Accurate Prediction of Postoperative Outcome in Mesial Temporal Lobe Epilepsy

A Study Using Positron Emission Tomography With \textsuperscript{18}Fluorodeoxyglucose

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**Background:** Recent studies suggest that positron emission tomography may be a reliable predictive indicator of clinical outcome following surgical treatment for epilepsy.

**Objective:** We evaluated 30 patients with documented medial temporal lobe epilepsy to determine if prediction of postoperative outcome is improved with the use of positron emission tomography with \textsuperscript{18}fluorodeoxyglucose.

**Patients and Methods:** We performed a discriminant analysis to determine the combination of metabolic asymmetry indexes in temporal and extratemporal regions defined by magnetic resonance imaging that best predicted the postoperative outcome. Seizure outcome was assessed at least 2 years after surgery: patients were classified as seizure free (n=14, group A), mostly improved (n=10, group B), or as having persistent seizures (n=6, group C).

**Results:** Discriminant analysis was first performed in groups A and C. The temporal pole seemed to be the only temporal region for which metabolism was a significant predictor of the postoperative outcome ($F_{1,18}=10.19$; $P=0.005$). The predictive value of positron emission tomography with \textsuperscript{18}fluorodeoxyglucose was considerably improved by the multivariate analysis ($F_{4,15}=7.21$; $P=0.002$), which correctly predicted the 2-year prognosis in 100% of the patients using 4 regions: the temporal pole, the medial temporal region, the anterior part of the lateral temporal neocortex, and the basofrontal region. As a validation, we performed this 4-region analysis in the patients in group B. The difference among the 3 groups was highly significant ($F=15.5$, $P<0.001$).

**Conclusion:** These findings suggest that the interictal metabolic pattern reliably predicts the 2-year prognosis after surgery in patients with medial temporal lobe epilepsy.

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REDICTION OF seizure outcome is an important issue in surgery for temporal lobe epilepsy. Recent studies suggest that positron emission tomography (PET) may be a reliable predictive indicator of clinical outcome following surgical treatment.\textsuperscript{1-3} The presence of an interictal temporal hypometabolism seems clearly correlated with seizure relief after surgery. However, the prognostic value of the exact location of the hypometabolism within the temporal lobe is still debated because numerous regions, including the uncal,\textsuperscript{4} medial,\textsuperscript{5} and anterolateral temporal regions,\textsuperscript{6} seem to correlate with a good postoperative outcome.

For our study, we hypothesized that seizure outcome prediction would be improved by analyzing the pattern of metabolic abnormalities in a larger, multiregion brain network that may be involved in seizure genesis and propagation rather than in a single temporal region. To test this hypothesis, we performed a multivariate statistical analysis in 30 consecutive patients with medial temporal lobe epilepsy (MTLE) who underwent surgery and experienced different postoperative outcomes. Using this method, we demonstrated that PET with \textsuperscript{18}fluorodeoxyglucose (FDG) could be a reliable and specific tool in predicting the surgical outcome and thus in the planning of surgery for patients with epilepsy.

**RESULTS**

**OUTCOME**

After surgery, all patients were improved. Twenty-four patients (80%) were free of disabling seizures: 14 (47%) were totally seizure free (category A) and 10 were markedly improved (category B). Six patients (20%) were improved but had rare disabling seizures after surgery (category C).
PATIENTS AND METHODS

PATIENTS

We evaluated 30 consecutive patients (13 men, 17 women; mean age, 29 years) with intractable MTLE who underwent FDG-PET scans and anterior temporal lobectomies at the Salpêtrière Epilepsy Unit, Paris, France. In addition to the PET scan, the presurgical investigation included a video electroencephalographic (EEG) monitoring with surface electrodes, a standard neuropsychological test battery, an intracarotid amobarbital (Amytal; Eli Lilly and Company, Indianapolis, Ind) test for lateralization of speech, and a volumetric magnetic resonance imaging (MRI) measurement of the hippocampus. The FDG-PET scans were obtained as part of a systematic research protocol, and each subject gave informed consent for the procedure. In addition, 6 patients underwent EEG-video with intracranial depth electrodes because of bilateral interictal and ictal abnormalities found on scalp EEG scans. The diagnosis of MTLE was based on history, clinical features of seizures, interictal and ictal EEG data, and MRI and FDG-PET findings. All patients but 1 had unilateral temporal lobe hypometabolism on interictal FDG-PET findings, and all patients but 3 had hippocampal atrophy diagnosed using volumetric MRI measurement of the hippocampus with no other structural abnormality.

