Unitemporal vs Bitemporal Hypometabolism in Mesial Temporal Lobe Epilepsy

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Background: Patients with mesial temporal lobe epilepsy (TLE) often show bilateral temporal hypometabolism (BTH), but the nature of this finding has not been well established.

Objective: To compare the clinical characteristics between unitemporal hypometabolism (UTH) and BTH patients in mesial TLE.

Design: Cross-sectional study.

Setting: Epilepsy center at university hospital in Seoul, Korea.

Patients: We enrolled 95 patients with mesial TLE, 87 of whom had subsequently undergone surgery. Seizures, interictal and ictal electroencephalography (EEG), brain magnetic resonance imaging, Wada test, and neuropsychological test results were reviewed. 18F-fluorodeoxyglucose positron emission tomography scans were interpreted visually. Patients were divided into 2 groups: UTH and BTH.

Results: There were 59 UTH patients and 36 BTH patients. Semilogic analysis showed that UTH patients had higher frequencies of aura and unilateral dystonic posturing, whereas BTH patients had higher frequencies of a nonlateralized bilateral ictal EEG pattern and bilateral interictal spikes. Moreover, BTH patients had more frequent symmetric Wada memory scores and white matter changes in the bilateral temporal lobes on brain magnetic resonance imaging than UTH patients. All UTH patients with bilateral TLE on scalp EEG showed unilateral seizure onset on intracranial EEG.

Conclusions: The characteristic clinical findings of mesial TLE with BTH were a more frequent nonlateralized ictal EEG pattern, bitemporal interictal spikes, symmetric Wada memory score, and the anterior temporal white matter changes, and less frequent aura and unilateral dystonic posturing. Surgical outcomes were similar and good in both groups, although surgery could not be performed in 8 BTH patients (22%).

Confl Neurol. 2004;61:1074-1078

PATIENTS WITH UNITEMPORAL hypometabolism (UTH) apparent on 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans are good surgical candidates, and many achieve a long-term, seizure-free status.1 In contrast to UTH, the phenomenon of BTH has received little attention. Several studies2-4 have found that patients with BTH have features distinct from those with UTH and BTH was associated with more frequent bilateral magnetic resonance (MR) imaging changes, seizure onset on scalp telemetry, worse social and cognitive functioning, and a less successful surgical outcome. However, in our experiences, a considerable number of patients with BTH have shown a good surgical outcome. Thus, we thought that a more detailed analysis of clinical features was necessary to identify those factors that contribute to BTH and to determine their relationships with surgical outcome. The aims of our study were to investigate (1) differences between the clinical and neuroimaging findings of UTH and BTH patients, (2) the causes of BTH, (3) the clinical implication of BTH, and (4) whether BTH affects surgical outcome in mesial temporal lobe epilepsy (TLE).

METHODS

Patients

We included 95 patients with mesial TLE who had undergone FDG-PET at the Samsung Medical Center in Seoul, Korea, from 1995 to 2001. All patients underwent presurgical evaluation. Clinical characteristics registered for each patient included age of seizure onset, duration of epilepsy history, age at PET, a history of febrile convulsions, and the presence of hippocampal sclerosis on MR imaging. When the
available data failed to provide a convergent lateralization of the epileptic focus, bitemporal depth or strip electrodes were implanted.

FDG-PET IMAGES

The FDG-PET images were obtained (GE Advance PET scanner, GE Medical Systems Inc, Milwaukee, Wis) after patients had fasted for 4 or more hours and then received an intravenous injection of 7 to 10 mCi (259-370 MBq) of FDG. Electroencephalography (EEG) during the uptake period demonstrated no EEG seizure activity in all patients. One neurologist (E.Y.J.) and one neuroimaging analyst (W.S.T.), blinded to clinical identities, interpreted the FDG-PET results. Hypometabolism apparent on FDG-PET was determined semiquantitatively by visual assessment using calibrated color scales (Figure 1). A graduated color scale in 2% increments was used for display and analysis.

