Magnetic Resonance Imaging Correlates of Depression After Ischemic Stroke

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Background: Depression affects up to 40% of patients with ischemic stroke. The relationship between site and size of brain infarcts and poststroke depression is still not well characterized. Further possible contribution and interaction of white matter lesions and brain atrophy has not been studied previously. We conducted a magnetic resonance image–based study of the radiologic correlates of depression in a large, well-defined series of patients with ischemic stroke.

Methods: Modified DSM-III-R and DSM-IV criteria were used to diagnose depressive disorders during a comprehensive psychiatric evaluation in 275 of 486 consecutive patients aged 55 to 85 years 3 to 4 months after ischemic stroke. A standardized magnetic resonance imaging protocol detailed side, site, type, and extent of brain infarcts and extent of white matter lesions and brain atrophy.

Results: Depressive disorders were diagnosed in 109 patients (40%). Patients with depression had a higher number and larger volume of infarcts affecting the prefrontosubcortical circuits, especially the caudate, pallidum, and genu of internal capsule, with left-sided predominance. Extent of white matter lesions and atrophy did not differ in patients with and without depression. Independent correlates of poststroke depression in a logistic regression model were mean frequency of infarcts in the genu of internal capsule on the left side (odds ratio [OR], 3.2; 95% confidence interval [CI], 1.0-10.1), mean frequency of infarcts in the pallidum of any side (OR, 1.6; 95% CI, 1.1-2.3), and mean volume of infarcts in the right occipital lobe (OR, 0.98; 95% CI, 0.96-0.99).

Conclusion: Lesions affecting the prefrontosubcortical circuits, especially on the left side, are correlates of depression after ischemic stroke.

Arch Gen Psychiatry. 2001;58:925-931
PATIENTS AND METHODS

PATIENTS

The Helsinki Stroke Aging Memory Study was conducted at Helsinki University Central Hospital in Helsinki, Finland, between December 1, 1993, and March 1, 1995. The detailed clinical, psychiatric, and radiologic procedures have been published previously. Patients with suspected stroke, defined as sudden or rapidly evolving transient or permanent symptoms or signs indicating a local or focal neurological dysfunction of suspected vascular origin, were identified by daily survey of admissions to the emergency department at Helsinki University Central Hospital. Included patients were aged 55 to 85 years at the onset of illness, resided in Helsinki, and spoke Finnish. A total of 486 patients were initially evaluated 3 months after having a stroke. Recruitment of the consecutive patients for the psychiatric study started 3 months after and ended 1 month before recruitment for other procedures. Patient flow and reasons for nonenrollment are shown in the Figure. Of the 275 patients included in the study, 233 were living at home, 12 were in nursing homes, and 30 were hospitalized. Patients excluded from the psychiatric evaluation were more often dependent in activities of daily living and had more severe physical handicaps, more cognitive disturbances (as measured by the Mini-Mental State Examination), and a more severe stroke (as measured by the Scandinavian Stroke Scale) (Table 1).

The study was approved by the ethics committee of the Department of Clinical Neurosciences, Helsinki University Central Hospital.

PROCEDURES

The protocol included a detailed structured clinical interview with the patient and a knowledgeable informant and a structured clinical and neurological examination by board-certified neurologists (T.P. and R.V.). The cases were also reviewed by a senior neurologist (T.E.). Cognitive function was assessed using the Mini-Mental State Examination, stroke severity using the Scandinavian Stroke Scale, aphasia using the Acute Aphasia Screening Protocol, and impairment in activities of daily living using the Barthel Index.

Magnetic resonance imaging was performed with a 1.0-T system 3 to 4 months after the stroke occurred. All images were reviewed by a single neuroradiologist (R.M.) blinded to the clinical data. Reliability of the visual rating was tested by review of 60 MRI scans independently by the same rater (R.M.), a board-certified neuroradiologist (O.S.), and a general radiologist (H.J.A). For the reliability of rating WMLs, weighted k values for intraobserver agreement were 0.72 to 0.95 and for interobserver reliability were 0.72 to 0.93. For the reliability of rating brain atrophy, intraobserver reliability was 0.75 to 0.82 and the corresponding interobserver reliability was 0.61 to 0.74.