SURGERY AND OUTCOME

Anterior temporal lobectomies consisted of excising the temporal pole, a mean of 30 mm of lateral temporal cortex, amygdala, hippocampus, and parahippocampal gyrus. The postoperative follow-up was assessed at least 2 years after surgery (mean, 3.3 years; range, 2.1-5.3 years). Outcome was derived from Engel’s classification4: category A was equivalent to Engel’s class Ia (completely seizure free since surgery); category B was equivalent to Engel’s class Ib, c, and d (non disabling simple partial seizures only since surgery, some disabling seizures after surgery, but free of disabling seizures for at least 2 years, and generalized convulsion with antiepileptic drug withdrawal only); and category C was equivalent to classes II and III (rare disabling seizures or worthwhile improvement).

FDG-PET STUDY

The FDG-PET was performed at the Commissariat à l’Énergie Atomique, Orsay, France, using a high-resolution, head-dedicated PET camera (ECAT 953/31B; CTI Siemens, Knoxville, Tenn). This tomograph has 5.8-mm in-plane and 5-mm axial resolution.10 In each of the 30 patients, 31 transverse sections of the brain, spaced 3.37 mm apart, were acquired simultaneously in the hippocampal plane according to a method previously described.11 In the MRI examination, we acquired axial T1-weighted slices to obtain a set of MRI scans superimposable on the PET images.12 Fluorodeoxyglucose was injected intravenously at a mean dose of 29.6×10³ Bq per 70 kg of body weight. Twenty-three blood samples were collected from the radial artery. Image acquisition was started 30 minutes after the FDG injection and ended 20 minutes later. The investigations were made interictally under close clinical supervision. Ambient light and noise in the laboratory were controlled in a standardized fashion.

GROUP ANALYSIS

Three temporal regions exhibited a statistically significant hypometabolism: the medial hippocampal region, the temporal pole, and the anterolateral temporal region. Table 1 shows the degree of metabolic and MRI hippocampal asymmetry indexes in these 3 temporal regions for groups A, B, and C. The metabolism of the temporal pole was the only parameter that was statistically significant across the 3 prognosis groups with a more pronounced hypometabolism associated with a better outcome.

DISCRIMINANT ANALYSIS

Discriminant analysis was performed as described in the “Patients and Methods” section. The 14 patients with a good outcome (category A) were compared with the 6 patients with the worst outcome (category C).

Single-Region Discriminant Analysis

The univariate discriminant analysis revealed that the temporal pole hypometabolism was the only reliable predictor of postoperative prognosis (P=.005) (Table 2). A temporal pole metabolic asymmetry greater than 19.5% represented the cutoff value predictive of a good postoperative outcome. Using this criterion, the equation correctly classified 80% of the patients; 86% of the patients were correctly classified in category A, and 67% were correctly classified in category C. The discriminant equations were not statistically significant in the 8 other temporal and extratemporal regions (P range, .65-.98).