Significant temporal lobe hypometabolism was defined when the hypometabolic area was seen in 3 or more contiguous slices of the temporal lobe on coronal PET images compared with the extratemporal cerebral glucose metabolism. Unilateral hypometabolism was defined when the metabolism of one temporal lobe showed a 20% or more reduction, compared with the extratemporal regions showing normal metabolism, and the metabolism of the other temporal lobe looked normal or showed a 10% or less reduction. Bitemporal hypometabolism was defined when the metabolisms of both temporal lobes showed a 20% or more reduction compared with the extratemporal regions showing normal glucose metabolism, irrespective of asymmetry.2

ANALYSIS OF CLINICAL SEIZURES AND EEG

We reviewed and described every seizure carefully. The presence of aura was determined by the patient’s memory postictally or by the patient’s pressing of a seizure button.

Long-term Video EEG Monitoring

The 10/10 system scalp electrodes and sphenoidal electrodes were placed. Antiepileptic medication was usually reduced or completely stopped to facilitate the recording of seizures.

Interictal EEG Classification

Unilateral temporal lobe interictal epileptiform discharge (IED) was defined as a strictly unilateral IED or if bilateral IED was present as a 75% or more preponderance of IED to one temporal lobe.3,5 Bilateral temporal lobe IED was defined as a 74% or less preponderance to one temporal lobe.

Ictal EEG Classification

The location of each seizure was determined using the following criteria: (1) location of ictal discharges, including temporal, left or right (if the amplitude ratio of the temporal vs the parasagittal chain was higher than 2:1 in bipolar montages and
higher than 2:1 for the 2 sides in referential montages), bilateral, lateralized left or right (bilateral involvement with an amplitude ratio >1:1 but <2:1 in favor of one side in bipo- 
lar and referential montages), or bilateral, nonlateralized; and (2) characteristic ictal EEG patterns, with each seizure also analyzed for bilateral independent seizures, temporal asynchrony of the ictal discharges over the 2 temporal lobes, and switch of lateralized ictal activity from one hemisphere to the other.

**WADA TEST**

Wada memory scores were calculated using the choice recognition memory test. The formula used was the number of items remembered correctly 10 minutes after an amobarbital sodium injection divided by the total numbers of items, in our case 12. A difference of 3 points or more (≥25%) in the retention score between the scores on each side was defined as asymmetric and a difference of less than 3 points (<25%) as symmetric.

**BRAIN MR IMAGING**

Volumetric brain MR imaging was performed (GE Signa 1.5-T; GE Medical Systems Inc), and the MR images were independently reviewed by 2 observers (E.Y.J. and W.S.T.) who were blinded to clinical findings and the EEGs. They assessed the MR images to determine whether there was evidence of white matter change (WMC) of the anterior temporal lobe and hippocampal atrophy. The criteria used to determine a WMC of the anterior temporal lobe included an increased signal for temporal white matter and a decreased demarcation between the anterior temporal lobe and hippocampal boundaries. Normalized HV of the right and left sides were calculated by the following formula: HV/whole cerebral volume × 106.

**Table. Patient Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>UTH Group (n = 59)</th>
<th>BTH Group (n = 36)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>30/29</td>
<td>17/19</td>
<td>.73</td>
</tr>
<tr>
<td>Normal hippocampus volume, patients, No.</td>
<td>1</td>
<td>3</td>
<td>.15</td>
</tr>
<tr>
<td>Bilateral hippocampal atrophy, patients, No.</td>
<td>2</td>
<td>1</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Right/left/bilateral mesial TLE, patients, No.</td>
<td>22/29/8</td>
<td>16/15/5</td>
<td>.76</td>
</tr>
<tr>
<td>Seizure onset, mean ± SD, y</td>
<td>14.0 ± 6.8</td>
<td>15.1 ± 8.1</td>
<td>.51</td>
</tr>
<tr>
<td>Duration of epilepsy history, mean ± SD, y</td>
<td>13.8 ± 7.0</td>
<td>13.8 ± 7.3</td>
<td>.99</td>
</tr>
<tr>
<td>Age at PET, mean ± SD, y</td>
<td>28.0 ± 7.6</td>
<td>29.0 ± 9.4</td>
<td>.53</td>
</tr>
<tr>
<td>Febrile convulsion, patients, %</td>
<td>50</td>
<td>46</td>
<td>.68</td>
</tr>
</tbody>
</table>

Abbreviations: BTH, bitemporal hypometabolism; PET, positron emission tomography; TLE, temporal lobe epilepsy; UTH, unilateral hypometabolism. *P<.05; t test for seizure onset, duration of epilepsy history, and age at PET, χ2 test for M/F, right/left/bilateral TLE, and the presence of febrile convulsion; Fisher exact test for normal hippocampus volume and bilateral hippocampal atrophy.

