Positron emission tomography (PET) scan in epilepsy

Chaichon Locharernkul, Supatporn Tepmongkol, Chusak Limota, Jakrin Loplumlert
Division of Neurology, Department of Medicine, Division of Nuclear Medicine, Department of Radiology, Chulalongkorn Comprehensive Epilepsy Program (CCEP), Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand

Positron Emission Tomography (PET) has an advantage in localizing epileptogenic zones for successful surgery in several epileptic syndromes. Among the most radiopharmaceutical used in PET studies in epilepsy are $^{18}$F fluorodeoxyglucose (FDG) and $^{11}$C flumazenil (FMZ). Unilateral temporal hypometabolism (UTH) seen in FDG-PET was shown to correlate well with ictal EEG origins in 60-90 % of temporal lobe epilepsy (TLE) patients. PET aids in surgical decision-making in TLE patients with discordant data from initial presurgical evaluation, in bitemporal disease and in nonlesional TLE. However, PET adds little in lesonal TLE with congruent data. The extent of glucose hypometabolic area was shown to correlate with post-operative outcomes. PET may reduce the need for invasive EEG in bitemporal epilepsy. Abnormal FMZ binding has been proposed to guide the location of subdural electrode placement in extratemporal epilepsy (ETE). FMZ-PET and FDG-PET were shown to be sensitive in visualizing areas of cortical dysgenesis. Focal FDG-PET abnormality was demonstrated in 20 % of children with West’s syndrome and has provided a revolutionary approach for surgical treatment. Resection of the focal hypometabolism has rendered good control of infantile spasms and restoration of developmental delay. PET use of alpha-$^{11}$C methyl-L-tryptophan (AMT), a serotonin precursor, has been shown to selectively localize epileptogenic tuber in the tuberous sclerosis complex as well as in identifying epileptic residual tissue following surgical failure. PET has potential in determining eloquent brain areas and in studying mechanisms of epilepsy. In epilepsy surgery, PET can be used with worthwhile cost-benefit even in a country with limited resources.

Keywords: AMT-PET, epilepsy surgery, FDG-PET, FMZ-PET, intractable epilepsy, presurgical evaluation.

Positron emission tomography (PET) scan is a powerful noninvasive imaging technique which enables the measurement of brain function in vivo. By using various radiopharmaceuticals, PET provides measurement of neural metabolism, receptor binding and cerebral blood flow. Today, rapid expansion of PET applications has gone beyond the scope of research and has influenced many aspects of clinical practice. Its noninvasiveness, simple procedure and wide range of applications have outweighed its expense and complexity of the nuclear infrastructure. PET has emerging roles in epilepsy and other neurological and psychiatric diseases for diagnosis, study of pathophysiology, assessing prognosis and monitoring therapeutic response. However, promotion of PET should be exercised with care, especially in countries with limited resources. This review will outline basic principles, techniques, interpretations and applications of PET scan in epilepsy. For abbreviations, see the last section in the text.

Basic principles of PET

Performing PET scanning requires 3 main components: cyclotron, radiopharmaceutical laboratory and the PET scanner. A cyclotron produces charged particles for preparing positron-emitting isotopes such as $^{18}$F, $^{11}$C, $^{15}$O or $^{13}$N. The isotope is incorporated into biologically active compounds in the radiochemistry synthetic module to produce a tracer. The most widely produced tracer is $^{18}$F fluorodeoxyglucose or FDG. After passing the quality control of radioactivity and microbial safety, the tracer is then transferred to the scan area for administration. The subject is scanned into computerized high resolution scanners so that PET images are constructed for further interpretation.

Correspondence to: Chaichon Locharernkul, M.D. Division of Neurology, Department of Medicine, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand. E-mail: drchaichon@yahoo.com
Most tracers used in clinical epilepsy contain isotopes which have relatively short half-lives (Table 1). This allows the tracer to reach equilibrium in the body rapidly, without exposing the subjects to prolonged radiation. The tracer containing $^{18}$F has a relatively longer time of decay. It can be transported to the scanners at some distance. Tracers containing $^{11}$C, $^{13}$N and $^{15}$O, on the other hand, need on-site scanner to cyclotron.

By using different tracers, various functional abnormalities of the brain can be visualized by PET scan. Under normal conditions, brain cells utilize glucose in high amounts by turning it into glucose-6-phosphate for energy production. FDG is also taken up by cells the same way as glucose but after turning into FDG-6-phosphate, the compound becomes stable and accumulates in the cell. Cerebral metabolism can therefore be measured using $[^{18}$F$] $ FDG. Localized changes in glucose metabolism have long been observed in patients with focal epilepsy undergoing FDG-PET scan [1].

