neuroimaging, histopathological findings and clinical outcome. EEG: Electroencephalogram; BI: Before Injection of F18-FDG; AI: After Injection of F18-FDG; MRI: Magnetic Resonance Imaging; PET/CT: Positron Emission Tomography; ECoG: electrocorticography; M: Male; F: Female; FCD: Focal Cortical Dysplasia; PLEDs: Periodic Lateralized Epileptiform Discharges; EA: Epileptiform Activity; US: Ultrasound; mo: Months; y: Years; d: Days; (*): This patient operated on twice is considered an individual patient for each operation; (**): This patient also had interictal PET study.

Location of the hypermetabolic foci and LGR index, and its correlation with the video-EEG, MRI, pre and post resection ECoG, intraoperative ultrasound and histopathology findings are shown in Table 2.

Case	Hypermetabolic focus	PET	PET LGR An	PET LGR Non An	Concordant Video-EEG	MRI	ECoG before/ after resection	Intraoperative US	Histopathology
1	R frontal		1,42	1,39	+	+	+/-	+	FCD IIb
2	R occipital		1,50	1,53	+	+	+/+	NP	FCD IIa
3	R temporal		1,89	1,73	+	+	+/NP	-	FCD IIa
4	R hippocampus		1,73	1,07	+	+	NP	NP	FCD IIb
5	R hippocampus amygdala	+	1,26	0,72	NP	-	+/-	NP	HS
6	L frontal		1,14	1,26	+	-	+/+	NP	FCD Ia
7	R frontal		1,24	1,27	+	+	+/-	+	Heterotopia

Table 2: LGR: Lesion-to-grey matter ratio; An: analogous contralateral measure, Non An: Frontal, parietal and temporal contralateral mean measure; ECoG: Intraoperative electrocorticography; US: Ultrasonography; NP: Not performed. FCD: Focal Cortical Dysplasia; HS: Hippocampal Sclerosis. PET hypermetabolic foci location and LGR index, and its correlation with video-EEG, MRI, pre and post resection ECoG, intraoperative US and histopathology findings.

Hypermetabolic lesions showed a mean LGR of 1.45 (SD: 0.28) with regards to the analogous cortex and a LGR of 1.40 (SD: 0.45) with regards to the non-analogous cortex (mean frontal, temporal, and parietal uptake). Type II FCD had a significantly higher (p: 0.02) hypermetabolism (mean LGR: 1.63, SD: 0.22) than the rest of lesions corresponding to Type I FCD, heterotopia and hippocampal sclerosis (mean LGR: 1.21, SD: 0.06).

Discussion

The main goal of the presurgical evaluation of patients with medically refractory epilepsy is to identify the group of cortical neurons that generate aberrant electrical activity [9]. Isotopic techniques are of great help in determining the epileptogenic zone and they are mainly represented by ictal SPECT (Single Photon Emission Computed Tomography) and the interictal PET [10]. Interictal SPECT has limited value as an isolated screening method and it is only useful when compared with an ictal SPECT taken during or immediately after a seizure [11].

The radiopharmaceutical most commonly used in brain PET imaging is 18F-FDG [12]. Its usefulness in focal epilepsy lies in that the epileptogenic cortex shows less glucose uptake than normal brain parenchyma [13]. Since this condition of metabolic deficit is maintained over time, the interictal 18F-FDG PET can be performed at any time during the intervals without seizures. The extension of the hypometabolic areas tends to be greater than the area determined by the interictal EEG and brain MRI [14] thus the reason why it is usually said that interictal PET overestimates the focus extension. Ictal PET has been described as functional brain imaging, performed during a seizure, which shows hypermetabolic cerebral areas, meaning, an increase in the uptake of 18F-FDG when compared to normal cortex [5,15,16]. The first reported cases were “incidental” due to the fortuitous occurrence of spontaneous seizures during an intended interictal study [17-19].

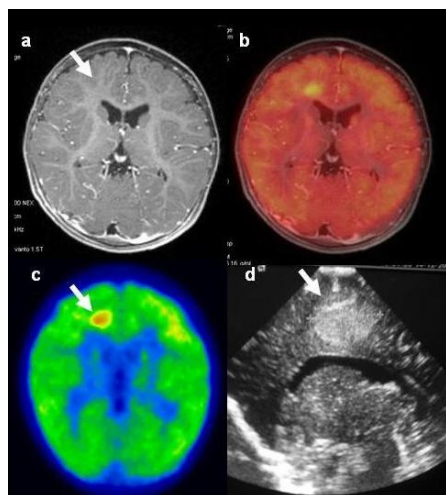


Figure 1: T1 gadolinium MRI (a), fusion PET/MRI (b), PET (c) and intraoperative US (d) of patient with frontal right focal refractory epilepsy. Histopathology: Type II b FCD.

