
Ipsilateral and Contralateral Thalamic Hypometabolism as a Predictor of Outcome After Temporal Lobectomy for Seizures

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FDG PET is often used to help localize the seizure focus before surgery in patients with medically refractory temporal lobe epilepsy. However, the ability of certain patterns of metabolic landscape to predict postsurgical seizure outcome has not been well characterized. The purpose of this retrospective study was to determine whether FDG PET abnormalities elsewhere in the brain, in combination with those in the temporal lobes, can be used to predict seizure outcome after surgery. **Methods:** Eighty patients with refractory temporal lobe seizures were imaged with PET after intravenous administration of 115 $\mu\text{Ci}/\text{kg}$ FDG. Images were interpreted without knowledge of clinical information by an experienced reviewer to determine seizure focus and regional metabolic changes in the brain. Metabolic activity scores were assigned for cortical and subcortical structures using the following criteria: 4 = normal activity, 3 = mildly decreased activity, 2 = moderately decreased activity, 1 = severely decreased activity, and 0 = no activity. A laterality index for each region was calculated using the equation $100 \times [\text{right} - \text{left}] / [1/2 \times (\text{right} + \text{left})]$. Seizure focus localization was based on the laterality of temporal lobe metabolic activity and was compared with that determined by scalp and depth electrodes and MRI results. Comparisons were made between asymmetries in metabolic activity in various brain structures and postoperative seizure frequency. Postoperative outcome was determined on the basis of cessation (complete disappearance of seizures) or continuation of seizure activity, regardless of frequency, compared with the preoperative state. **Results:** All 64 patients who were free of seizures postoperatively had either no thalamic asymmetry or reduced metabolism on the side from which the temporal lobe was removed. In contrast, 5 of 16 patients (31%) with postoperative seizures of any frequency had hypometabolism in the thalamus contralateral to that of the removed temporal lobe. All 5 patients with reverse thalamic asymmetry had postoperative seizures. Patients with thalamic hypometabolism ipsilateral to the removed temporal lobe also had an increased risk of postoperative seizures, but this risk was not as high as in patients with the contralateral abnormality. In these patients, the temporal lobe (which appeared hypometabolic on PET) was determined to be the site of the seizure on the basis of information besides that provided by PET before surgery. **Conclusion:** This study indicated that, in patients with temporal lobe epilepsy, thalamic

metabolic asymmetry, particularly in the reverse direction to that of the temporal lobe asymmetry, was associated with a poor postsurgical outcome compared with no or matched asymmetry. This determination may be important in evaluating patients for, and selecting optimal candidates for, surgical intervention.

Key Words: PET; seizure; thalamus; outcome

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Complex partial seizures that are refractory to medical intervention can often be treated successfully with temporal lobectomy in selected individuals. Several diagnostic tests have been used to localize the epileptogenic zone, and attempts have been made to determine the ability of such studies to predict postoperative seizure outcome. Specifically, PET, MRI, Wada's test, and electroencephalography (EEG, both surface and intracranial) have all been examined to determine whether they are capable of assessing outcomes after surgery (1,2). On FDG PET studies, temporal lobe hypometabolism has been shown to predict postoperative seizure outcome (3–5). Thus, after temporal lobectomy, patients with greater temporal lobe hypometabolism on the side that EEG determined to be the focus of the seizure tend to have a better postoperative outcome than do patients without temporal lobe hypometabolism on that side.

The purpose of this study was to review FDG PET findings for a large sample of patients with temporal lobe epilepsy and determine the most useful metabolic predictors of postoperative seizure outcome. Attention was focused on both cortical and subcortical structures to determine if widespread or unusual observations might be associated with a poor outcome. Such an association is clearly present in patients who show multiple seizure foci as assessed on EEG and FDG PET scans (4,6). Our aim was to determine the value of such analyses in predicting seizure outcome in patients with temporal lobe epilepsy after surgery.

