Original Article

Thalamic and basal ganglia metabolism on interictal 18F-FDG PET in temporal lobe epilepsy: an SUV-based analysis

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Abstract: The aim of this study was to investigate thalamic and basal ganglia (BG) metabolism in temporal lobe epilepsy (TLE) on interictal 18F-FDG PET using standardized uptake value (SUV). Retrospective review of data was undertaken for patients who were surgically treated for medically intractable TLE. All patients underwent 18F-FDG PET, MRI brain and EEG as preoperative workup, and subsequently underwent temporal lobe resection. Postoperative outcomes were analyzed as without or with residual disabling seizures. SUVmax and SUVpeak values were calculated for thalamus and BG. Subgroup comparisons were performed with non-parametric tests. Study sample consisted of 33 patients (58% female; mean age 44.7 years) and 33 age- and sex-matched controls. Mean SUVpeak for both right and left thalamus was significantly lower in TLE than controls (8.1 ± 1.9 vs. 9.7 ± 2.9 and 8.1 ± 1.9 vs. 9.8 ± 2.9, respectively, both P=0.035). Mean SUVpeak for thalamus on the epileptogenic side was overall significantly lower than the contralateral side (8.0 ± 2.0 vs. 8.3 ± 2.0, P=0.040). One (3%) patient with MRI- and EEG-congruent left TLE showed marked left thalamic hypometabolism as the only finding on PET. There was no evidence of basal ganglia hypometabolism. No correlation was noted between thalamic metabolic asymmetry and postoperative outcomes. Thalamic metabolism was significantly reduced in patients with TLE compared to controls, and on the epileptogenic compared to the contralateral side among patients. Thalamic hypometabolism can have value in seizure focus localization in patients without interictal temporal hypometabolism.

Keywords: Temporal lobe epilepsy, interictal 18F-FDG PET, thalamic hypometabolism, SUV

Introduction

Hypometabolism of one temporal lobe, or asymmetric bitemporal hypometabolism with more severe hypometabolism of one temporal lobe, is the sine qua non abnormality on an interictal 18F-FDG PET in temporal lobe epilepsy (TLE) [1]. While the exact mechanism underlying interictal hypometabolism in epilepsy patients is unclear, it has been hypothesized to be due to decreased glucose transporter activity with resultant GABAergic disinhibition and neuronal loss leading to a decrease in synaptic activity [1]. The sensitivity of 18F-FDG PET in detecting the epileptic focus in patients with TLE has been reported to be 60-90% [2]. 18F-FDG PET has been shown to be most clinically useful when previous magnetic resonance imaging (MRI) results were normal or did not show unilateral temporal lesions, or when ictal electroencephalogram (EEG) results were not consistent with MRI findings or videotaped seizure semiology [3]. Ipsilateral temporal hypometabolism on 18F-FDG PET has been shown to have a predictive value of 86% for good post-operative outcome with greater degree of temporal hypometabolism associated with greater subsequent seizure control [4].

Multiple studies have demonstrated hypometabolism in extratemporal cortical and subcortical structures on 18F-FDG PET in TLE [5-12]. The thalamus ipsilateral to the affected temporal lobe is the extratemporal site most likely to demonstrate hypometabolism in TLE [1] and thalamic hypometabolism has been reported in 25-63% of medically intractable mesial TLE [5-9]. Thalamic hypometabolism in TLE has attracted a great deal of research interest on
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Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.7 (14.1)</td>
<td>42.9 (14.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>Male:Female ratio</td>
<td>14:19</td>
<td>15:14</td>
<td></td>
</tr>
<tr>
<td>Age at onset of seizures (years)</td>
<td>13.5 (14.9)</td>
<td>13.5 (13.9)</td>
<td>0.25</td>
</tr>
<tr>
<td>Duration of epilepsy (years)</td>
<td>30.2 (14.5)</td>
<td>30.5 (15.1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Number of antiepileptic drug trials</td>
<td>2.2 (0.7)</td>
<td>2.3 (0.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Length of follow-up after surgery (years)</td>
<td>4.4 (2.4)</td>
<td>4.6 (2.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Lateralized by PET to one temporal lobe (yes:no)</td>
<td>23:10†</td>
<td>23:10†</td>
<td></td>
</tr>
<tr>
<td>Mesiotemporal sclerosis on MRI (yes:no)</td>
<td>23:10†</td>
<td>23:10†</td>
<td></td>
</tr>
<tr>
<td>Lateralized by EEG to one temporal lobe (yes:no)</td>
<td>33:0</td>
<td>34:0</td>
<td></td>
</tr>
<tr>
<td>Surgical laterality (right:left)</td>
<td>18:15</td>
<td>18:15</td>
<td></td>
</tr>
<tr>
<td>Mesiotemporal sclerosis on pathology (yes:no)</td>
<td>19:12§</td>
<td>19:12§</td>
<td></td>
</tr>
<tr>
<td>Engel class I:Engel class II, III, IV</td>
<td>25:8</td>
<td>25:8</td>
<td></td>
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</tbody>
</table>

†Although ratios are identical, patients with PET lateralization did not necessarily have mesiotemporal sclerosis on MRI and vice versa.
§Pathology sample was limited or indeterminate for 2 patients.

