Mesial Temporal Cortex Hypoperfusion Is Associated With Depression in Subcortical Stroke

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Background and Purpose
This study was conducted to evaluate local cerebral blood flow changes in patients with depression after a subcortical stroke.

Methods
Clinical and neuropsychological assessments were performed in 15 patients with a single subcortical lesion. Depression was assessed by DSM-III-R. In addition, the Hamilton Rating Scale for depression, the Zung Self-Rating Depression Scale, and the Beck scale were administered to each patient. Single-photon emission-computed tomography study was performed with 99mTc hexamethylpropyleneamine oxime.

Results
In all patients cortical regions ipsilateral to subcortical lesions were significantly less perfused than the contra-lateral cortex. Cerebral blood flow values were significantly lower in depressed patients (n=8) than in nondepressed patients (n=7) only in the mesial temporal cortex of the affected hemisphere. Cerebral blood flow values in the mesial temporal cortex of the affected hemisphere significantly correlated with the severity of depression.

Conclusions
Temporal lobe hypoperfusion may reflect a dysfunction of the limbic system, suggesting that this location may be critical for the occurrence of depressive symptoms in patients with subcortical stroke. (Stroke. 1994;25:980-985.)

Key Words • depression • subcortical infarction • tomography, emission-computed

Subjects and Methods

Patients
We studied 15 consecutive patients with a single subcortical infarct in the deep territory of the middle cerebral artery after 1 to 5 months from the onset of disease (mean, 2.5±1.5 months). Exclusion criteria were age older than 80 years, history of previous neurological diseases, personal and/or familial history of depression, severe comprehension difficulties, treatment with tricyclic or other antidepressants, heart and kidney failure, neoplasms, and severe stenosis of neck vessels. The group comprised 8 women and 7 men with a mean age of 67.8±9.6 years.

Clinical and Neuropsychological Assessment
Neurological impairment was determined by both the Canadian Neurological Scale and the Barthel Index. Psychiatric examination was conducted in the late morning or early afternoon to minimize any possible effect of diurnal mood variation. Identification of depressive symptoms was obtained by using the structured clinical interview from the Diagnostic and Statistical Manual of Mental Disorders, edition 3, revised (DSM-III-R).

In addition, the Hamilton Rating Scale for depression, the Zung Self-Rating Depression Scale, the Beck scale, and the Mini-Mental State Examination (MMSE) were administered to each patient. All patients underwent cerebral computed tomographic (CT) scans and/or magnetic resonance imaging. A neuroradiologist blind to both clinical and SPECT findings of the patients measured the volume of cerebral lesions. The lesions were outlined on a monitor screen with a cursor and the volumes calculated in each patient by taking into account the thickness of the tomograms.

Cerebral Blood Flow Measurement
Measurements of CBF were performed by SPECT after an intravenous injection of 20 mCi of 99mTc hexamethylpropyleneamine oxime (HMPAO). The patient's head was positioned
with the orbitomeatal line perpendicular to the floor, using a laser reference system and ink dots on the skin. The head was then fixed to the head holder by tape. Patients were studied at rest (eyes closed, ears unplugged) in a dimly lit room with external stimuli reduced to a minimum. Scans started 5 minutes after tracer injection and lasted 25 minutes. Head radioactivity distribution was measured by a Tomomatic 564 (Medimatic) equipped with a high-resolution collimator. Six slices were obtained for each study with a spatial resolution of 9 mm and a slice thickness of 10 mm. After tomographic image reconstruction, 21 irregular regions of interest (ROIs) were located on the cortical ribbon and the deep gray matter of the unaffected hemisphere and then automatically mirrored onto the affected hemisphere by a vertical axis of symmetry (Fig 1).

For the location of the ROIs, we referred to a template set of transverse cuts parallel to the orbitomeatal line with anatomic landmarks. Counts in ROIs belonging to the same anatomic-functional area were averaged, thereby obtaining a total of eight cortical regions (prefrontal, basal frontal, motor, mesial temporal, basal temporal, lateral temporal, parietal, and occipital areas) and three subcortical regions (thalamus, caudate nucleus, and lenticular nucleus) in each hemisphere. The size of the 11 regions varied from 2.2±0.4 cm² to 15.7±1.9 cm² in accordance with the more or less extensive representation of the different cerebral structures on the six SPECT tomograms analyzed. Frontal and temporal lobes were studied in more detail because they were found to be functionally affected in depressed patients in previous reports. Because absolute CBF values are not achieved using Tc-HMPAO, we considered the ratio between mean counts in each region and the mean counts of all the ROIs as an index of CBF distribution.