We counted the frequency and volumes of all infarcts affecting different brain regions in the 2 patient groups (Tables 3 and 4, respectively). Patients had $3.2 \pm 2.5$ brain infarcts, of which $1.7 \pm 1.6$ were located on the right hemisphere and $1.6 \pm 1.4$ on the left hemisphere. Twelve patients fulfilling the clinical criteria for ischemic stroke and thus included in our study had no lesions fulfilling the radiologic criteria (ie, diameter <3 mm) for brain infarct. There was no difference in the total number of infarcts, the number of infarcts in the right or left hemisphere, or the number of infarcts in different lobes of the brain in patients with and without depression after stroke. However, patients with depression after stroke more frequently had lesions affecting the prefrontosubcortical circuits or some of its substructures (the caudate, pallidum, genu of internal capsule, and anterior capsule), especially in the left hemisphere (Table 3). Five of 6 pa-
White matter lesions were rated on proton density–weighted images in 6 areas: around the frontal and posterior horns; along the bodies of lateral ventricles; and in subcortical, deep, and watershed areas. \(^{10,20} \) Periventricular WMLs around the frontal and posterior horns were classified based on size and shape into small cap (\( \leq 5 \) mm), large cap (5-10 mm), and extending cap (\( > 10 \) mm) and WMLs along the bodies of lateral ventricles into thin lining (\( \leq 5 \) mm), smooth halo (6-10 mm), and irregular halo (\( > 10 \) mm). White matter lesions in the subcortical, deep, and watershed areas were classified based on size (greatest diameter) and shape into small focal (\( \leq 5 \) mm), large focal (6-10 mm), focal confluent (11-25 mm), diffusely confluent (\( > 25 \) mm), and extensive (diffuse hyperintensity without distinct focal lesions affecting most of the white matter area). The number of each type of hyperintensity was counted, and extensive WMLs were rated as absent or present. Moderate and severe degrees of WMLs included large and extending caps at the periventricular area; smooth halo and irregular halo along the bodies of lateral ventricles; and focal confluent, diffusely confluent, and extensive WMLs in the subcortical, deep, and watershed areas. In addition, the extent of WMLs was graded using the 4-point scale of Fazekas et al. \(^{26} \)

Brain atrophy was first rated as none, mild, moderate, or severe by comparison to standard images according to the methods of Scheltens \(^{29} \) and Erkinjuntti \(^{29} \) and their coworkers. Cortical atrophy was rated in the frontal, parietal, and occipital lobes; central atrophy in the temporal, frontal, and occipital horns and bodies of the lateral ventricles; and mediotemporal lobe atrophy in the entorhinal cortex and hippocampus. Cortical atrophy and central atrophy were expressed as the mean of the rating in all the bilateral areas rated and were divided into 2 groups: none to mild vs moderate to severe.

The clinical psychiatric examination was carried out after the MRI examination, 12 to 20 weeks (mean ± SD, 15.5 ± 1.7 weeks) after the index stroke. The examination included the computer-assisted structured interview Schedules for Clinical Assessment in Neuropsychiatry. \(^{29} \) The main content of the schedules is the 10th version of the Present State Examination, \(^{30} \) whose earlier version (ninth version) has been widely used in research concerning the elderly and physically ill patients. Most patients (n=220) were examined by a senior psychiatrist (A.L.). The senior psychiatrist also supervised the afterwards data entry concerning patients examined by a resident psychiatrist (n=55). Both were blinded to the radiologic data. The data from the interviews were entered directly into a computer. Finally, the program evaluated a prediagnosis profile for the DSM-III-R \(^{31} \) and ICD-10 \(^{32} \) categories. Severity of depression was measured using the Montgomery–Asberg Depression Rating Scale. For the final diagnoses of depressive disorders, all psychiatric data from the clinical psychiatric examination, interviews with the close informants of patients when possible, psychiatric rating scales, and the Schedules for Clinical Assessment in Neuropsychiatry protocol were combined.

We included all patients with any DSM-IV \(^{33} \) depressive disorders 3 to 4 months after stroke (Table 2). Also, the 54 patients (20%) who had had depressive episodes before the index stroke and the 83 (30%) with previous stroke episodes were included.

**STATISTICAL ANALYSIS**

In the statistical analysis we compared patients with and without depression after stroke. According to our hypothesis, we expected to find more damage in the anatomic structures constituting the prefrontosubcortical circuits in depressed patients. First, we created a sum variable model of these circuits (see the "Procedures" subsection) and compared the number and volume of infarcts affecting the circuits and their substrutures between the 2 groups.