Table 2. Comparison of SUVs between patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUV\text{max} right BG</td>
<td>12.4 (2.8)</td>
<td>12.8 (3.8)</td>
<td>0.47</td>
</tr>
<tr>
<td>SUV\text{peak} right BG</td>
<td>9.8 (2.1)</td>
<td>10.8 (3.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>SUV\text{max} left BG</td>
<td>12.3 (2.8)</td>
<td>12.8 (3.8)</td>
<td>0.47</td>
</tr>
<tr>
<td>SUV\text{peak} left BG</td>
<td>9.9 (2.2)</td>
<td>10.8 (3.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>SUV\text{max} right thalamus</td>
<td>9.8 (2.4)</td>
<td>11.3 (3.4)</td>
<td>0.068</td>
</tr>
<tr>
<td>SUV\text{peak} right thalamus</td>
<td>8.1 (1.9)</td>
<td>9.7 (2.9)</td>
<td>0.035</td>
</tr>
<tr>
<td>SUV\text{max} left thalamus</td>
<td>9.8 (2.3)</td>
<td>11.3 (3.4)</td>
<td>0.068</td>
</tr>
<tr>
<td>SUV\text{peak} left thalamus</td>
<td>8.1 (1.9)</td>
<td>9.8 (2.9)</td>
<td>0.035</td>
</tr>
</tbody>
</table>

account of several reasons. Thalamic metabolic dysfunction is believed to reflect a significant role for thalamic structures in the pathophysiology of TLE [9]. Thalamic hypometabolism contralateral or ipsilateral to the epileptic focus has been related to poor surgical outcome, compared with no thalamic hypometabolism [5]. Finally, thalamic hypometabolism has been shown to correlate with interictal cognitive and behavioral dysfunctions in TLE, independent of temporal lobe hypometabolism [9].

We sought to investigate thalamic and basal ganglia (BG) metabolism on interictal $^{18}$F-FDG PET in relation to temporal hypometabolism using our institutional database of patients with medically intractable TLE and compare the results to the published literature. Our analysis was based on standardized uptake value (SUV), which constitutes the current standard of semi-quantitative $^{18}$F-FDG uptake measurement in clinical practice.

Methods and materials

Patients and controls

Retrospective review of data was undertaken for patients who were surgically treated for medically intractable TLE at our institution between 2005 and 2015. Exclusion criteria included patients with semiology different from TLE seizures, patients with any structural lesions except for mesial temporal sclerosis, and patients with prior stroke or intracranial surgery. All patients underwent $^{18}$F-FDG PET, MRI brain and EEG as preoperative workup to detect and localize the seizure focus for surgical excision. These patients also underwent computed tomographic scan, Wada's (intracarotid amobarbital) test, surface and intracranial interictal and ictal EEG neuropsychological tests, or long-term video EEG monitoring when necessary. All patients subsequently underwent temporal lobe resection. Age- and sex-matched controls were selected from a separate database consisting of patients undergoing $^{18}$F-FDG PET/CT for oncologic staging. Exclusion criteria included patients with history of stroke, seizures, intracranial malignancy/metastases, or dementia. The study was approved by our Institutional Review Board.

Surgical procedure and outcomes

All patients were treated with temporal lobe resection, which consisted of either standard anterior temporal lobectomy or selective amygdalohippocampectomy. The laterality of the epileptic focus and hence the surgical side was determined from an integrative assessment of clinical, electrophysiologic, and anatomic and functional imaging data. Postoperative outcomes were analyzed as either without disabling seizures (Engel class I) or with residual disabling seizures (Engel class II, III, and IV) [13].

PET imaging

$^{18}$F-FDG PET images were obtained before surgery. Both patients and controls fasted for a minimum of 6 hours prior to radiotracer injection. Diabetic patients withheld their diabetic medications for 6 hours and blood glucose measurements were required to be less than
200 mg/dl at the time of radiotracer injection. Both patients and controls were injected intravenously with $^{18}$F-FDG, 0.14 mCi/kg with a minimum dose of 10 mCi (± 20%). Both groups then relaxed for approximately 45 to 60 minutes in a dark, quiet room, avoiding unnecessary activity. No patient showed clinical seizure activity during the PET procedure.