Multiple-Region Discriminant Analysis

The multivariate analysis considerably improved the prediction of the surgical outcome by correctly classifying 100% of the tested patients. The equation combining the metabolism of the temporal pole, the basofrontal cortex, the anterior part of the lateral temporal neocortex, and the medial temporal cortex was highly significant (F4,15=7.21; P=.002). Strong and positive coefficients were attributed to the temporal pole and the basofrontal cortex (39.8 and 32.6, respectively), whereas negative coefficients were associated with the anterolateral temporal region and the hippocampal region (−32.6 and −15.0, respectively). This multivariate equation correctly classified 14 of the 14 category A patients and 6 of the 6 category C patients, predicting correctly the 2-year prognosis in 100% of these patients. The normalized Z values of the equation ranged from 3.70 to 0.18 in the 14 category A patients (mean±SD, 1.43±1.10), whereas the normalized Z score values ranged from −0.69 to −2.33 in the 6 category C patients (1.43±0.65) (Table 3; Figure 2).
Reconstructed images were corrected for attenuation by use of gallium 68–germanium 68 transmission scans. Regional cerebral metabolic rates of glucose consumption \((rCMRglu)\) expressed in milligrams per minute per 100 g of tissue were then calculated according to the method of Sokoloff et al\(^1\) as modified by Huang et al.\(^2\) We calculated absolute metabolic values (milligrams \(\times\) minutes \(^{-1}\) \(\times\) 100 g \(^{-1}\)) and normalized metabolic values (the ratio of the temporal region to the extratemporal cortical \(rCMRglu\)). Absolute metabolic values were used to calculate asymmetry index (AI), defined as the \(rCMRglu\) of the contralateral region minus the \(rCMRglu\) of the ipsilateral region divided by the \(rCMRglu\) of the contralateral region (AI=\([rCMRglu_{contra}−rCMRglu_{ipsi}] / rCMRglu_{contra}\)).

Temporal lobe regional metabolic values were determined in 3 temporal anatomic regions using an MRI-PET automatic 3-dimensional registration method.\(^3\) These regions were (1) the medial temporal cortex, including the hippocampus and the parahippocampal gyrus; (2) the temporal pole; (3) the anterior part of the temporal neocortex; (4) the middle part of the temporal neocortex; and (5) the posterior part of the temporal neocortex (Figure 1). The regional metabolism of these 5 anatomic regions was estimated by pooling the \(rCMRglu\) values from a template of 52 regions of interest across 6 MRI sections parallel to the hippocampal plane, and then transferred onto the registered PET images. The choice of the hippocampal plane restricted the selection of the extratemporal regions. Extratemporal metabolic values were therefore determined in 4 regions: (1) the basofrontal cortex; (2) the striatal region, including the head of the caudate nucleus and the anterior part of the putamen; (3) the thalamus; and (4) the medial and lateral occipital cortex.

When we tested this equation in the 10 patients with intermediate prognosis (category B), we expected them to have intermediate \(Z\) values and, as expected, the equation generated intermediate individual normalized \(Z\) scores ranging from 1.99 to −1.89. The difference between the 3 groups was highly significant (\(F=15.4;\) \(P<.001\)) as verified by post hoc comparisons (group A vs group B and group B vs group C (\(P=0.05;\) mean±SD, 1.43±1.10, 0.08±1.23; −1.43±0.65, respectively).

**DATA ANALYSIS**

The relationship between surgical outcome and cerebral metabolism was assessed using 2 different statistical analyses. We first performed a group analysis using the \(t\) test and analysis of variance to examine the relationships between the postoperative outcome and the regional metabolism. We then performed a discriminant analysis using a dedicated analysis software (GBstat 5.4; Dynamic Microsystems Inc, Silver Spring, Md, 1990). The discriminant analysis was performed to correlate the postoperative outcome with the pattern of hypometabolism within the temporal lobe. In short, with this analysis, we found the combination of variables (here, the metabolic asymmetry indexes) that best predicted the category, ie, the postoperative outcome to which a case belonged. To perform this discriminant analysis, we compared patients with the best prognosis (category A patients) with those with the worst (category C patients). We first performed a univariate discriminant analysis that used as its single dependent variable the metabolic asymmetry of each individual anatomic region and as its independent variable the postoperative outcome. This analysis determined the region in which metabolism was the best predictor of postoperative prognosis. Then we performed a multivariate discriminant analysis using as multiple dependent variables the regional metabolic asymmetries. We wanted to determine whether the regional pattern of hypometabolism was a better predictor of surgical prognosis than that of a single region. In a second step, we validated the most statistically significant multivariate equation in the group with intermediate prognosis (category B).

The major finding of this study is that the pattern of hypometabolism in a specific network of connected regions achieves better prediction of seizure prognosis than the hypometabolism in a single temporal region. The predictive value of FDG-PET was best achieved by the multivariate analysis that correctly classified 100% of the patients using 4 cortical regions. By contrast, on the monovariate analysis, the temporal pole that was the only statistically significant single region only correctly classified 80% of the patients. This demonstrates that seizure postoperative outcome is better predicted by describing metabolic abnormalities over a network of cortical regions rather than in a single, highly focused cortical area.