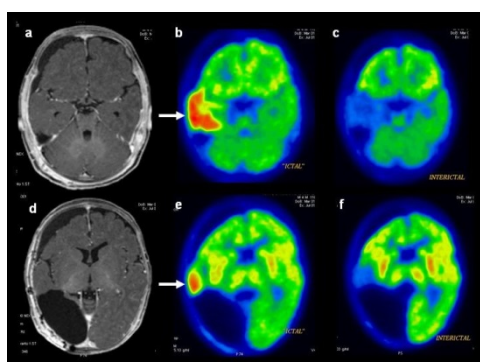


Figure 2: Patient of case 3, previously resected right occipital lesion. T1 gadolinium MRI (a,d) shows post-surgery changes and extradural right collection. Ictal PET (b,e) shows an intense hypermetabolic right temporal lobe. The next day an interictal PET is performed (c,f), and the same territory is now intensely hypometabolic. Histopathology: Type II a FCD and polymicrogyria.

Of these reported cases, only a few publications make a reference to EEG monitoring during a PET scan. In our presented series, all but one patients were subjected to EEG monitoring and had ictal or interictal epileptiform activity during or immediately after the FDG injection, some of them with no clinical manifestation whatsoever. For this reason, the only way to recognize the aforementioned subclinical group is by conducting EEG monitoring during a PET scan.

The relationship between abnormal electrical brain activity and abnormalities in glucose uptake has been mentioned by some authors mainly in interictal studies. Series which use interictal PET suggest that repetitive interictal epileptiform discharges may increase brain carbohydrate metabolism in some individuals with focal epilepsy, even without clinical events [20,21]. Luat et al. describe a close relationship between interictal epileptiform activity and an increase of brain

glucose uptake in children with continuous spike-and-wave activity during slow-wave sleep [22]. Furthermore, Nishida et al. showed a positive correlation between the brain uptake of glucose and gamma oscillations in patients with non-lesional epilepsy [23].

The physiopathological mechanism which increases the uptake of 18F-FDG is still not completely understood, although it seems to be related to the increase of perfusion observed in cerebral perfusion studies with SPECT. Several authors have shown a correlation between perfusion and glucose metabolism during seizures. While using PET with [15O]H₂O and 18F-FDG, Bittar et al. described a metabolism/perfusion relationship when interictal spikes are evoked in patients with reflex epilepsy [24]. However, different levels of decoupling between perfusion and metabolism have been described during ictal and postictal periods, resulting in areas with a significant increase in glucose consumption which are not accompanied by a corresponding increase in blood flow [25,26]. This may mean greater sensitivity or at least a greater contrast resolution of the PET technique over SPECT in ictal studies.

Performing PET studies during epileptic events is technically difficult if we consider the relatively short half-life of 18F-FDG, and the necessity of frequently having to wait for long periods of time for a crisis to occur. On the other hand, taking into account that glucose uptake in cerebral cortex is a gradual process which lasts approximately 30-45 minutes, in the case of injection during a seizure, the final uptake of obtained glucose shall be a combination of the ictal phase with a postictal period, and eventually the interictal phase for the same injection. That is the reason why it is more probable that the ictal PET is feasible only in patients with frequent clinical seizures, or ictal or interictal epileptiform activity while the EEG is being performed.

Although clinical usefulness of an ictal PET scan for detecting the epileptogenic focus has been suggested by some authors [27-29], to date, this presumed utility has not been solidly demonstrated with an adequate anatomopathological correlation or through long term postoperative follow-ups.

Although our descriptive study includes a small series of patients, it is successful since it demonstrates that in all cases the hypermetabolic foci corresponded to histopathologically abnormal cerebral tissue, most of them corresponding to FCD. The cortical lesion showed a 45% greater uptake than the normal contralateral cortex. This hypermetabolic response was significantly more evident for type II FCD with regards to the rest of histopathological lesions, which suggests a unique usefulness of an ictal PET for this type of cortical malformation.

As it is shown in Case 2 (a newborn who underwent two ictal PET and two surgeries), an active epileptogenic area identified during an ictal PET could mask others lesser active foci. For this reason, we must be careful reading ictal PET, especially in cases with large FCD lesions. Performing comparative interictal PET and intraoperative electrocorticography could help to solve this problem.

Our study shows a high correlation between PET characterization of hypermetabolic focus, final surgical resected area and histopathological analysis, and it demonstrates that ictal PET is capable of drawing accurately epileptogenic zone. We believe that it contributes towards considering that an ictal PET can be of great diagnostic and prognostic value in patients with refractory focal epilepsy.

We believe it is essential to carry out EEG monitoring when performing a PET in every patient being studied for epilepsy, and to contextualize the PET metabolic findings according to the electrical brain activity. Many equivocal results from an interictal PET may be due to subclinical electrical activity that occurs during the dynamic process of brain glucose uptake. As observed in one of the cases we have presented, an area of FCD may alternatively appear as hypometabolic in an interictal study or hypermetabolic in an ictal study.

Series with a greater number of patients with ictal PET images, histopathological correlation, and long term postsurgical follow-up are necessary in order to determine which clinical group will benefit more from this test. Most likely, patients with frequent seizures or epileptic status will be preferentially eligible as we observed in our study. It is possible that cortical development malformations, such as FCD, are a particular group of brain lesions in which ictal PET studies become particularly important.

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