The benzodiazepine receptor (BZP-R) is a modulatory site of GABA A-R complex. Altered GABAAergic transmission and reduced BZP-R binding were found in epileptogenic tissues obtained from patients who underwent epilepsy surgery [2]. The degree of GABA receptor binding can be visualized using $[^{11}$C$] $ FMZ, a central benzodiazepine receptor antagonist [3]. Serotonin was found at high content in resected epileptogenic tissue in patients with epilepsy [4]. Quantification of serotonin synthesis can be measured by PET using $[^{11}$C$] $ AMT, a serotonin precursor [5].

**PET techniques**

Most PET used in epilepsy has been studied by measurements of cerebral glucose metabolism using $[^{18}$F$] $ FDG and BZP receptor binding capacity using $[^{11}$C$] $ FMZ. Because of the long duration of the steady state of glucose uptake compared with the few-minute duration of most seizures, FGD-PET is mostly performed during an interictal period. The patient should be positioned comfortably in a quiet dimly lit room several minutes before FDG-administration and during the uptake phase of FDG (at least 20 min). The patient should be instructed not to speak, read or otherwise be active. It is desirable to have the cannula for intravenous administration in place 10 min before FDG injection starts. For preoperative evaluation of epilepsy, continuous scalp EEG recording is recommended to ensure that the scan is free of ictal events or active interictal discharges. Interictal epileptic activities can appear as hypermetabolic areas by increasing neocortical energy consumption. This may cause false lateralization on interpretation [6]. EEG monitoring should start before injection (ideally 2 hours) in order to make sure FDG is not administered in a postictal period of an unrecognized seizure and should be maintained for at least 30 minutes post injection.

For accurate image interpretation, it is of critical importance to be aware of the nature of the last clinical seizure and timing prior to imaging [7]. It is also necessary to have the patient’s oral antiepileptic drugs (AED) maintained preceding the scan. The acquisition of PET imaging should not start earlier than 30 minutes post injection. It is recommended to use a standardized protocol with a fixed time for start of scanning (e.g. 30 minutes or 60 minutes post injection) to make the data from different patients or repeated scans reliably and comparably [7].

Intravenous injection of the $[^{11}$C$] $ FMZ, a tracer with a short half-life, must be done rapidly at an exact time so the calculated dose is accurate. The time of scanning is also crucial so the results of different injections can be compared. The scan time usually begins 20 to 40 minutes post injection of FMZ. The patient should be free of all BZP, vigabatrin or tiagabine treatment for at least 2 weeks [8].

Table 1. Half-lives ($t^{1/2}$) of commonly used PET isotopes in epilepsy.

<table>
<thead>
<tr>
<th>Isotopes</th>
<th>t (min)</th>
<th>Location of cyclotron &amp; PET scanner</th>
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<tbody>
<tr>
<td>$^{18}$F</td>
<td>110</td>
<td>distant</td>
</tr>
<tr>
<td>$^{11}$C</td>
<td>20</td>
<td>on-site</td>
</tr>
<tr>
<td>$^{13}$N</td>
<td>10</td>
<td>on-site</td>
</tr>
<tr>
<td>$^{15}$O</td>
<td>2</td>
<td>on-site</td>
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Interpretation of PET

Most PET images are read by visual analysis. The results are considered reliable when analysed by an expert. Computer-aided analyses afford objective and more reliable assessments of functional abnormalities. Analyses are based on voxel-by-voxel analysis in the stereotactic space. Of these, Statistical Parametric Mapping (SPM) [9] software is the most widely used. The patient’s images are compared with scans of normal subjects leading to facilitation of localization and lateralization of PET abnormalities in epileptic individuals [10, 11]. PET overlaid to 3D-MRI can improve the quality of the images by correlating the areas of abnormal uptake to the cortical anatomy. Three-dimensional stereotactic surface projection (3D-SSP) [12] is another automated program that helps analyze data. The resulting images are surface projection images in 8 different views. Pixel-by-pixel comparison between subjects can be made with either t or z statistics. This program has been used for SPECT in epilepsy and can also be applied with PET [13].