After testing this hypothesis we analyzed all other areas covered by the MRI protocol to find other possible independent radiologic correlates for the poststroke depression. The Fisher exact test (2-tailed) was applied for categorical data and the Mann-Whitney nonparametric test was applied for continuous data throughout. No adjustments were made for multiple comparisons in statistical approaches. The alpha level of significance was \( P < .05 \). There were no missing data in any of the analyses described. The radiologic variables that significantly differentiated patients in the 2 groups (Table 3 and Table 4) were set to an adding multiple logistic regression analysis to find the independent MRI correlates of depression after stroke. The statistics were analyzed using the BMDP \(^{34} \) and SAS \(^{35} \) computer programs. Data are given as mean ± SD.

Table 2

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of Patients</th>
<th>Depression</th>
<th>No Depression</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcortical lesions</td>
<td>120</td>
<td>60</td>
<td>60</td>
<td>.43</td>
</tr>
<tr>
<td>Deep lesions</td>
<td>120</td>
<td>60</td>
<td>60</td>
<td>.43</td>
</tr>
<tr>
<td>Watershed lesions</td>
<td>120</td>
<td>60</td>
<td>60</td>
<td>.43</td>
</tr>
</tbody>
</table>

...and left (14.2±31.3 vs 14.4±30.2 cm\(^3\); \( P = .43 \)) hemispheres did not differ significantly. Depressed patients had significantly larger lesions affecting the deep middle cerebral artery territory; caudate; pallidum; genu and anterior part of internal capsule; posterior corona radiata; and the amygdala, with a left-sided predominance (Table 4). Larger lesions in the right occipital lobes, however, were found in patients without depression.

No differences between the depressed and nondepressed groups were found in the percentage of moderate to severe WMLs; in mean Fazekas WML score; or in the extent of central, cortical, or mediotemporal lobe atrophy (Table 6). We also compared the lesion site and size in patients with major (n=71) and minor (n=38) depression. Patients with major depression had more infarcts affecting the prefrontosubcortical circuit area on any side...
Evidence for the importance of pallidum in mood regulation is emerging from neuropathologic studies. We systematically assessed the interaction among infarct side, site, number, and extent; WMLs; and atrophy. Depression after stroke is related to ischemic lesions affecting the prefrontosubcortical circuit, namely, the caudate, pallidum, and thalamocortical projection, including the genu of internal capsule and anterior capsule, especially in the left hemisphere. In a multivariate analysis, the independent correlates of depression after stroke were number of infarcts in the genu of internal capsule on the left side (odds ratio [OR], 3.2; 95% confidence interval [CI], 1.0-10.1), mean frequency of infarcts in the pallidum of any side (OR, 1.6; 95% CI, 1.1-2.3), and mean volume of infaracts in the right occipital lobe (OR, 0.98; 95% CI, 0.96-0.99).

To our knowledge, this is the first large MRI-based study that explores the radiologic correlates of depression after stroke. We systematically assessed the interaction among infarct side, site, number, and extent; WMLs; and atrophy. Depression after stroke is related to ischemic lesions affecting the prefrontosubcortical circuit, namely, the caudate, pallidum, and thalamocortical projection, including the genu of internal capsule and anterior capsule, especially in the left hemisphere. In a multivariate analysis, the independent correlates of depression after stroke were number of infarcts in the genu of internal capsule on the left side (OR, 3.2) and number of lesions in the pallidum of any side (OR, 1.6). Our results support the idea that lesions affecting the prefrontosubcortical circuits relate to a higher risk of depression after stroke. Evidence for the importance of pallidum in mood regulation is emerging from neuropathologic studies. Furthermore, lesions in the pallidum have been related to reduced glutamatergic input to the dorsolateral prefrontal cortex and to depression. The distinct prefrontosubcortical circuits, ie, orbitofrontal, dorsolateral, and anterior

(1.8 ± 1.7 vs 1.2 ± 1.4; df=107; P = .03, Mann-Whitney test) or on the right side (0.83 ± 0.93 vs 0.49 ± 0.86; P = .02). No significant differences in the size of the infarcts, the severity of WMLs, and the extent of brain atrophy were found between these patient groups (data not shown).