MATERIALS AND METHODS

Subject Selection

Eighty patients with medically refractory temporal lobe seizures (43 women, 37 men; age range, 17–56 y) were referred for FDG

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PET as part of a preoperative assessment protocol. Sixty-nine patients were right handed, and 11 were left handed. Medical failure was defined as a lack of therapeutic response or allergy to a least 3 anticonvulsant drugs in monotherapy and 1 combination (7). These patients also underwent Wada's test, surface and intracranial (when necessary) interictal and ictal EEG neuropsychologic tests, and MRI to detect and identify the possible seizure focus for surgical excision (7). All patients subsequently underwent temporal lobectomy.

Surgical Procedure

A standard excision was performed on all patients, although a modest trend was seen toward removing a larger amount of posterior mesial tissue over the duration of the study (7). In patients with dominant lobectomies, the resection was typically carried back laterally approximately 4.5–5.0 cm from the temporal tip. In patients with nondominant lobectomies, the resection measured 5.0–5.5 cm from the temporal tip. The amygdala and the anterior 1.5–3.0 cm of the hippocampus were removed.

Postoperative Seizure Outcome

Patients were evaluated for postoperative seizure frequency at regular intervals (2 wk, 2 mo, 6 mo, and 1 y) for 1 y after surgery and were categorized as either seizure free or not seizure free at 1 y.

PET

PET was performed according to previously described methods (8). Briefly, an intravenous catheter was inserted under local anesthesia. The eyes were open, the ears were nonoccluded, and ambient noise and light was kept to a minimum during the study. FDG, 115 μ Ci/kg, was then injected intravenously. PET was initiated 40 min after the administration of FDG. Images were obtained with the PENN PET (9) scanner (UGM, Philadelphia, PA) with a resolution of 5.5 mm in all 3 planes. The head was fixed in place throughout the study, and the correctness of the positioning was monitored by an investigator or technologist. EEG was not performed at the time of PET. Three-dimensional data were acquired with this system, and the images were reconstructed in all 3 planes, with a slice thickness of 6–8 mm. Attenuation was corrected using the method of Chang (10).

Image Analysis

The metabolic activity of various anatomic structures as visualized on images was evaluated by an experienced nuclear medicine physician who was unaware of clinical or other localizing information. All 3 planes were examined for this analysis, and particular attention was paid to the coronal-section abnormalities, which were considered critical for the aim of this study. Individual areas of the temporal, frontal, parietal, and occipital lobes and the thalami and basal ganglia were qualitatively scored for the degree of metabolic activity using the following rating system: 4 = normal activity, 3 = mildly decreased activity, 2 = moderately decreased activity, 1 = severely decreased activity, and 0 = no activity. The level of metabolic activity was defined relative to adjacent structures and the overall pattern by reviewing the entire image set. The FDG PET result was considered abnormal if any decrease in metabolism was seen, and asymmetry was considered present if a difference of 1 point or more in the qualitative score occurred. The reviewer had considerable experience in the evaluation of FDG PET scans of both healthy volunteers and patients with central nervous system disorders (11). A laterality index (LI) was calculated for each area, as well as for the medial, lateral, and inferior aspects of the

temporal lobes, using the equation $100 \times [\text{right} - \text{left}] / [1/2 \times (\text{right} + \text{left})]$. The medial, lateral, and inferior aspects of the temporal lobes were evaluated with separate scores for the transaxial images and the coronal images.

Data Analysis

Seizure outcome data were compared with preoperative metabolic measures for each structure using the Fisher exact test. Exact 95% binomial confidence intervals around the estimates or risk were calculated.

RESULTS

Of the 80 patients studied (Table 1), 64 (80%) were seizure free and 16 (20%) had postoperative seizures at the 1-y follow-up evaluation. Of the 64 patients who were seizure free postoperatively, all had either no thalamic metabolic asymmetry or asymmetry in the same direction as that of the removed temporal lobe (i.e., the thalamus ipsilateral to the hypometabolic temporal lobe appeared to have reduced metabolism; Fig. 1). No patients who were seizure free had thalamic asymmetry in the reverse direction to that of the removed temporal lobe (i.e., the thalamus contralateral to the hypometabolic temporal lobe appeared to have reduced metabolism). In contrast, 5 of 16 patients (31%) with postoperative seizures of any degree had thalamic asymmetry in the reverse direction to that of the removed temporal lobe (Fig. 2). Furthermore, all 5 patients with this reverse thalamic asymmetry were found to have some degree of postoperative seizures. All patients in the study underwent similar surgery based on their clinical findings, and patients with postoperative seizures, in retrospective analysis, had no identifiable differences in the surgery performed. Further, patients with postoperative seizures did not have conflicting clinical results preoperatively that might have indicated the potential for a poorer postsurgical outcome.

