FDG-PET Images Quantified by Probabilistic Atlas of Brain and Surgical Prognosis of Temporal Lobe Epilepsy

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Summary: Purpose: This study evaluated the relation between hypometabolism, diagnosed by fluorodeoxyglucose positron emission tomography (FDG-PET), and the surgical outcome of a large and homogeneous series of cases of mesial temporal lobe epilepsy (mTLE), by using a probabilistic atlas of the human brain (statistical probabilistic anatomical maps: SPAM).

Methods: Ninety-five surgically proven intractable mTLE patients and 22 age-matched controls were spatially normalized to the average brain PET template of international consortium of brain mapping (ICBM). The diagnosis of mTLE was confirmed by the presence of hippocampal sclerosis on magnetic resonance imaging (MRI) and video-EEG monitoring. Counts from normalized PET images were multiplied by the probability from 98 volumes of interest (VOIs) of SPAM. Asymmetric indexes (AIs) reflecting the severity of hypometabolism were calculated by counts of selected 12 VOIs from SPAM images in both temporal lobes. Extent of hypometabolism was determined by the number of voxels showing decreased metabolism in each VOI segmented by SPAM.

Results: Of the 95 patients studied, 76 (80%) were seizure free, and 19 (20%) had postoperative seizures for the ≥2-year follow-up period. No significant association between the severity of hypometabolism in each VOI of the temporal lobe and surgical outcome was identified (p > 0.05). The number of voxels showing decreased hypometabolism was not significantly different between the good- and poor-outcome groups (p > 0.05).

Conclusions: Our results demonstrated that focal severity and extent of hypometabolism quantified by a probabilistic atlas of brain were not related to the surgical outcome in mTLE patients who had hippocampal sclerosis on MRI. We should develop a more localized and specified anatomic map for mTLE for further results. Key Words: FDG-PET—Mesial temporal lobe epilepsy—Statistical probabilistic anatomic map (SPAM)—Surgery—Prognosis.

The role of [18F] fluorodeoxyglucose–positron emission tomography (FDG-PET) is well established in the diagnosis of lateralization of a seizure focus in mesial temporal lobe epilepsy (mTLE). In the interictal state, the epileptogenic temporal lobe demonstrates decreased glucose metabolism in ~80% of these patients (1–4). Furthermore, recent studies suggest that FDG-PET may be a reliable indicator of clinical outcome after surgery (5–7). The presence of a hypometabolic temporal lobe is predictive of favorable surgical outcome in mTLE (1,6–9).

However, the presence of a specific focal hypometabolic region related to surgical outcome is still a controversial issue. Some studies have suggested that the asymmetry index of the mesial temporal lobe might be a better predictor for a good outcome, although on average, the asymmetry index of the lateral temporal lobe is greater than that of the mesial temporal lobe (1,10). Other studies have found that uncal (8), lateral (5), anterolateral (9), or temporopolar regions (11) seem to correlate better with a good surgical outcome.

The visual assessment of FDG-PET is a widely used approach in clinical situations, but the results depend on the observers’ experience (12). Sometimes objective data are needed to support subjective analysis in cases of subtly decreased metabolism. For that reason, methods of objective quantification have been developed. The use of regions of interest (ROIs) has been developed to quantify PET images. However, defining ROIs is not fully objective. The way in which ROIs are defined varies from one study to another, making data comparison very difficult. For example, results vary depending on ROI size. Other troublesome factors are variations in ROI shape from image to image because of intersubject variability and the proportion of gray matter sampled. More-
over, the process is very time consuming when a large number of ROIs are involved.

To solve these problems, voxel-based approaches, such as statistical parametric mapping (SPM) have been introduced (13–15), and these methods facilitate the interpretation of PET brain images in a clinical setting. However, if we are interested in a specific anatomic area such as the hippocampus, another method is needed because SPM does not provide information about anatomic structure.

Recently many kinds of brain mapping methods have been developed, including automated registration and segmentation. One of these is statistical probabilistic anatomic mapping (SPAM) (16). This was designed to overcome cross-subject variations in brain structure, as a project of the International Consortium for Brain Mapping (ICBM). SPAM consists of 98 brain structures including multiple cortical gyri, white matter, cerebrospinal fluid, etc. Most of the studies that have used SPAM have been concerned with anatomic differences and volume measurements in magnetic resonance imaging (MRI) images, but application to functional images also has been suggested (17). We have already demonstrated the clinical usefulness of SPAM to support visual assessment of PET images in mTLE (18).