The two most widely studied PETs in epilepsy were FDG-PET and FMZ-PET. They have been accepted for evaluation of patients with intractable focal epilepsy when surgery is a treatment option, although the nature of the FDG-PET hypometabolic area in relation to the epileptogenicity is not well understood. There was correlation between the abnormalities seen in interictal FDG-PET and in ictal 99mTc hexamethylpropylene amine oxime (HMPAO) SPECT in intractable TLE [14]. The degree of low FDG-PET uptake correlated with the severity of hippocampal neuronal loss in MTLE [15]. There was a close association between invasive EEG and FDG-PET findings in the detection of seizure foci and in the surgical outcome [16]. Evidences from literature showed that epileptogenic sites typically showed reduced FDG uptake in 70 % of patients with medically refractory focal seizures. This correlated with epileptogenic lesions in MRI [17]. Unilateral temporal hypometabolism (UTH), corresponding with the seizure focus, was seen in 86 % of lesional TLE. Following resection of the ipsilateral UTH, 86 % of the patients had good outcomes. In 67 % of the patients with intractable ETE, FDG hypometabolic regions were relevant to the epileptogenic focus. In nonlesional TLE, the extent of the hypometabolic region on the preoperative FDG-PET was found to be predictive of good outcomes following surgery [18]. Although, one study found poor agreement between the degree of FDG-PET regional hypometabolism and the electrical activities on stereo EEG (SEEG) [19], most studies have shown that the FDG-PET abnormalities correlated with scalp and intracranial EEG findings, structural brain abnormalities, as well as surgical outcome data. In focal epilepsy, the area of interictal hypometabolism in FDG-PET may determine regional functional disturbances of cerebral circuitry associated with the epileptogenic zone of unclear mechanism.

Regional hypometabolic areas were shown to be dynamic and correlated with several factors. In a longitudinal PET study, the hypometabolic regions were clearly correlated with change in seizure frequency [20]. Children whose seizure frequencies had decreased, showed reduced areas of hypometabolic cortex on follow-up scans while those with increased or persistent seizures showed enlargement. Reduction in the extent of the hypometabolic region could be seen after resection of the ipsilateral epileptogenic zone in MTLE patients, and such areas were shown to correlate with the area of ictal hyperperfusion demonstrated by SISCOM [21], and with the area containing interictal EEG slow waves [22]. It was presumed that the hypometabolic areas represent seizure propagation zones and dysfunctional areas, possibly a field of reduced neuronal inhibition, associated with the seizure onset zone.

The extent of FDG-PET abnormality could also be affected by duration since the last seizure [23]. The longer the post ictal period prior to the FDG-PET scan, the relatively smaller the hypometabolic area. Other factors which have been shown to influence the degree of FDG-PET abnormality included duration of epilepsy [24] and medical control of seizures [25]. Depression associated with epilepsy can cause reduced glucose metabolism of the entire cortex, mainly in the orbitofrontal areas [26]. Types of temporal lobe seizures, which preceded a PET scan, could also affect the degree of hypometabolism [27]. Focal seizures with mild semiology showed limited areas of glucose metabolism, while those with severe manifestations and with generalized tonic clonic convulsions (GTC) had wider areas of abnormalities. Underlying anatomical defects of the brain such as unilateral temporal lobe atrophy or focal encephalomalacia can appear as a hypometabolic region in FDG-PET scan. The above factors need to be considered when interpreting FDG-PET images in patients with epilepsy.
FMZ-PET was suggested as a useful tool for localizing the epileptogenic zone [28]. The area of reduced BZP-receptor binding, as documented by preoperative FMZ-PET, corresponded to the seizure onset zone and was smaller than the interictal hypometabolism documented by FDG-PET [29]. FMZ-PET is more sensitive, more accurate and more specific in localizing epileptogenic regions than FDG-PET [8, 30, 31]. Complete resection of the cortex with decreased FMZ binding also predicts good surgical outcome in selected patients with intractable focal epilepsy.

**PET applications in epilepsy**

PET has been used mostly in epilepsy to identify the epileptogenic zone for surgical resection in pharmaco-resistant focal epileptics. Generally, congruence of multimodality presurgical diagnostic tests is needed to ensure the best surgical seizure control. Initial work-up usually includes medical history, clinical semiology, ictal and interictal scalp EEG, MRI and occasionally ictal SPECT. ictal EEG has been regarded as the “gold standard” for localizing or lateralizing the ictal onset zone. As a functional imaging, FDG and FMZ-PET have been shown to provide additional data to enhance confidence in defining the epileptogenic area for surgical options, especially in ambiguous cases. FMZ-PET may also have an advantage in guiding the location of subdural electrode (SDE) implantation for invasive EEG monitoring [32]. More specific and sensitive PET tracer such as AMT has shown unique advantages in localizing epileptogenic foci in certain epileptic syndromes such as tuberous sclerosis or surgical relapse [33]. The applications of PET in epilepsy are summarized in Table 2.