The risk for postoperative seizures (Table 1) in patients with reverse thalamic asymmetry was calculated to be 1.0 (95% confidence interval, 0.48–1.0), whereas the risk in patients with thalamic asymmetry in the same direction as the temporal lobe asymmetry (ipsilateral asymmetry) was 0.22 (95% confidence interval, 0.10–0.38) and the risk in patients without thalamic asymmetry was 0.08 (95% confidence interval, 0.02–0.21). Thus, the patients with the lowest risk of postoperative seizures were those with no thalamic

TABLE 1
Relationship Between Thalamic Asymmetry and Postoperative Seizures

Type of asymmetry	Seizures	No seizures	% Seizures
Reverse thalamic asymmetry (n = 5)	5	0	100
No thalamic asymmetry (n = 38)	3	35	8
Thalamic asymmetry (n = 37)	8	29	22

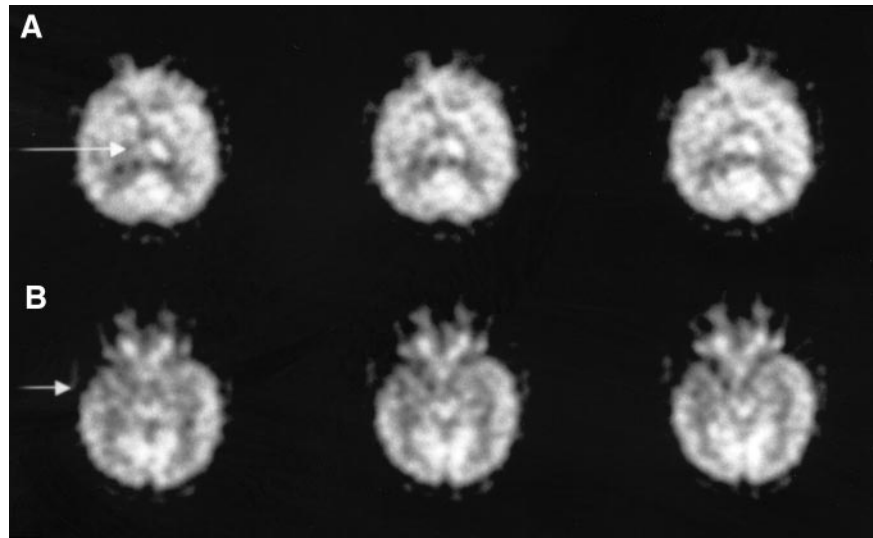


FIGURE 1. Transaxial images of patient with temporal lobe epilepsy show markedly decreased metabolism in right temporal lobe (B) and in ipsilateral thalamus (A).

asymmetry. Patients with ipsilateral thalamic asymmetry had a higher risk, and patients with reverse thalamic asymmetry had the highest risk. For the general test of association between seizure occurrence and thalamic asymmetry, the Fisher's exact test revealed a probability value less than 0.001. A between-group comparison of patients with thalamic asymmetry in the same direction as the temporal lobe asymmetry and patients with no asymmetry yielded a probability value of 0.113 for the Fisher's exact test; between patients with reverse thalamic asymmetry and patients with thalamic asymmetry in the same direction as that of the temporal lobes, the Fisher's exact test revealed a probability value of 0.002; and between patients with reverse thalamic asymmetry and patients with no thalamic asymmetry, the Fisher's exact test revealed a probability value of 0.001. We discerned no MRI, EEG, surgical, or other clinical factors that could account for the postoperative seizure outcome. That is, patients with postoperative sei-

zures had no identifiable cause that distinguished them from patients without postoperative seizures.