Patients were imaged at approximately 60 minutes with GE Advance, GE Discovery LS, GE Discovery VCT or GE Discovery 710 scanners. Scans were acquired for 5, 15, or 20 minutes per bed position in two-dimensional and/or three-dimensional modes and were reconstructed without and with attenuation correction. Controls were imaged at approximately 60 minutes with GE Discovery VCT or GE Discovery 710 scanners. Scans were acquired for 3-5 minutes per bed position in three-dimensional mode and were reconstructed without and with attenuation correction.

**Image analysis**

Metabolic activity in the temporal lobes, thalamus, and BG was visually analyzed. Metabolic activity of the particular structure was examined in comparison to the opposite side and adjacent structures as well as in context of the overall pattern by reviewing all the images for each patient. It was qualitatively classified as either reduced or normal/preserved.

Metabolic activity in the thalamus and BG was further analyzed semi-quantitatively using SUVs. SUVs are a measure of the radiotracer concentration in a defined region of interest (ROI) normalized to the average radiotracer concentration in the body, which is approximated as the injected dose divided by patient body size. Body weight is the most frequently used correlate of body size, others being lean body mass and body surface area. SUVs were measured in two ways as SUV$_{\text{max}}$ and SUV$_{\text{peak}}$ using an interactive workstation (Mirada Medical XD3, Oxford, UK). ROIs were drawn separately for each subcortical structure. SUV$_{\text{max}}$ measured the highest voxel value within each ROI, and SUV$_{\text{peak}}$ measured the local average SUV value within a 1-cm$^3$ spherical volume surrounding the voxel with the highest activity.

**Statistical analysis**

Numerical data was reported as mean ± SD. Subgroup comparisons of SUV$_{\text{max}}$ and SUV$_{\text{peak}}$ were done with the Wilcoxon rank sum test or the Kruskal-Wallis test, and the Benjamini-Hochberg method was used to adjust for multiple testing. All statistical tests were two-sided, and 5% (P<0.05) was set as the level of sig-
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The study sample consisted of 33 patients (58% female; mean age 44.7 years) and 33 age- and sex-matched controls. Table 1 summarizes the demographic and clinical characteristics of the patient group.

Mean SUV\textsubscript{peak} for both right and left thalamus was significantly lower in patients than controls (8.1 ± 1.9 vs. 9.7 ± 2.9 and 8.1 ± 1.9 vs. 9.8 ± 2.9, respectively, both P=0.035) (Table 2). Similar statistical trend was noted for SUV\textsubscript{max} for both sides (9.8 ± 2.4 vs. 11.3 ± 3.4 and 9.8 ± 2.3 vs. 11.3 ± 3.4, respectively, both P=0.068).

On visual analysis, PET demonstrated normal symmetric metabolism in bilateral basal ganglia and thalamus and mesial temporal cortex in all controls (Figure 1). There was unilateral temporal hypometabolism in 22/33 (67%) patients (Figure 2). Two patients (6%) had bilaterally reduced temporal metabolism, with one of the two patients showing greater reduction in metabolic activity on the suggested side of epileptic focus by MRI and EEG. Furthermore, two (6%) patients were noted to have unilateral thalamic hypometabolism. For one of these two patients, there was no associated temporal hypometabolism, and reduced thalamic activity was the solitary finding on PET (Figure 3). For both patients, the laterality of thalamic hypometabolism was congruent with the suggested side of epileptic focus on other tests. There was no evidence of BG hypometabolism or metabolic asymmetry.

On the SUV-based analysis, mean SUV\textsubscript{peak} for thalamus on the epileptogenic side was overall significantly lower than the contralateral side among patients (8.0 ± 2.0 vs. 8.3 ± 2.0, P=0.040) (Table 3). Mean difference in SUV\textsubscript{peak} thalamus between the two sides was -0.3 ± 0.9 (range -3.2 to +1.4). Both patients visually noted to have thalamic hypometabolism on the epileptic side showed lower SUV\textsubscript{peak} on that side compared to the opposite side by 3.2 and 2.4, respectively, indicating good correlation between the visual and SUV-based analyses. Interestingly, one patient with left temporal seizure focus showed reverse thalamic asymmetry in which SUV\textsubscript{peak} for the right thalamus was lower than the left by 1.4. Again, there was no asymmetry in BG metabolism.