Another goal of PET in presurgical evaluation is as substitute for the invasive and complicated diagnostic methods such as intracranial EEG, cortical stimulation mapping or Wada test with PET scan [16]. In order to identify functioning cortices necessary to preserve from surgery, Wada test, direct cortical stimulation mapping via subdural electrodes, and intraoperative stimulation during wake operation are among the invasive techniques being used. There have been studies of PET in successful localization of the eloquent areas although more studies are needed. PET has been reported to determine the outcome after temporal lobectomy as well as to study mechanisms of different epileptic syndromes. In this article, advantages of PET in presurgical evaluation of different intractable epilepsies will be described. Ideally, different presurgical diagnostic techniques should be used and interpreted together to improve the localization and to predict the surgical outcomes of intractable focal epilepsy.

**Lesional temporal lobe epilepsy**

HS is the main lesion found in more than two thirds of intractable TLE. In several FDG-PET studies, UTH was shown to correlate well with ictal EEG onset in 60-90% of TLE patients [34]. Diffuse EEG abnormalities are associated with less characteristic PET findings [35]. UTH contralateral to EEG foci was rarely reported (3%) [17]. Following ipsilateral temporal lobe resection, 86% of patients with UTH obtained good seizure control [17]. The FDG-PET hypometabolic regions commonly extend beyond the temporal lesion or the epileptogenic zone into extratemporal regions. They show no EEG seizure activity such as at ipsilateral parietal and frontal cortices, thalamus, and contralateral temporal lobe [8, 31]. FDG-PET has non-significant superior sensitivity to SPECT (PET vs. SPECT 94 vs. 88% [36] and 100 vs. 90% [37]. Ictal SPECT, using HMPAO or ECD, was shown to accurately lateralize the ictal onset in 84% to 97% of unilateral TLE patients [38]. However, ictal SPECT procedure contains several technical difficulties as compared to those of interictal PET scanning [39]. FDG-PET was found to be slightly less sensitive than MRI in detecting temporal lobe abnormalities (MRI vs. PET 86 vs.80% ) and in predicting surgical outcomes in one study (MRI vs. PET 83 vs.71%) [40], but slightly superior to MRI in

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**Table 2. PET applications in epilepsy.**

<table>
<thead>
<tr>
<th>1. Presurgical evaluation for epilepsy</th>
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<tr>
<td>a. Localizing the epileptogenic zone for resection</td>
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<tr>
<td>b. Identifying the eloquent cortex for preservation</td>
</tr>
<tr>
<td>2. Determining prognosis after epilepsy surgery</td>
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<tr>
<td>3. Guiding the location of subdural electrode placement for intracranial EEG recording</td>
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<tr>
<td>4. Studying the mechanisms of various epileptic syndromes and some therapeutic interventions</td>
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other studies (MRI vs. PET sensitivity 81 vs. 85 %; 
accuracy to EEG 67 vs. 82 % [41], accuracy in 
predicting good outcomes 77 vs. 86 % [42]).

The area of abnormal FMZ-PET uptake was 
usually more confined to the ictal origin than that 
of FDG-PET [32] and larger than that of MRI 
abnormalities [8]. FMZ-PET has a sensitivity of 
67 % for seizure origin detection in TLE with HS 
[43].

Although both FDG and FMZ-PET provide 
corresponding results for lesional TLE with concordant 
data of scalp EEG and MRI, PET adds little help for 
making surgical decisions. A study by Kilpatrick [44] 
showed that FDG-PET did not significantly correlate 
with improved surgical outcomes in his group of 
patients (67 % Engel class I outcome) compared to 
EEG (77 %), semiology (69 %), MRI (76 %) or neuro-
psychology (74 %) after a 5.9 year postoperative 
follow-up. However, PET was found useful in surgical 
selection of some TLE with discordant initial data, 
although the surgical outcomes may not be as excellent 
as those with concordant data. A study from the 
authors’ comprehensive epilepsy program [45] showed 
that FDG-PET had an impact on surgical decision-
making in 53 % of TLE patients having incongruent 
pre-surgical evaluation (n=19). PET localized the 
epileptogenic zone for resection in 5/8 cases of HS 
with discordant data (62.5 %), in 3/8 cases of bilateral 
HS (37.5 %), in 1 of 2 cases of TLE with dual 
pathology and in one case of non-lesional TLE. 
Intracranial EEG and the risk of implantation could 
be avoided in some patients (Fig. 1).