An analysis of temporal lobe findings showed an 88% sensitivity and 95% specificity for PET seizure focus localization based on a comparison between the observed temporal lobe hypometabolism and the final site of temporal lobectomy.

Using the LI, temporal lobe metabolism was compared with postoperative seizure outcome. Using the transaxial images, no clear pattern was seen for overall temporal lobe hypometabolism and the presence of postoperative seizures. However, the LI calculated using the coronal images showed several relationships between temporal lobe hypometabolism and postoperative seizure frequency (Table 2). In particular, greater temporal lobe asymmetry (as shown by an increased LI) for the entire temporal lobe, the lateral temporal lobe, and the inferior temporal lobe was associated with a relatively lower occurrence of postoperative seizures.

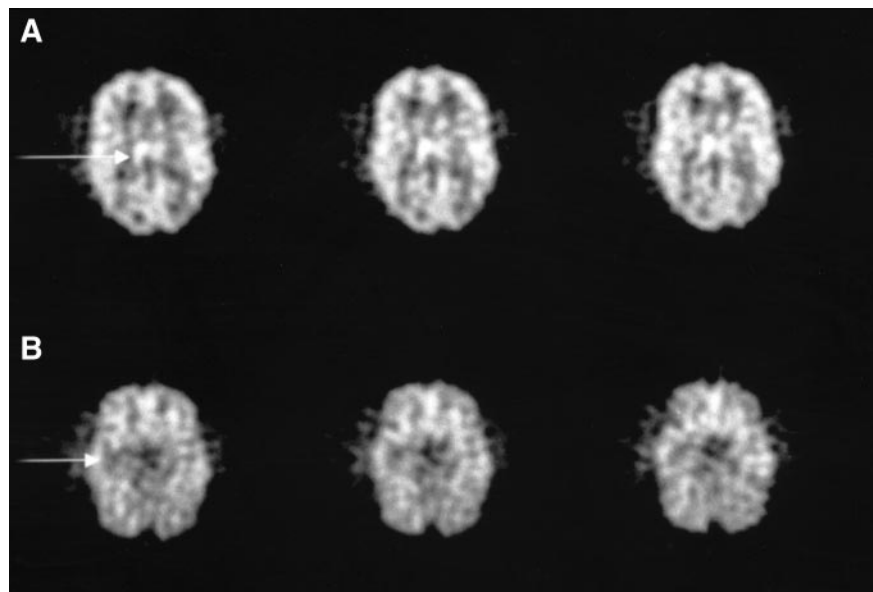


FIGURE 2. Transaxial images of patient with temporal lobe epilepsy show markedly decreased metabolism in right temporal lobe (B), particularly in medial aspect, and in contralateral thalamus (A).

TABLE 2
Percentage of Patients with Postoperative Seizures Based on LI Determined Using Coronal Images

Lobe	LI = 0	LI < 40*	LI ≥ 40
Entire temporal	2/6 (33)	9/37 (24)	7/45 (16)
Medial temporal	5/20 (25)	8/36 (22)	8/41 (20)
Lateral temporal	4/8 (50)	10/39 (26)	6/38 (16)
Inferior temporal	2/10 (20)	8/31 (26)	8/46 (17)

*Number of patients includes those with LI = 0.

Values are expressed as number of patients with postoperative seizures over total number of patients with that value of LI; percentage is given in parentheses. For purposes of this analysis, absolute value of LI was calculated to combine patients with right and left temporal lobe epilepsy. The higher the LI, the greater is asymmetry. Value of 40 was used as cutoff point because it corresponds to difference of 1 point on qualitative score between the 2 sides (thus, scores less than 40 represent least degree of asymmetry possible).

However, the LI for the medial temporal lobe showed no clear association with postoperative seizures. Also, no other cortical or subcortical regional asymmetries correlated significantly with postsurgical seizure frequency.