In this study, we applied SPAM to the PET images of patients with mTLE to evaluate the relation between the degree and extent of hypometabolism on FDG-PET and surgical outcomes in a large and homogeneous series of mTLE.

METHODS

Patients and controls

Ninety-five consecutive patients of intractable mTLE (62 male, 33 female; mean age, 27.6 ± 16.8 years) were included in this study. They underwent FDG-PET and anterior temporal lobectomy between 1995 and 1998. Presurgical evaluation included MRI to evaluate structural lesions and hippocampal sclerosis (19), video-electroencephalographic (EEG) monitoring, FDG-PET scans, interictal and ictal single-photon emission computed tomography (SPECT) if possible, neuropsychological evaluation, and the intracarotid amobarbital procedure. Patients were diagnosed with mTLE in this study if (a) a definite unilateral hippocampal sclerosis showed on the brain MRI, and (b) the anterior temporal ictal onset was identified during video-EEG monitoring or if an invasive study with intracranial electrodes confirmed a mesial temporal onset. As a result, all patients had a definite hippocampal sclerosis diagnosed on MRI. Patients with space-occupying lesions identified by MRI were excluded. Patients with bitemporal independent ictal onsets confirmed by invasive study also were excluded.

Twenty-two healthy volunteers underwent FDG-PET as a control group. They were of mean age 28 ± 9 years. Sixteen were men, and six were women. None of the subjects had any history of neurologic or psychological disease, and they were not taking any drugs known to affect PET studies. Informed consent was obtained from each volunteer after each was given an explanation about the purpose and procedures of this study. The average asymmetry index of 21 controls for total temporal lobe was 1.66 ± 2.77 (Table 1). The procedure was approved by IRB of Seoul National University Hospital.

Surgical outcome

All patients had been followed up for ≥2 years after surgery. Patients were categorized as either free of disabling seizure (Engel class I; good outcome) (20) or not (poor outcome).

PET imaging

For those subjects undergoing PET, 370 MBq (10 mCi) of [18F]FDG was injected intravenously, with the patients’ eyes open and the room lights dimmed. Images were acquired ∼30 min after tracer injection, by using a CTI ECAT Exact 47 PET camera (Siemens, Knoxville, TN, U.S.A.). After taking a transmission scan for 5 min with a Ge-68 rod source, the emission scan was performed for 25 min in two-dimensional mode.

Emission scan images were reconstructed by using a back-projection method with a Shepp-Logan filter (cut-off frequency of 0.35), and the attenuation effects were corrected with transmission images. The resolution (full width, half maximum (FWHM)) of the PET camera was 6.2 × 6.2 × 4.3 mm, and the dimension of the image matrix was 128 × 128 pixels.

Registration of PET images with SPAM

We applied the statistical probabilistic anatomic map (SPAM) images of ICBM to calculate the PET counts

<table>
<thead>
<tr>
<th>TABLE 1. Asymmetry index (%) of controls</th>
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<tbody>
<tr>
<td>Total T</td>
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<tr>
<td>Avg</td>
</tr>
<tr>
<td>SD</td>
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</table>

AI was calculated by the equation \((\text{Rt} - \text{Lt})/(\text{Rt} + \text{Lt}) \times 200\).

T, temporal lobe; Med, medial; Lat, lateral; Amy, amygdala; HF, hippocampal formation; Phg, parahippocampal gyrus; STg, superior temporal gyrus; MTg, middle temporal gyrus; ITg, inferior temporal gyrus; Avg, average; SD, standard deviation; AI, asymmetry index.
objectively (Fig. 1). SPAM consists of 98 volumes of interest (VOIs) images including bilateral cortical gyri, and each image consists of the probability from 0 to 1 that it belongs to a specific region.