Non-lesional TLE

TLE with normal MRI was reported in 15-30 % 
of patients [41, 46]. Invasive EEG recordings were 
often needed at most centers to reliably localize the 
epileptogenic zone. Basal temporal ictal EEG onset 
and unilateral regional interictal discharges have been 
shown to predict favorable surgical outcomes in a 
study in which PET was not included [47]. Recently, 
a series of TLE with negative MRI and unilateral FDG-

![Fig. 1 FDG-PET scan (a) of an adult male with left HS (b) and discordant presurgical data showing hypometabolism on both anterior temporal lobes, more on the left side (thick arrow). His video-scalp EEG recording showed right hemispheric semiology in 1 out of 6 non lateralized seizures and right anterior temporal EEG onsets in all seizures, contralateral to his MRI lesion. Ictal SPECT (c) also pointed to the side opposite to the HS. Bilateral subdural strip recordings (d) revealed that all ictal discharges (e) started from left mesial temporal region (arrow-1) then propagated to the right side (arrow-2) and ended on the right temporal region (arrow-3). He has become seizure free after left anterior temporal lobectomy with amygdalo-hippocampectomy. In this case, FDG-PET helps to confirm the location of the epileptogenic zone proven by intracranial EEG (A case from Chulalongkorn Comprehensive Epilepsy program at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.)](image-url)
PET hypometabolism was shown to predict favorable surgical outcomes comparable to TLE with HS and was found to be another distinctive surgical remediable syndrome [48].

Both FMZ and FDG-PET were shown to be beneficial in nonlesional TLE. Higher sensitivity and less widespread abnormalities were seen in FMZ-PET than in FDG-PET [8, 49]. FDG-PET sensitivity was found in 87% of EEG lateralized TLE. This was higher than those of MRI hippocampal volume measurement and MRS [50]. When hippocampal volume and MRS were combined, the sensitivity approached that of FDG-PET (83%). Ryvlin et al found that FDG-PET had 80% sensitivity in detecting epileptic EEG foci so it may be useful in nonlesional TLE with incongruent scalp EEG, and SPECT findings [37]. In a study of medically intractable complex partial seizures, the sensitivity was comparable to ictal SPECT (PET vs. SPECT 88 vs. 94%, no statistical significance) [36]. FDG-PET was shown to be concordant with unilateral temporal interictal spikes in 70% of nonlesional TLE patients who had good surgical outcomes [51]. The predictive value of Engel class I postoperative outcome was higher for FDG-PET and EEG than for SPECT in a study of nonlesional TLE although no single diagnostic test alone was sufficient to localize the epileptogenic zone [52]. Its accuracy in lateralization was 88%; superior to ictal SPECT (55%) in another comparative study [42]. Due to its high sensitivity and accuracy in predicting good surgical outcome, FDG-PET should be applied in the surgical selection of nonlesional TLE and may reduce the need for intracranial EEG in some cases (Fig. 2).

Abnormal FMZ bindings were found in 80-88% of TLE patients with normal MRI with 44% concordance to clinical and EEG findings [49]. Either increased or decreased FMZ binding could be seen in temporal and extratemporal regions, ipsilateral and contralateral to the EEG focus. Its clear superiority to FDG-PET and its correlation to good surgical outcomes have not been shown in nonlesional TLE [51, 53].

Bitemporal epilepsy

Epilepsy with bitemporal onset presents another challenge in the selection of good surgical candidates. Incidence of bitemporal independent seizure onset was found in 20% of patients using depth electrodes [54]. Independent bitemporal interictal discharges (IED) accounted for 60% of TLE patients formerly exhibiting unilateral discharges on routine scalp EEG [55]. Tumor is a likely etiology of TLE with bitemporal IED rather than febrile convolution [56]. Patients with bitemporal independent IEDs were less likely to have lateralized ictal EEG patterns than those having unilateral IEDs [57]. Prognosis of surgery was poor in patients showing bitemporal asynchronous pattern, shift of lateralization and bitemporal independent onsets, all of which represent bitemporal epileptogenicity [58]. Patients with bitemporal seizure onsets recorded by subdural electrodes were less likely to benefit from surgical treatment than those having lateralized onsets [59]. No surgery was indicated if bitemporal-independent seizures were recorded without other conclusive additional testing [60]. Most bitemporal TLE needed invasive EEG monitoring for localization of the

![Fig. 2](image-url)
epileptogenic zone. Some bitemporal disease patients can do well after surgery if there were concordant MRI abnormality, history of febrile convulsion or lateralized intracranial EEG [61]. However, focal abnormalities shown by FDG-PET may help in identifying some good surgical candidates in this group of patients and intracranial EEG can be avoided [62].

In a study of TLE with bilateral independent IED, FDG-PET showed 60 % sensitivity and 67 % accuracy in lateralizing the ictal onset compared to depth EEG findings [63]. Bilateral temporal low glucose utilization reflected independent bilateral seizure onsets in 53 % of the patients. However, patients not associated with bilateral MRI abnormalities might still be successfully operated [64]. Ictal SPECT ($^{99}$m Tc-ECD or HMPAO) was shown to have 58 % accuracy in bitemporal disease [65]. The low result probably depended upon the rapid seizure propagation and the chance of detecting ictal onset in bilaterally independent episodes [66]. Decreased FMZ was reported to have high (100 %) sensitivity in patients with bilateral HS; and 67 % of the cases showed bilateral FMZ abnormalities [43, 60, 62]. Although invasive EEG provided high sensitivity and accuracy (80 %), FDG-PET can replace complicated intracranial recording in some patients (Fig. 3).