**Statistical Analysis**

Statistical analysis was performed by \( \chi^2 \), ANOVA for non-repeated measures, Mann-Whitney \( U \) statistic, and regression analysis.

**Results**

Of the 15 patients, 8 were depressed and 7 nondepressed according to DSM-III-R. Demographic and clinical characteristics of both groups of patients are shown in Table 1.

<table>
<thead>
<tr>
<th>Age, y</th>
<th>70.6 (8.1)</th>
<th>64.3 (11.8)</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio, M/F</td>
<td>3:5</td>
<td>4:3</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration, mo</td>
<td>2.6 (1.5)</td>
<td>2.3 (1.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Affected hemisphere</td>
<td>4L, 4R</td>
<td>4L, 3R</td>
<td>NS</td>
</tr>
<tr>
<td>CNS</td>
<td>6.8 (1.7)</td>
<td>6.3 (1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Barthel Index</td>
<td>59.4 (23.8)</td>
<td>66.6 (22.3)</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE</td>
<td>18.2 (9.9)</td>
<td>20 (10.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Hamilton scale</td>
<td>14.9 (3.4)</td>
<td>5.6 (2.4)</td>
<td>.0001</td>
</tr>
<tr>
<td>Beck scale</td>
<td>15.4 (2.6)</td>
<td>4.9 (3.3)</td>
<td>.0001</td>
</tr>
<tr>
<td>Zung scale</td>
<td>42.9 (6.9)</td>
<td>28.6 (4.7)</td>
<td>.0005</td>
</tr>
</tbody>
</table>

CNS indicates Canadian Neurological Scale; MMSE, Mini-Mental State Examination; L, left; and R, right. Values are expressed as mean (SD).
Single-photon emission-computed tomographic (SPECT) cerebral blood flow (CBF) images and diagrams show location of regions of interest (ROIs). On the six CBF SPECT images, from the orbitomeatal line (OM) to OM plus 100 mm (OM+100), 21 irregular ROIs were drawn on the unaffected hemisphere and automatically mirrored onto the affected hemisphere, according to an anatomicofunctional representation on corresponding schematic cuts (adapted from Damasio and Damasio). Counts in ROIs belonging to the same anatomicofunctional area were averaged, obtaining 11 regions, as follows: basal temporal (T) region (1); basal frontal (F) region (2); lateral temporal cortex (3, 7, 14); mesial temporal cortex (4); prefrontal region (5, 12, 16); motor areas (6, 13, 17, 20); parietal (P) cortex (18, 21); occipital (O) cortex (8, 15, 19); caudate nucleus (9); lenticular nucleus (10); and thalamus (11).

temporal cortex of the affected hemisphere were significantly correlated with the severity of depression as measured by the Beck scale (r = .59, P = .02) but not with either the volume of the subcortical lesion or the severity of the motor deficit (Canadian Neurological Scale score). Correlations between CBF values in the mesial temporal cortex and Hamilton and Zung scales did not reach statistical significance (r = .41 and r = .35, respectively).

**Discussion**

Depression was found to affect more than 50% of the patients in our series. The occurrence of depression is reported to be from 20% to 60%. However, our series is too small and may not be representative. The severity of depression did not correlate with the degree of neurological disability and with the extent or location of the lesion on CT or magnetic resonance imaging scans, in agreement with previous reports. In fact, poststroke depression studies performed with CT scan showed that location rather than extension of lesions is critical in depression. Although major depression after stroke has been described to be associated with either left anterior or right posterior lesions, this relation has not been confirmed. It is still uncertain whether there is a link between poststroke depression and location of brain damage. It has also been reported that subcortical lesions are associated with depression with the same frequency and severity as cortical lesions.

Our data, although obtained in a limited number of patients with subcortical stroke, show that neither location (white matter or basal ganglia) nor side (right or left) of lesions correlates with the occurrence of depression. That is, anatomic aspects of the lesion per se do not correlate with the occurrence of depression.