DISCUSSION

A major new finding from this study was that patients with relative contralateral thalamic hypometabolism, compared with the surgically removed temporal lobe (i.e., reverse thalamic asymmetry), were not seizure free postoperatively. Further, 31% of patients with any degree of postoperative seizure activity had reverse thalamic asymmetry. The observation that contralateral thalamic hypometabolism may be associated with a poor postoperative seizure outcome may have a physiologic explanation. Reverse thalamic asymmetry may reflect diffuse disease such that a greater portion of the temporal lobe or other areas, possibly even in the contralateral hemisphere, are involved in generating the seizure disorder. Patients with diffuse or multiple seizure foci will likely have a greater likelihood of postoperative seizures than those with limited and definable epileptogenic sites.

Although all 5 patients with reverse thalamic asymmetry had some degree of seizures postoperatively, reverse thalamic asymmetry was not a common finding. A larger sample size may show that some patients with reverse thalamic asymmetry have successful surgical outcomes. Furthermore, a closer analysis of postoperative seizure patterns showed that in patients with reverse thalamic asymmetry, seizures improved somewhat although residual seizure activity remained. Therefore, although patients with reverse thalamic asymmetry may have a poorer postoperative seizure outcome than patients without this metabolic pattern, until further prospective studies are performed, patients should not be excluded on this basis from surgery for temporal lobe seizures.

Thalamic hypometabolism ipsilateral to the temporal lobe

seizure focus has previously been reported for temporal lobe epilepsy (12–14). Similarly, an interictal SPECT study revealed ipsilateral thalamic hypoperfusion (15). However, these studies did not correlate this finding with postsurgical outcome and did not report any cases of contralateral thalamic hypometabolism or hypoperfusion. We did find thalamic hypometabolism ipsilateral to the temporal lobe seizure focus, and these patients were at higher risk of postoperative seizures than were patients with no thalamic asymmetry. However, reverse thalamic asymmetry carried the highest risk of postoperative seizures.

Several studies have shown that a greater degree of hypometabolism found by FDG PET in the affected temporal lobe is associated with a higher likelihood of a seizure-free postoperative course (3,4,5,16). Furthermore, postoperative seizure outcome is improved in patients with hypometabolism restricted to the temporal lobes (4). Patients with extratemporal hypometabolism tend to have a higher likelihood of postoperative seizure activity (4,6,17). Other studies have shown that patients with a greater degree of hypometabolism in the temporal lobe (i.e., a more distinct asymmetry) tend to have a better outcome than those with a milder degree of asymmetry between the 2 sides (5,18,19). Patients without significant hypometabolism of 1 temporal lobe (i.e., minimal asymmetry between the temporal lobes) may conceivably suffer from extratemporal or bitemporal seizure origins. These patients may not, therefore, be optimal candidates for surgical resection. Several studies have indicated that patients with mesial temporal hypometabolism on PET had a higher probability of becoming seizure free postoperatively than did patients with hypometabolism in other parts of the temporal lobe (18). However, other studies have suggested that lateral temporal lobe hypometabolism is a better predictor of a seizure-free postoperative course (19). Our study suggests that the greater the temporal lobe hypometabolism, particularly in the lateral and inferior aspect (as determined by an increased LI), the lower is the chance of postoperative seizures. Thus, the more asymmetric the temporal lobes, the better was the subject's chance of being seizure free postoperatively. This finding is consistent with the findings of previous studies (3,4,5,18,19). However, 2 other studies have not shown such a clear relationship between temporal lobe hypometabolism and postoperative outcomes (20,21).

CONCLUSION

This study investigated metabolic patterns that might predict poor postoperative seizure outcome in patients with temporal lobe epilepsy. The overall success rate of temporal lobectomy for medically refractory seizures was similar to that previously reported (22). Lower metabolism in the removed temporal lobe was associated with a lower risk of postoperative seizures. Thalamic asymmetry was the only other finding associated with postoperative seizure outcome. Reverse thalamic metabolic asymmetry was associated with a significantly higher likelihood of postoperative seizures

than was no asymmetry or asymmetry in the same direction as that of the temporal lobes. However, thalamic asymmetry in the same direction as that of the temporal lobes also was associated with a higher likelihood of postoperative seizures after temporal lobectomy than was no asymmetry.

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