Epilepsy with dual pathology

Dual pathology is usually defined as HS in the presence of a potentially epileptogenic extrahippocampal lesion, mostly cortical dysplasia. Other lesions can be benign tumors or scars. Associated microscopic CD with preoperative MRI negative cortex may also be included. The incidence of dual pathology was estimated to be 15-20 % of adults with refractory TLE [67]. Higher incidence of associated CD (67 %) was found in children [68].

FDG-PET showed high sensitivity in TLE with dual pathology. Areas of hypometabolism were mostly seen corresponding to the unilateral HS as well as to other lesions, including areas of microscopic CD [69] (Fig. 4). The patients with neocortical temporal microscopic CD with concurrent HS were associated with more prominent lateral temporal metabolic dysfunction compared with isolated HS in temporal lobe atrophy.

FMZ-PET was also sensitive in detecting both lesions [32, 70]. The reduced FMZ binding in nonlesional cortical regions other than the HS raised the possibility of “occult” dual pathology. Another study has found decreased FMZ binding in areas beyond the resected primary focus which also showed epileptogenicity on invasive EEG. These areas were postulated to represent secondary epileptogenic foci [71]. PET findings may suggest the role of dual pathology in epileptogenicity and support the removal of both lesions to render the best outcome [72]. Further studies are necessary to confirm the roles of FDG and FMZ-PET in patients with dual pathology.

**Fig. 3** A case of bitemporal epilepsy with bilateral HS, more prominent on the right side (a). Presurgical evaluation was inconclusive showing non-lateralized clinical seizures and bilateral temporal ictal EEG onsets. FDG-PET (b) disclosed hypometabolism on both temporal lobes (thin arrows) but more marked on right anteromedial temporal region (thick arrows). Resection of the right anterior temporal lobe rendered him seizure freedom. In this patient, FDG-PET localized to correct side of the epileptogenic zone providing the opportunity for successful surgery and invasive EEG could be avoided. (A case from Chulalongkorn Comprehensive Epilepsy program at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.)
Extratemporal epilepsy

Extratemporal epilepsy (ETE) has less favorable surgical outcomes than TLE [73]. The success of surgery depends upon the correct localization of the epileptogenic zone to be totally removed and the identification of the adjacent functioning cortices to be spared. MRI has important prognostic implication. Nonlesional ETE usually has much worse postoperative prognosis than ETE with lesion [74]. Abnormalities correlated with intracranial ictal EEG were found by MRI in 70 % of cases [75]. Preoperative assessment of ETE often needs intracranial EEG when scalp EEG fails to localize the ictal onset.

In ETE, PET was found to have less advantage than ictal SPECT. Spencer et al reported sensitivity of 81 % and accuracy of 93 % in ictal SPECT while FDG-PET showed sensitivity of 33 % and accuracy of 95 % [34]. In ETE with negative MRI, FDG-PET had shown low accuracy (9 % correct, 35 % non-localized). However, in another study of MRI negative FLE, FDG-PET showed 85 % sensitivity with 80 % accuracy when corresponding to the scalp EEG ictal onset [76]. When subgroups of ETE were studied, FDG-PET showed correct localization of the seizure origin in half of the patients who had good surgical outcomes. In FLE, FDG-PET correctly localized the seizure onset in 55 % of the patients (73 % in lesional FLE and 36 % in nonlesional FLE); the yields were comparable either by using visual analysis or SPM [11]. By using FDG PET quantification in FLE, Swartz et al reported an increase in sensitivity of FDG-PET to 96 %, and accuracy to 78 % [77]. In parietal lobe epilepsy (PLE), the accuracy of FDG-PET in localizing