Out of the 33 patients, 27 (82%) were treated with standard anterior temporal lobectomy and 6 (18%) underwent selective amygdalohippocampectomy. One patient with EEG evidence of right frontotemporal seizure onset underwent right frontal gyrus resection in addition to right anterior temporal lobectomy. During a
mean follow-up of 4.4 ± 2.4 years, 25 (76%) patients remained free of disabling seizures while 8 (24%) patients showed residual disabling seizures. There was not enough evidence to conclude a correlation between thalamic metabolic asymmetry and postoperative outcomes (Table 4).

**Discussion**

While the exact mechanism underlying subcortical hypometabolism in TLE remains elusive, it is postulated to be related to corticothalamic diaschisis and chronic metabolic dysfacilitation due to hippocampal neuronal loss [9, 14]. Several studies have disclosed unilateral monosynaptic, reciprocal projections among widespread mesial and lateral temporal areas, particularly the amygdala and anterior portions of the hippocampal formation, and the thalamus in primates. Diaschisis results from reduced efferent outflow to the striatum and thalamus due to hippocampal cell loss leading to diminished subcortical synaptic activity and hence reduced metabolism. This leads to defective reciprocal inhibition of cortical and limbic ex-
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Citability, increasing the likelihood of seizure development in the remaining hippocampal cells [7]. Recent volumetric and morphometric studies have demonstrated bilateral thalamic volume loss in unilateral temporal lobe epilepsy, more commonly ipsilateral to the epileptic focus [1, 15-18]. Moreover, a longer duration of TLE was associated with more severe hypometabolism in the thalamus ipsilateral to the seizure focus [19], and thalamic volume was inversely correlated with duration of epilepsy [15]. Autopsy studies in patients with chronic epilepsy have shown frequent histopathologic evidence of damage in the thalami, often with greater damage on the side of greater interictal neurologic dysfunction [9]. Interestingly, the alteration in thalamic metabolism may be reversible following anterior temporal resection in TLE [20, 21].

For the first time, SUVs have been used to directly study and report thalamic metabolism in relation to temporal hypometabolism. Previous studies have used mean asymmetry index values and region-to-cerebral hemisphere ratios [22], visual assessment [5, 20, 22], regional cerebral glucose metabolism [6, 7, 23], or quantitative anatomic analysis of the emission tomographic data [8, 9] for this purpose. We have reported metabolism in each subcortical structure of interest in terms of both SUVmax and SUVpeak. Being the highest voxel value within the ROI, SUVmax is independent of ROI definition but more susceptible to image noise. Currently, SUVmax is most commonly used because it is less observer-dependent and has high reproducibility. SUVpeak is a hybrid measurement of the local average SUV value in a group of voxels surrounding the voxel with the highest activity. It has been suggested as a more robust alternative and is less affected by noise [24, 25]. Discrepancies in our results with respect to SUVmax and SUVpeak values are likely related to the differences in the definitions and properties of these parameters. Despite its limitations and host of biologic and technologic factors that can impact its accuracy [24], SUV is an increasingly popular semi-quantitative measure of PET data. It can offer a simple, convenient, and accurate method to estimate thalamic metabolism in TLE and/or supplement the visual-based qualitative analysis. Absolute quantification of 18F-FDG uptake is technically challenging, complex and is impractical for routine clinical practice [26].

This study is the first to show a statistically significant decrease in thalamic metabolism in patients with TLE when compared to age- and sex-matched controls using the largest study sample size to date of 33 subjects for patient and control group each. Hashiguchi and colleagues visually found thalamic hypometabolism in nine out of 26 patients (34.6%) with intractable medial TLE, but semi-quantitative analysis of the same did not reveal a significant difference between patients and controls [22]. Similarly, Rubin et al. did not find regional metabolic values for thalamus in TLE patients to be significantly different from controls, either ipsilateral or contralateral to the seizure focus [23].

Our results lend a SUV-based confirmation of ipsilateral thalamic hypometabolism in patients with TLE as shown by multiple previous studies. We had one (3%) patient with MRI- and EEG-congruent left TLE for whom marked left thalamic hypometabolism was the only finding on PET. Two prior studies have shown thalamic hypometabolism on the side of the epileptogenic zone as the only PET abnormality without hypometabolism in the temporal lobe in 3% and 4% of their examined patient cohorts respectively [9, 20]. Interestingly, the frequency of such a finding appears similar in all these studies. While the exact mechanism of isolated thalamic hypometabolism is speculative, it may be related to the primary role of thalamus in the initiation, propagation, and/or regulation of seizures in several types of epileptic disorders [14]. Two neuropathological studies have suggested thalamus to be directly damaged by ictal activity, rather than by secondary degeneration from the cortex [27, 28]. Pappata et al. suggested the phenomenon of thalamocortical diaschisis in which significant ipsilateral corti-