SPECT study of CBF offers the opportunity to evaluate functional changes occurring in the cerebral cortex after a subcortical lesion. Using Tc HMPAO as a tracer, quantitative measurements of CBF are not feasible. Our results are expressed as the ratio between

**Table 2. Normalized Cerebral Blood Flow Values of Cortical and Subcortical Regions In Depressed and Nondepressed Patients**

<table>
<thead>
<tr>
<th>Region</th>
<th>Depressed (n=8)</th>
<th>Nondepressed (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affected</td>
<td>Unaffected</td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lateral</td>
<td>0.92±0.03</td>
<td>1.06±0.06</td>
</tr>
<tr>
<td>Basal</td>
<td>0.89±0.06</td>
<td>0.99±0.07</td>
</tr>
<tr>
<td>Mesial</td>
<td>0.90±0.07*</td>
<td>1.04±0.05</td>
</tr>
<tr>
<td>Frontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prefrontal</td>
<td>0.91±0.04</td>
<td>0.98±0.07</td>
</tr>
<tr>
<td>Basal</td>
<td>0.95±0.08</td>
<td>1.01±0.06</td>
</tr>
<tr>
<td>Motor</td>
<td>0.94±0.04</td>
<td>1.03±0.05</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.93±0.04</td>
<td>1.07±0.09</td>
</tr>
<tr>
<td>Occipital</td>
<td>1.09±0.06</td>
<td>1.15±0.08</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.99±0.10</td>
<td>1.14±0.03</td>
</tr>
<tr>
<td>Lenticular nucleus</td>
<td>0.83±0.19</td>
<td>1.05±0.05</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td>0.93±0.16</td>
<td>1.17±0.05</td>
</tr>
</tbody>
</table>

*P = .03, Mann-Whitney U statistic.
radioisotope activity in a given region and the mean global activity. The data, therefore, represent relative perfusion indexes.

This study shows that mesial temporal cortex ipsilateral to subcortical ischemia is significantly less perfused in depressed than in nondepressed patients. This pattern is observed in depressed patients with damage in either the left or the right hemisphere, indicating that the side of the subcortical lesion is not relevant in inducing local CBF abnormalities.

Reduction of CBF in the cerebral cortex of stroke patients may reflect oligemia/ischemia on a hemodynamic basis and/or disconnection from subcortical nuclei with widespread cortical projections (ie, diaschisis).20-22 The reduction of CBF in the mesial temporal cortex found in our patients with a subcortical ischemic stroke in the middle cerebral artery territory, however, is more likely due to diaschisis because the mesial temporal cortex is supplied by posterior circulation. In addition, patients with severe stenosis of the neck vessels were excluded from our study.

Subcortical lesions could determine, through the interruption of corticosubcortical connections, a functional impairment of limbic cortex responsible for depressive disorder. This hypothesis is partially supported by the observed significant correlation of CBF values between mesial temporal and basal temporal cortices in the affected hemisphere. In addition, mesial temporal hypoperfusion was significantly associated with the degree of depression.

Our results are not in agreement with two previous studies that investigated CBF in poststroke depression. Yamaguchi et al35 studied CBF in 60 patients with one or more supratentorial cerebrovascular lesions using the 133Xe inhalation bidimensional method. The authors found that the severity of depression was inversely correlated with regional CBF values in the parieto-occipital region of the right hemisphere and in the anterior temporal region of the left hemisphere. However, in this study bilateral lesions were present in approximately one third of the patients, and large lesions were also included. Schwartz et al36 studied regional CBF and depression in 14 stroke patients and found that depression scores correlated with the extent of hypoperfusion as measured by SPECT. However, SPECT hypoperfusion coincided with CT lesions that were heterogeneous, widespread, and often involved both cerebral hemispheres. Therefore, no conclusive data resulted from these previous studies because the cerebral cortex was often directly and extensively involved by the lesions. In our study only patients with a single subcortical lesion were selected to better evaluate a possible relation between depression after stroke and functional abnormalities in structurally healthy cortex.

A specific functional involvement of temporal areas in poststroke depression has not been previously described by SPECT CBF studies. However, frontal and temporal glucose hypometabolism has been observed in major depression and in depression associated with other neurological diseases, using positron emission tomography.29,30 In primary depression some authors found metabolic abnormalities involving both frontal and temporal cortices,31 whereas others described glucose hypometabolism in either temporal32 or frontal cortices.29 In depression secondary to Parkinson's disease and Huntington's disease, Mayberg et al30-36-37 found metabolic abnormalities in the orbital inferior frontal and temporal regions regardless of disease etiology.

These previous observations, combined with the results of our study, suggest that interruption of pathways linking specific mesial temporal lobe regions may underlie depressive phenomenology. Temporal lobe hypoperfusion and/or hypometabolism likely reflects a dysfunction of the limbic system, suggesting that this location may be critical for the onset of mood symptoms.

References


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