Fig. 4 A 40-year old right handed female with intractable epilepsy. She had dual pathology on her MRI (left HS [a] and left lateral temporal gliotic encephalomalacia from previous depressed skull fracture [b]). One out of her 5 seizures showed right hemispheric lateralization but ictal scalp EEG were non-lateralized. FDG-PET (c) revealed wide area of hypometabolism of the left hemisphere more marked at left mesial temporal region (thick arrow) and around the encephalomalacia (thin arrow). Subdural grid monitoring disclosed ictal EEG onset from a single mesial temporal contact. Cortical stimulation found no eloquent area over the lateral temporal scar. Resection of both HS and the gliotic lesion rendered the patient seizure free for over one year with transient but well-recovered dysphasia. FDG-PET did not help in localizing the seizure onset in this case but correlated with the epileptogenicity of both lesions. (A case from Chulalongkorn Comprehensive Epilepsy program at King Chulalongkorn Memorial Hospital, Bangkok, Thailand.).
ictal origins of 40 patients who later became seizure-free after surgery was 50%, while MRI was 64.3%, ictal SPECT 45.5% and ictal scalp EEG 37.5% [78]. FDG-PET showed an accuracy of 50% in occipital lobe epilepsy (OLE), when compared to MRI (62%), EEG (62%) and ictal SPECT (25%) [79]. For nonlesional neocortical epilepsy, FDG-PET showed an accuracy of 42.9% while ictal EEG and ictal SPECT showed 67.9% and 33% accuracy respectively [80]. When ictal scalp EEG data was not localizing, PET has been shown to provide a less invasive means than intracranial EEG recording for evaluating resectable epileptogenic zones [81].

In FLE with normal MRI, FMZ-PET was shown to be more sensitive and correlate better with the intracranial EEG-proven epileptic focus than FDG-PET [30]. Abnormal FMZ binding was seen in 72 to 100% in FLE with normal MRI and with 100% sensitivity in FLE with MRI acquired lesion [82]. Hammers et al. showed focal FMZ abnormalities by using parametric mapping in 75% of nonlesional neocortical epilepsy [83]. Another study on FLE with MRI lesions, including cortical dysplasia, found abnormalities in FMZ-PET in 55% and hypometabolism in FDG-PET in 45% [8]. The sensitivity of FMZ-PET was superior to FDG-PET in providing lateralization or localizing information in FLE. However, Muzik et al. compared FMZ and FDG PET with intracranial EEG and noted that both types of PET had low specificity in correlating with seizure onset [84]. Advantages of both FDG and FMZ PET were not shown in patients with bilateral frontal discharges [8].

Areas of reduced FMZ binding in ETE appeared to be restricted to ictal origin whereas FDG hypometabolism usually extends in wide areas outside the ictal origin [8, 31, 85]. Increased as well as decreased FMZ binding can be found within and outside the presumed region of seizure onset [83]. The location of remote FMZ-PET abnormalities suggests that these areas may represent regions connected with the primary seizure onset zones and were involved by the rapid spread of seizures via some anatomic pathways [86]. The possibility of secondary epileptic foci in these remote areas of abnormal BZP bindings was also suggested [87] with corresponding ictal EEG onset demonstrated on these areas of FMZ abnormality [31]. FMZ-PET was considered to be useful in guiding the locations of subdural electrode placement in ETE in order to cover all the possible epileptogenic zones [16].

Malformations of cortical development (cortical dysgenesis)

Among common malformations of cortical development (MCD) are focal cortical dysplasia (FCD), polymicrogyria, band and grey matter heterotopia which are frequently associated with epilepsy. Although not all of the cases are difficult to control, some can be intractable and identifying the epileptogenic zone for successful resection is challenging. Surgical outcomes are poor when the extent of the dysplastic lesion is uncertain or overlaps the eloquent brain areas.

In the presence of MCD, FDG- and FMZ-PET are more sensitive (>80%) than MRI (50%) and ictal SPECT (44%) [89, 90]. Moreover, in FCD with normal looking MRI [82, 89], FDG- and FMZ-PET can provide 78% and 83% sensitivity respectively. Areas of abnormal FMZ uptake could show both increased and decreased uptake. They frequently extend beyond the MRI lesions or appear without MRI correlation.

Infantile spasm (West’s syndrome)

FDG-PET has played a significant role in the modern treatment strategy of infantile spasm. The discovery of unifocal FDG-PET abnormality in some 20% of MRI negative West’s syndrome children has resulted in benefits from surgical treatment in this refractory epileptic syndrome [91]. Resection of the FDG-PET focal hypometabolic region concordant with video-EEG findings has rendered seizure freedom as well as improvement in cognitive developmental [92]. Most of the lesions were histopathologically proven to be FCD.

Multifocal hypometabolism was found in 64% of West’s syndrome, bitemporal pattern in 10% and diffuse pattern in 5%. Patients with multifocal abnormalities are not considered surgical candidates. The non-focal pattern suggested metabolic or genetic etiologies and prompted the clinicians to plan further investigations.