<table>
<thead>
<tr>
<th>Table 4. Difference in SUVs between the epileptogenic and contralateral sides by postsurgical outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>No disabling seizures (n=25)</td>
</tr>
<tr>
<td>SUVmax BG</td>
</tr>
<tr>
<td>SUVpeak BG</td>
</tr>
<tr>
<td>SUVmax thalamus</td>
</tr>
<tr>
<td>SUVpeak thalamus</td>
</tr>
</tbody>
</table>
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cal hypometabolism was frequently found in patients with thalamocapsular or thalamic lesions and neuropsychological impairment [29]. In a separate work by the same authors, thalamotomy induced a significant fall in bilateral cortical metabolic rates, more conspicuous on the operated than on the contralateral side [30]. One case of reverse thalamic asymmetry was noted in our study which, similar to bilateral thalamic hypometabolism, is a conceivable but less common pattern of thalamic metabolic alteration in TLE [5, 20, 22, 31]. We conclude that thalamic hypometabolism can be of significance in localizing the seizure focus in patients without interictal temporal lobe hypometabolism. It should be assessed in combination with electroclinical and other imaging data to prevent false lateralization due to possibility of contralateral or bilateral thalamic hypometabolism.

We could not prove our a priori hypothesis that greater thalamic metabolic asymmetry between the epileptogenic and contralateral sides would correlate with a higher likelihood of postoperative seizures due to the small sample size. While presence of extratemporal cortical hypometabolism is generally believed to lead to a worse surgical outcome [11, 32-34], independent prognostic significance of thalamic hypometabolism in TLE has been more controversial. Previous studies have indicated mixed results for association of thalamic metabolic asymmetry with poor postsurgical outcome [5, 22, 31]. These studies have been discordant, at least in part, due to the differences in sample size, methods of ascertainment of metabolic activity, and definition of good versus poor surgical outcomes.

Our results did not show asymmetry involving BG metabolism in TLE. Conversely, previous studies have shown ipsilateral BG metabolic involvement in TLE [7, 8, 35-37]. Reduced thalamic metabolism is the predominant pattern of extratemporal hypometabolism in TLE. BG metabolism in TLE has been studied less extensively in literature as compared to thalamic hypometabolism. The ipsilateral putamen was more likely to be hypometabolic in patients with TLE showing dystonic posturing during seizure activity than those without ictal dystonia [37]. Margerison and Corsellis did not find striatal or pallidal damage in any of their patients with TLE [38]. Bouilleret and colleagues showed a bilateral and symmetric decrease in 18F-fluoro-L-dopa uptake in the BG of patients with refractory TLE, which was disproportionately more than expected for the degree of subcortical gray matter volume atrophy detected on MRI. These dopamine functional changes were not associated with decreased BG glucose metabolism [39]. Our results are congruent with this study in that reduced BG metabolism may not always be seen in TLE and alternate pathophysiologic mechanisms could underlie functional BG changes in some cases of TLE. Absence of BG metabolic asymmetry should not be construed as non-localization of epileptic focus in TLE. More studies are required to further examine BG metabolism on 18F-FDG PET in TLE.

Our study has a few limitations. Visual-based qualitative analysis was performed for temporal metabolism. Theodore et al. reported visual interpretation to be less accurate and suggested that a quantitative asymmetry measurement should be made when 18F-FDG PET is used to identify epileptic foci for surgical resection [12]. Patients and controls were scanned using different scanners and image acquisition techniques as detailed in the methods section which might challenge their direct comparability. We had an under-representation of the subgroup with residual disabling seizures in comparison to subjects free of disabling seizures, which might compromise the power to detect a difference. More studies are needed to examine the significance of thalamic hypometabolism for predicting seizure outcome after surgery in TLE.

Conclusion

Thalamic metabolic activity was significantly reduced in patients with TLE when compared to controls, and on the epileptogenic compared to the contralateral side among patients. Thalamic hypometabolism can be of significance in localizing the seizure focus in patients without interictal temporal lobe hypometabolism. It should be assessed in combination with electroclinical and other imaging data to prevent false lateralization due to possibility of contralateral or bilateral thalamic hypometabolism. There was not enough evidence to conclude a correlation between thalamic metabolic asymmetry and postoperative outcomes. No asymmetry involving BG metabolism in TLE was noted.
Acknowledgements

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Disclosure of conflict of interest

None.

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