**NEUROPSYCHOLOGICAL TESTING**

All patients received neuropsychologic assessment preoperatively. Postoperative assessment with the logical memory test and the Rey-Osterrieth figure test was performed in 59 UTH patients and 28 BTH patients.

**STATISTICAL ANALYSIS**

Numerical data are given as mean (SD). The t test (2-tailed, unpaired) and the χ2 test were used. P<.05 was considered statistically significant. All analyses were performed using SPSS statistical software, version 10.0 (SPSS Inc, Chicago, Ill).

**RESULTS**

**PATIENT CHARACTERISTICS**

There were no statistical differences in seizure onset, duration of epilepsy history, age at PET, and the presence of febrile convulsion between the 2 groups. Based on ictal EEG findings, right, left, or bilateral mesial TLE was diagnosed (Table).

**CLINICAL SEIZURE ANALYSIS**

The UTH patients showed more frequent auras (58% in the UTH group and 38% in the BTH group, P=.04) and contralateral dystonic posturing (77% in the UTH group and 52% in the BTH group, P=.04) of the upper arm than BTH patients (χ2 test).

**SCALP EEG FINDINGS**

**Intercital Epileptiform Discharges**

The BTH group (48%) had more frequent bilateral interictal spikes than the UTH group (25%) (P=.02, χ2 test). Eighty-five percent of the IEDs were recorded on the temporal lobes in both groups, and 15% of the IEDs were
detecting extratemporal areas (frontal or frontopolar regions).

Ictal EEG Classification

The mean number of seizures recorded was 6.4 per patient in the UTH group and 6.9 seizures per patient in the BTH group (P = .13, t test). The seizures in the BTH group showed more frequent nonlateralized (2% in the UTH group and 20% in the BTH group) and bilateral ictal EEGs (3% in the UTH group and 11% in the BTH group) (P = .002, χ² test). The BTH group had more frequent bilateral independent seizures (2% in the UTH group and 16% in the BTH group) and switched ictal activity (9% in the UTH group and 29% in the BTH group) (P = .002, χ² test).

WADA TEST

Two UTH patients (3%) and 11 BTH patients (31%) showed a reversed Wada memory score asymmetry, meaning that the Wada memory score of the normal hemisphere was smaller than that of the epileptic side. More frequent symmetric Wada memory scores in the BTH group (16% in the UTH group and 48% in the BTH group) (P = .01, χ² test) suggested that the memory function differential between the epileptogenic and nonepileptogenic hemispheres was smaller than that of the UTH patients.

WMC OF ANTERIOR TEMPORAL LOBES AND HV

Bilateral WMC was seen only in the BTH group (absent, unilateral, and bilateral WMC: 62%, 38%, and 0% in the UTH group vs 24%, 30%, and 45% in the BTH group, respectively) (P < .001, χ² test). Normalized HVs of the ipsilateral and contralateral hemispheres to the seizure focus were not significantly different in the 2 groups.

NEUROPSYCHOLOGICAL TEST

The numbers of patients with a 20% or greater reduction in score postoperatively were 15 (25%) in the UTH group (9 with left TLE and 6 with right TLE) vs 6 (21%) in the BTH group (4 with left TLE and 2 with right TLE) (P = .32, χ² test) without statistical difference. Absolute reduction scores of postoperative neuropsychological tests from preoperative tests were not different between the UTH and BTH groups (P = .74, t test). In the BTH group, 4 patients with left TLE with reversed asymmetry according to the Wada test showed greater reduction of postoperative scores (22%) compared with those (12%) of the remaining patients (P = .004, Mann-Whitney U test).

SURGICAL OUTCOME

Standard anterior temporal lobectomy with amygdalo-hippocampectomy was performed in 59 UTH patients and 26 BTH patients. Intracranial EEGs in 8 UTH patients showed unitemporal seizure onset and all underwent resective surgery, whereas the intracranial EEGs in 5 BTH patients showed bitemporal seizure origins; thus, these patients did not undergo surgery. The mean postoperative follow-up period of all patients was 35.9 ± 9.2 months.