Tuberous sclerosis

Increased serotonin (5HT) content was observed in human epileptogenic tissue obtained from surgery [4]. [11C] methyl-L-tryptophan or AMT, a precursor of 5HT, has recently been used as a new PET tracer for measuring in vivo serotonin synthesis [5, 93]. [11C] AMT is converted to Alpha-[11C]methyl-5HT in the brain and accumulates in the serotonergic terminals of the epileptogenic area [94]. AMT-PET was
successfully used to differentiate between the epileptogenic and non-epileptogenic tubers in TS patients [33], while FDG-PET showed hypometabolic areas in both types of lesions [95]. $^{[1]}$C[AMT], therefore, can serve as a specific marker of the epileptogenic cortex as compared with FDG in patients with TS complex. The area of increased $^{[1]}$C[AMT] uptake was shown to correspond with the seizure onsets identified by surface or intracranial EEG [31]. Intractable seizures were shown to decrease or completely disappear after removal of the epileptogenic tuber [96]. The selective increase uptake of the epileptogenic tuber of AMT-PET has provided surgical options for TS patients with multiple lesions.

**Surgical relapse**

AMT-PET was also useful in visualizing the remaining epileptic cortex in patients whose seizures relapsed after surgery [97]. Increased AMT uptake was demonstrated on the site of previous cortical resections. Reoperation of the localized lesion identified by AMT-PET resulted in marked improvement or seizure freedom.

**Surgical prognosis determined by PET**

Patterns of FDG-PET abnormalities were studied to determine the surgical prognosis of TLE. Good surgical outcome was found in cases with localized hypometabolism in the mesial temporal region [98], temporal lobe with white matter change in MRI [99] and temporal lobe ipsilateral to resection [10]. On the contrary, poor outcome was seen in bitemporal hypometabolism [100], hypometabolism contralateral to EEG focus [99], asymmetric contralateral thalamic hypometabolism [101] and extratemporal hypometabolism [41, 102].

**Identifying the eloquent cortex**

When the epileptogenic zone lies in proximity to functioning areas, precise confinement of these regions are needed so that the resection of the epileptogenic zone will cause minimal or no postoperative functional decline. $^{[1]}$H$_2$O–PET was used to measure blood flow to study language laterality comparing it with the Wada (intracarotid amytal procedure) test [103]. Language lateralization by Wada test and blood flow PET was highly correlated. Blood flow PET could even localize the language areas while Wada test provided only lateralization information. Its accuracy was found to be higher than the Wada test and substitution of the invasive procedure by PET has been proposed.

**Mechanisms of epilepsies and its treatment**

Mechanisms of many epileptic syndromes and epilepsy interventions have been explored using PET scans. These included FDG-PET in idiopathic generalized epilepsy which showed bilateral basal ganglia hypometabolism [104]. Biraben studied $^{[1]}$F$\text{Fluoro-l-DOPA}$ PET in patients with ring chromosome-20 (RC20) epilepsy and found a reduction of striatal dopamine [105]. Impaired mechanisms that interrupt seizures in the basal ganglia were postulated in RC20 epilepsy. In hypothalamic hamartoma, FDG-PET focal hypometabolism was found to be ipsilateral to the EEG findings and the side of the MRI lesion [106]. The antiseizure effect of VNS therapy was also studied using $^{[1]}$H$_2$O PET [107]. A widespread increase in cerebral blood flow was caused by stimulation of the vagal nerve in the neck.

Visualization of a secondary epileptogenic focus has been suggested by using FMZ-PET which demonstrates remote FMZ-PET abnormalities in association with early onset and long duration of epilepsy [31]. Decreased FMZ binding was demonstrated in areas beyond the primary epileptic focus after being surgically removed, which also correlated with ictal EEG findings [71].

**List of abbreviation**

AED = antiepileptic drug,  
AMT = alpha methyl tryptophan,  
BZP = benzodiazepine,  
EEG = electroencephalogram,  
ETE = extratemporal epilepsy,  
FCD = focal cortical dysplasia,  
FDG = florodeoxyglucose,  
FLE = frontal lobe epilepsy,  
FMZ = flumazenil,  
HA = hippocampal atrophy,  
HMPAO = hexamethylpropylene amine oxime,  
HS = hippocampal sclerosis,  
IED = interictal epileptiform discharges,  
MCB = malformation of cortical development,  
MET = methionine,  
MRI = magnetic resonance imaging,  
MRS = magnetic resonance spectroscopy,  
OLE = occipital lobe epilepsy,  
PLE = parietal lobe epilepsy,  
PET = positron emission tomography,
RC20 = ring chromosome-20,
SEEG = stereoEEG,
SISCOM = subtraction ictal-interictal SPECT co-registered to MRI,
SPECT = single photon emission computerized tomography,
SPM = statistical parametric mapping,
SSEP = somatosensory evoked potential,
TLE = temporal lobe epilepsy,
TS = tuberous sclerosis,
UTH = unilateral temporal hypometabolism.

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