The topography of this network was of interest, since it included the 3 temporal regions that are the most consistently hypometabolic in patients with MTLE\(^2,14,16\): the temporal pole; the medial and the anterolateral temporal regions; and a frontobasal region, which may also be hypometabolic in such patients.\(^17\) From the 4 regions that were implicated in this network, the temporal pole played the most determining role, exhibiting the higher and more positive discriminant coefficient. This result was expected because the temporal pole was the only single region that was significant in predicting the outcome in both group and monovariate analyses.

However, reviews of the regions related to a good seizure outcome in previous studies demonstrate that these regions are mostly near or within the temporal pole. For instance, the medial temporal region associated with a good outcome in the study by Mann et al\(^8\) was in the uncinal region, ie, the medial part of the temporal pole; whereas the anterolateral region that emerged in the study by Wong et al\(^9\) as the best outcome predictor was chosen at the anterior part of the temporal pole. The few functional studies\(^16,18,19\) that show that temporal pole metabolism to be the most consistently and severely decreased in MTLE support the fact that the temporal pole is an important component of the epileptogenic network. This fact is also supported by the strong anatomic and functional connections that underlie the temporal pole to the medial temporal structures that are known to have a strong epileptogenic potential.

Previous animal studies using anterograde degeneration methods have reported efferent projections from
temporal pole to orbitofrontal regions, temporal cortex and anterior cingulate cortex, and afferent projections from both the amygdala and the hippocampus to the temporopolar cortex. Furthermore, recent MRI studies have demonstrated the existence of structural abnormalities with loss of the gray-white matter differentiation in the temporal lobe of patients with temporal lobe epilepsy. Since these 2 regions exhibited the same degree of hypometabolism among the 3 prognosis groups, it seems logical that they did not play a prominent role in the determination of the postoperative outcome. Therefore, the negative coefficients attributed to these regions must be related to the discriminant equation and balanced by the prominent role played by the temporal pole.

Finally, a key feature of this discriminant equation is that good prognosis is predicted by an anterior shift of the hypometabolism within the network. In patients with a good outcome, the preferential distribution of the hypometabolism to the temporal pole and the adjacent basofrontal cortex. This pattern of seizure spread may also explain the important prognostic role played by the basofrontal cortex in the network. This hypothesis of the role played by the seizure spread in outcome prediction is supported by the fact that both temporal pole and basofrontal cortex exhibited high and positive coefficients in the discriminant analysis, indicating that a more marked hypometabolism in these regions was associated with a better outcome.

A more intriguing fact was that the medial and anterolateral temporal regions exhibited negative coefficients, indicating that a less pronounced hypometabolism in these regions was associated with a better outcome. However, we know that the degree of FDG-PET hypometabolism does not parallel severity of hippocampal neuronal loss in medial temporal lobe epilepsy. Since these 2 regions exhibited the same degree of hypometabolism among the 3 prognosis groups, it seems logical that they did not play a prominent role in the determination of the postoperative outcome. Therefore, the negative coefficients attributed to these regions must be related to the discriminant equation and balanced by the prominent role played by the temporal pole.

Table 1. Asymmetry Indexes for Regional Metabolism and Hippocampal Atrophy*

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Seizure-Free</th>
<th>Not Seizure-Free</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td></td>
<td>(n = 14)</td>
<td>(n = 10)</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>−30 ± 13</td>
<td>−19 ± 9</td>
</tr>
<tr>
<td>Medial temporal</td>
<td>−17 ± 11</td>
<td>−16 ± 7</td>
</tr>
<tr>
<td>Anterolateral temporal</td>
<td>−16 ± 15</td>
<td>−14 ± 8</td>
</tr>
<tr>
<td>MRI hippocampal atrophy</td>
<td>−35 ± 15</td>
<td>−31 ± 12</td>
</tr>
</tbody>
</table>

*Metabolic asymmetry indexes are expressed as the rate of glucose consumption of the contralateral region minus the rate of the ipsilateral region divided by the rate of the contralateral region. Data are mean ± SD. MRI indicates magnetic resonance imaging.