The surgical outcomes of the UTH patients appeared to be slightly better than those of the BTH patients without statistical significance (P = .32) (Engel classification for the UTH group: 1, 56; II, 2; III, 0; IV, 1; Engel classification for the BTH group: 1, 25; II, 3; III, 0; IV, 0). A pathologic evaluation showed hippocampal sclerosis in all surgical patients, except the 4 patients with a normal MR imaging results who had a normal hippocampus or a hippocampus containing some dead neurons on pathologic examination. A logistic regression analysis of PET, MR imaging, and EEG findings showed no significantly different findings between a good outcome group (class I) and the others (class II-IV).

We found differential clinical characteristics between the UTH and BTH patients. Previous studies have used asymmetry indices of glucose metabolism to evaluate temporal lobe hypometabolism. Asymmetry indices of the temporal lobe against cerebellar or whole cerebral metabolism were used recently. However, the propagation of seizure discharges may lead to cerebellar damage, and cerebellar blood flow and glucose metabolism often decrease in patients with partial seizures. The method that used whole cerebral metabolism as a reference also may produce a false result due to frequent extratemporal hypometabolism in mesial TLE. The degree of hypometabolism is not always homogeneous through the whole temporal lobe. Thus, analysis using either the whole temporal or subtemporal regions as regions of interest may be insufficient to reflect the real status of glucose metabolism throughout a temporal lobe. To prevent possible errors, we decided to use a semiquantitative visual assessment. It was reported that results obtained by visually analyzing brain FDG-PET images correlate well with those obtained using statistical, quantitative, analytical methods in the evaluation of epilepsy patients. The paucity of aura or unilateral dystonic posturing in BTH is probably due to its more frequent bilateral presentation of ictal EEG onset. The frequencies of secondarily generalized seizures were not different between the 2 groups (19% in the UTH group and 28% in the BTH group, P = .21, χ² test), which suggests that early bitemporal ictal EEG is not related to a more frequent secondary generalization.

Bilateral independent seizure onsets and switched lateralized activity from one hemisphere to the other were almost exclusively associated with BTH. Because most patients with these ictal EEG features became seizure-free after surgery, these 2 ictal EEG patterns do not indicate a poor prognosis if other findings are concordant with unilateral TLE. It was reported that mesial TLE patients without auras showed bitemporal IED and ictal patterns suggestive of a bitemporal independent epileptogenicity significantly more often, which was similar to our result. A symmetric Wada memory score was observed more frequently in BTH, and the mean Wada memory score of the epileptic hemisphere in the BTH group (51.0% ± 20.9%) was lower than that in the UTH.
Several studies\textsuperscript{15,16} have suggested that bitemporal sei-

group (63.0\%±24.5\%) ($P=0.02$, t test). These findings sug-

ggest that BTH is associated with bitemporal memory dys-

function and more dysfunction of the ipsilateral tempo-

ral lobe. No significant difference of postoperative neuropsychological changes between the 2 groups sug-

gests that hypofunction of normal hemisphere in BTH is transient, is reversible, and may be related to the propa-

gation of repetitive epileptic discharges from the epilep-

tic side.

It was reported that the patients with WMC re-

ealed more severe hypometabolism of the ipsilateral tem-

poral lobes and that WMC is caused by repeated seizure propagations.\textsuperscript{8} Our study showed that bilateral WMC was obser-

ved only in BTH patients. This result suggests that WMC is associated with PET hypometabolism in TLE. Several studies\textsuperscript{15,16} have suggested that bitemporal sei-

zure are a poor prognostic sign.

However, most of our BTH patients (95\%) showed a good surgical outcome (Engel class I). The remaining 3 BTH patients rarely had residual complex partial sei-

zures, which represented a significant reduction (class II). The reasons for the good surgical outcomes in our BTH patients were attributed to the careful selection of surgical candidates and the exclusion of 5 patients with BTH and bilateral temporal lobe seizures on intracranial EEG from surgery. The remaining 3 BTH patients who had bitemporal lobe seizures on scalp EEG monitoring underwent additional drug trials. From the results of intracranial studies in our patients with mesial TLE, UTH in patients with bitemporal lobe epilepsy by scalp EEG monitoring strongly suggests unilateral seizure onset on intracranial EEG.

Accepted for publication February 24, 2004.

This study was supported by a grant (HMP-03-PJ1-
P3-21300-0033) from the Good Health R&D Project, Min-

istry of Health & Welfare, Republic of Korea.

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