FDG-PET images were count- and spatially normalized by using a 12-parameter affine (linear) transformation to the ICBM PET template provided in SPM99 software (Wellcome Department of Cognitive Neurology, London, U.K.). The counts from normalized PET images were multiplied by the probability from 98 VOIs of SPAM by using a program developed with Matlab (Mathworks Inc., Natick, MA, U.S.A.). The template we used in this study was an average of MRI images from 152 young normal volunteers of the ICBM. With this multiplication of normalized PET and SPAM, the probability-weighted counts were obtained for all VOIs. As a result, 98 VOIs, including bilateral cortical gyri segmented by SPAM, were overlaid on the patient’s spatially normalized PET.

**Computing time**

It took <10 min for each subject to normalize PET images by using SPM99b with an IBM-compatible personal computer (Pentium III 600-MHz CPU and 128-Mb memory). Probability-weighted counts were calculated by using the MATLAB program in batches for multiple subjects, and calculation took <1 min per subject.

**Severity of hypometabolism: calculation of asymmetric indexes**

We selected six pairs of VOIs to represent the temporal lobe. These consisted of the superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, hippocampus, parahippocampal gyrus, and the amygdala in each hemisphere (Figs. 1 and 2). The counts from normalized PET images were multiplied by the probability from these selected six pairs of VOIs of SPAM to assess the severity of hypometabolism. Asymmetric indexes (AIa) were calculated by using the equation $(C - I) \times 200/(C + I)$ where C and I are mean counts of contralateral and ipsilateral VOIs to the resected temporal lobe, respectively.

When the VOI contralateral to the resected temporal lobe was hypometabolic, AI had a negative value, and when AI was positive, the resected temporal lobe was hypometabolic.

We calculated means and standard deviations (SD) of AIs in each pair of VOIs. Student’s $t$ test was applied to test the relation between AI of each VOI and the surgical outcome. P values <0.05 were considered significant.

**Extent of hypometabolism determined by SPM and SPAM**

The differences between $[^{18}\text{F}]$-FDG-PET scans of each patient and those of the controls were statistically analyzed by using SPM 99 software (Institute of Neurology, University College of London, U.K.; Fig. 2). Before statistical analysis, all the images were spatially normalized into the ICBM standard template (see the registration of PET images with SPAM). Subtle differences between the transformed image and the template were removed by the nonlinear registration method, by using the weighted sum of the predefined smooth basis function used in discrete cosine transformation. Spatially...
normalized images were then smoothed by convolution with an isotropic gaussian kernel with 16-mm FWHM. The effect of global difference was removed by normalizing the count of each voxel to the global count of the cortical area (proportional scaling in SPM 99). A significant decrease of regional metabolism was estimated by comparing their PET images with those of controls by using T statistics for each voxel (Fig. 2). The voxels with p values <0.01 were considered to have significant difference, and parametric images of T values for significant voxels were composed for further analysis.

A VOI for each anatomic structure was defined by SPAM. Voxels with probability >0.5 were included in each VOI. The extent of the hypometabolic area for each VOI was determined by counting the number of voxels with significantly decreased hypometabolism in each VOI segmented by SPAM. We computed the number of significant voxels in VOIs of frontal, temporal, parieto-occipital, and thalamic areas between the good and the poor surgical-outcome groups. Volume of each voxel was 8 mm³ (2 × 2 × 2 mm).

Comparison with visual analysis

We compared the results of SPAM with those of visual analysis. Two observers (D.S.L. and Y.K.K.) graded subjectively the metabolic abnormalities in both temporal lobes on FDG-PET in a blinded fashion (grades 0–4). The hypometabolism of the ipsilateral temporal regions was graded considering extent and severity. The higher grade means more severe hypometabolism on the unilateral temporal lobe. Grade 0 means no asymmetric metabolism. The agreement between two observers was calculated. We also evaluated the correlation between visual grading and AI in the SPAM method.

RESULTS

Of the 95 patients studied, 76 (80%) were seizure free, and 19 (20%) had postoperative seizures at the 2-year follow-up evaluation. Figure 3 shows the AIs of six VOIs of the temporal lobe and the whole temporal lobe in the group of patients who became seizure free and the group of patients who did not become seizure free. No significant association between the severity of hypometabolism of each location (six VOIs of each temporal lobe and the whole temporal lobe) and surgical outcome could be identified (p > 0.05). We also compared the clinical outcome with the range of AIs of controls (Table 1). If the AI in each pair of VOIs was within 2 SD of normal controls, we assumed the AI as normal. The clinical outcome was not different between the patients with AI of normal range and those with AI outside this range (p > 0.05). There was no correlation between clinical outcome and the AIs outside this normal range (p > 0.05).