†Analysis of variance, P = .005; F = 6.68 (group A vs group C). Post hoc test shows that group A is significantly different from group C (P < .01).

Figure 1. Temporal regions of interest. The key at the top refers to the left column of pictures; the key at the bottom, to the single picture at the right. The numbers in the bottom key indicate the distance between the hippocampal plane and the magnetic resonance imaging slices parallel to this hippocampal plane.

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<td>−16±7</td>
</tr>
<tr>
<td>Anterolateral temporal</td>
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<td>−14±8</td>
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The basofrontal cortex may be related to a preferential pattern of seizure spread to the anterior part of the temporal lobe. It therefore seems logical that such patients who undergo an anterior temporal lobectomy may be seizure free after surgery. On the other hand, the prominent distribution of hypometabolism to the medial and anterolateral temporal structures suggests that a preferential way of spreading to the lateral temporal neocortex may constitute a predictor of worse outcomes.

This analysis demonstrated clearly that the metabolic pattern might help differentiate seizure-free patients from patients who are not seizure free. All of our patients underwent a similar standard surgical procedure, ie, a standard anterior temporal lobectomy. This standard surgical technique yields uniform data, and thus validates our results for the entire group. The different discriminant coefficients attributed to the temporal and frontal regions reflect the importance of the associated location of hypometabolism within and external to the temporal lobe and particularly in the temporal pole. This study provides further support to the logic of a direct connection between glucose consumption and outcome. Further prospective analysis is needed to validate this model to predict outcome after epilepsy surgery and determine which patients are likely and which are unlikely to experience seizure relief. This model, if validated, may have a significant impact on clinical and surgical decisions.

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Table 2. Univariate Analysis for Metabolic Asymmetry Indexes in 5 Temporal Regions

<table>
<thead>
<tr>
<th>Statistical Parameter</th>
<th>Medial</th>
<th>Pole</th>
<th>Anterolateral</th>
<th>Medium Lateral</th>
<th>Posterolateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discriminant coefficient</td>
<td>0.20</td>
<td>-10.87</td>
<td>-0.76</td>
<td>1.51</td>
<td>0.15</td>
</tr>
<tr>
<td>F ratio</td>
<td>0.0031</td>
<td>10.2</td>
<td>0.053</td>
<td>0.064</td>
<td>0.0004</td>
</tr>
<tr>
<td>P</td>
<td>.95</td>
<td>.005*</td>
<td>.82</td>
<td>.80</td>
<td>.98</td>
</tr>
<tr>
<td>Correct classification, %</td>
<td>55</td>
<td>80</td>
<td>50</td>
<td>53</td>
<td>42</td>
</tr>
</tbody>
</table>

* Statistically significant.

Table 3. Univariate and Multivariate Analyses for Metabolic Asymmetry Indexes

<table>
<thead>
<tr>
<th>Group</th>
<th>Outcome</th>
<th>Univariate Z Score</th>
<th>Multivariate Z Score</th>
<th>Degree of Hippocampal Atrophy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Ia</td>
<td>0.78 ± 0.93</td>
<td>1.43 ± 1.10</td>
<td>35 ± 16</td>
</tr>
<tr>
<td>B</td>
<td>Ib, c, d</td>
<td>-0.01 ± 0.59</td>
<td>0.08 ± 1.23</td>
<td>30 ± 12</td>
</tr>
<tr>
<td>C</td>
<td>II-III</td>
<td>-0.78 ± 1.16</td>
<td>-1.43 ± 0.65</td>
<td>32 ± 22</td>
</tr>
</tbody>
</table>

* Data are mean ± SD.

Figure 2. Variability of the regional pattern of hypometabolism in postoperative prediction. Temporal hypometabolism occurred in both patients, but it clearly predominated in the temporal pole (asymmetry index (AI)=−28%) and the adjacent basofrontal region (AI=−17%, not shown here) in the category A patient (left). Conversely, in the category C patient (right), it was less marked in the temporal pole (AI=−6%) and the orbitofrontal cortex (AI=−11%) than in the medial temporal region (AI=−26%) and the anterior part of the lateral temporal region (AI=−11%).

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