DISCUSSION

There was no difference in the number of voxels with significantly decreased hypometabolism in each lobe determined by SPM and SPAM between the good and the poor surgical-outcome groups (p > 0.05; Table 2). The visual grading and AI with the SPAM methods were significantly correlated (p < 0.0001, Table 3). The agreement between two observers (Y.K.K. and D.S.L.) was good (weighted kappa score = 0.535; Table 4). There was no correlation between clinical outcome and the degree of hypometabolism by visual analysis (p > 0.05; Table 5).
TABLE 2. Extent of hypometabolic area and surgical outcome

<table>
<thead>
<tr>
<th></th>
<th>Temporal</th>
<th></th>
<th>Parietooccipital</th>
<th>Parietal</th>
<th>Thalamus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipsilateral</td>
<td>Contra</td>
<td>Ipsilateral</td>
<td>Contra</td>
<td>Ipsilateral</td>
</tr>
<tr>
<td>Good</td>
<td>2.536 ± 1.741</td>
<td>470 ± 629</td>
<td>1.223 ± 1.343</td>
<td>525 ± 744</td>
<td>1.297 ± 1.785</td>
</tr>
<tr>
<td>Poor</td>
<td>2.415 ± 2.075</td>
<td>223 ± 340</td>
<td>1.992 ± 2.716</td>
<td>603 ± 1.198</td>
<td>1.583 ± 1.807</td>
</tr>
</tbody>
</table>

Differences between the 18F FDG-PET scans of each patient and those of the controls were statistically analyzed using SPM 99 software. The extent of the hypometabolic area for each VOI was determined by counting the number of voxels with significantly decreased hypometabolism in each VOI segmented by SPAM. The numbers of significant voxels in VOIs of frontal, temporal, parietooccipital, and thalamic areas were compared between the good and the poor surgical-outcome groups.

Data are expressed as means ± standard deviations. Temporal VOIs include hippocampal formation, amygdala, parahippocampal gyrus, inferior temporal gyrus, middle temporal gyrus, and superior temporal gyrus. Frontal VOIs include superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, postcentral gyrus, angular gyrus, supramarginal gyrus, superior parietal lobule, precuneus, occipital pole, inferior occipital gyrus, middle occipital gyrus, superior occipital gyrus, lingual gyrus, lateral occipitotemporal gyrus, and medial occipitotemporal gyrus.

Ipsilateral, ipsilateral to the epileptogenic temporal lobe; contralateral, contralateral to the epileptogenic temporal lobe; VOI, volume of interest.

TABLE 3. Correlation between visual grading and AI in SPAM methods

<table>
<thead>
<tr>
<th>VOs of SPAM</th>
<th>DSL</th>
<th></th>
<th>YKK</th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>r</td>
<td>p Value</td>
<td>r</td>
<td>p Value</td>
</tr>
<tr>
<td>Total temporal lobe</td>
<td>0.480</td>
<td>0.000</td>
<td>0.483</td>
<td>0.000</td>
</tr>
<tr>
<td>Medial temporal structure</td>
<td>0.421</td>
<td>0.000</td>
<td>0.473</td>
<td>0.000</td>
</tr>
<tr>
<td>Lateral temporal structure</td>
<td>0.498</td>
<td>0.000</td>
<td>0.518</td>
<td>0.000</td>
</tr>
</tbody>
</table>

The ASI of the SPAM method and the hypometabolic grading by visual analysis were significantly correlated (p = 0.0001, Spearman’s two-tailed correlation test). VOI, volume of interest; AI, asymmetric index; r, Spearman rank correlation coefficient; DSL, Dong Soo Lee; YKK, Yu Keong Kim; SPAM, statistical parametric anatomic map.
The presence of PET hypometabolism in patients with complex partial seizures of temporal origin usually reflects underlying temporal lobe focal gliosis and neuronal loss (25,27). The severity and anatomic distribution of neuronal loss is poorly correlated with the degree and spatial extent of PET hypometabolism (25,27,28). In patients with a mesial temporal lobe focus on EEG, hypometabolism ipsilateral to the seizure focus occurs more frequently and to a greater degree in the lateral than in the mesial temporal cortex (10). Hypometabolism in the lateral temporal region cannot be taken as evidence for an epileptogenic focus in the lateral neocortex. Other studies have found multiple areas of hypometabolism within and outside the temporal lobe (6,7,29). The cause of this hypometabolism remains controversial. Hypometabolism other than at the seizure focus may be due to physiologic dysfunction in regions functionally associated with the mesial temporal lobe, rather than cell loss in these regions (10,29). Henry et al. (28) found no correlation between hypometabolism in any cortical region and the degree of hippocampal cell loss on pathology. Diaschisis due to cell loss alone cannot account for these findings. It might also represent the structural abnormalities that are below the resolution of routine structural histopathologic studies (30). Lateral temporal hypometabolism may also be due to repeated seizures spreading to the temporal neocortex (31). Alterations in synaptic organization due to repeated seizures rather than neuronal loss, which can occur in experimentally kindled animals, could underlie metabolic changes (32). One study, comparing preoperative and postoperative glucose consumption in mesiobasal and lateral temporal lobe epilepsy, demonstrated marked increases in the regional cerebral metabolic rate of glucose, both in the ipsilateral and—significantly—in the contralateral hemisphere. Moreover, there was a trend toward a normalization of glucose metabolism in the ipsilateral temporal neocortex in patients with mTLE (33). Another study showed that patients who became seizure free after removal of a vascular malformation also had a significant regional increase of FDG uptake (34). If hypometabolism other than the epileptogenic focus might be due to physiologic dysfunction in regions associated with the mesial temporal lobe or to seizure spread, the hypometabolic areas in mTLE would not be an important indicator for prediction of surgical outcome, although they can correctly lateralize the seizure focus in a high proportion. Our results are consistent with this hypothesis. However, the predictive value of FDG-PET regarding surgical outcome in TLE still has clinical implications. In our study, we recruited a homogeneous series of mTLE cases. However, in some clinical settings of TLE, FDG-PET imaging can be useful as a screening procedure in presurgical evaluation to assess the localization of seizure focus and surgical outcome. There are patients with electrophysiologic localization of seizure onset to one temporal lobe, but without any accompanying definite hippocampal sclerosis on MRI. All the previous results are applicable to these patients. FDG-PET also can provide valuable data in patients with nonlocalized surface ictal EEGs. Theodore et al. (31) showed a close association between invasive EEG and PET localization.

We applied only one surgical technique on all patients (e.g., standard anterior temporal lobectomy with amygdalohippocampectomy). We resected 3.5 cm of lateral

<table>
<thead>
<tr>
<th>Parameter estimate</th>
<th>Standard error</th>
<th>Wald $\chi^2$</th>
<th>Pr $&gt; \chi^2$</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual DSL</td>
<td>0.0425</td>
<td>0.2017</td>
<td>0.0443</td>
<td>0.8333</td>
</tr>
<tr>
<td>Visual YKK</td>
<td>0.0822</td>
<td>0.2171</td>
<td>0.1435</td>
<td>0.7048</td>
</tr>
</tbody>
</table>

There was no correlation between the clinical outcome and hypometabolic grading by visual analysis. Pr, probability; OR, odds ratio; CI, confidence interval.
temporal cortex from the temporal tip for the left TLE and 4.5 cm of lateral temporal lobe for the right TLE. The surgical outcome is not significantly correlated with the laterality. Furthermore, the distribution of right and left TLE patients was not significantly different between the good- and the poor-outcome groups. However, there are some limitations in our study. We did not see specific hypometabolic patterns. Even though there is no focal hypometabolic area that can predict surgical outcome, certain specific combinations of hypometabolic areas may mean that different seizure foci and pathogenesis may be related with poor surgical outcome.

Our results demonstrated that focal severity and extent of hypometabolism quantified by a probabilistic atlas of brain were not related to the surgical outcome in mTLE patients who had hippocampal sclerosis on MRI. SPAM is useful for the quantification of VOIs in the PET data of patients with mTLE. We should develop a more localized and specific anatomic map for mTLE to improve results.

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REFERENCES