Of the 109 depressed patients, 77 had no depressive episodes before the index stroke and 32 had had 1 or more depressive episodes. The total number of brain infarcts was significantly smaller in patients with first-ever depression after the index stroke compared with patients with previous episodes of depression (2.8 ± 2.4 vs 4.1 ± 2.6; P = .01, df = 107, Mann-Whitney test), as was the number of right-sided infarcts (1.3 ± 1.5 vs 2.3 ± 1.8; P = .005). Furthermore, patients with first-ever depression had significantly fewer infarcts in the superficial medial cerebral artery area (0.9 ± 1.1 vs 1.2 ± 1.1; P = .02). There were no differences in the volumes of infarcts, severity of white matter changes, or extent of atrophy between these groups.

The independent MRI correlates of depression after stroke determined using logistic regression analysis were mean frequency of infarcts in the genu of internal capsule on the left side (odds ratio [OR], 3.2; 95% confidence interval [CI], 1.0-10.1), mean frequency of infarcts in the pallidum of any side (OR, 1.6; 95% CI, 1.1-2.3), and mean volume of infaracts in the right occipital lobe (OR, 0.98; 95% CI, 0.96-0.99).

Table 2. Depressive Disorders by DSM-IV Categories in 109 Patients With Depression in the Helsinki Stroke Aging Memory Study (N = 275)

<table>
<thead>
<tr>
<th>Category</th>
<th>Patients, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression</td>
<td></td>
</tr>
<tr>
<td>Depressive disorder due to stroke</td>
<td>5 (1.8)</td>
</tr>
<tr>
<td>Vascular dementia with depressed mood</td>
<td>13 (4.7)</td>
</tr>
<tr>
<td>Major depressive disorder, single episode</td>
<td>42 (15.3)</td>
</tr>
<tr>
<td>Major depressive disorder, recurrent</td>
<td>11 (4.0)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>71 (25.8)</td>
</tr>
<tr>
<td>Minor depression</td>
<td></td>
</tr>
<tr>
<td>Dysthymic disorder</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Adjustment disorder with depressed mood</td>
<td>22 (8.0)</td>
</tr>
<tr>
<td>Adjustment disorder with anxiety and depression</td>
<td>9 (3.3)</td>
</tr>
<tr>
<td>Major depressive disorder, in partial remission</td>
<td>4 (1.5)</td>
</tr>
<tr>
<td>Depressive disorder not otherwise specified</td>
<td>2 (0.7)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>38 (13.8)</td>
</tr>
</tbody>
</table>

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cingulate circuits,14 run closely adjacent to each other in the genu of internal capsule38 and are likely to be damaged together in case of an infarct in that area. In their seminal publication, Tatemichi et al41 showed that an infarct affecting the genu of internal capsule was related to dementia and “frontal lobe symptoms.” We hypothesize that anatomic closeness of the 3 frontosubcortical circuits at the capsular genu and the thalamocortical connection relate lesions in this area to depression after stroke.

The amygdala has multiple connections to the frontosubcortical circuit, namely, the prefrontal cortex, striatum, and thalamus. Infarcts affecting the amygdala are rare (2% of patients in the present series). The overrepresentation of depression in patients with infarcts affecting the amygdala is an interesting finding that awaits confirmation in future MRI studies.

Depression after stroke was statistically significantly less common in patients with a higher frequency and larger volume of infarcts in the right occipital lobe. This eventual “protective effect” against depression is difficult to explain. Although right-sided lesions have been related to bipolar affective disorders42 and mania,43 this association has not been reported earlier. However, in a study by Sinyor et al,44 2 patients with large right-sided posterior infarcts had to be excluded from the analysis before the association between poststroke depression and proximity of the left-sided lesion location from the anterior pole of the brain could be demonstrated.

Patients with previous depressive episodes had more brain infarcts—reflecting more severe CVD—than patients with first-ever depression after stroke, consistent with the vascular depression hypothesis11-13 of the relationship between chronic vascular disease and vulnerability to depression.

In accordance with our core result, anterior lesions and lesions affecting the prefrontosubcortical circuit have been previously related to depression in many studies4,45-47 but not in all.48-50 Factors related to these inconsistent findings include selection of patients, distinction between major and minor depression, timing of evaluation, and, brain imaging techniques.2,7 Differentiation between major and minor depression bears some difficulty after stroke,48 and in the major analyses of the present series we did not make this distinction. However, in a subanalysis, infarcts affecting prefrontosubcortical circuits on any side or on the right side seemed to be more common in patients with major depression. Thus, minor and major depression might be pathoanatomically different entities, as suggested by some authors.51 However, no specific location within these circuits (eg, the pallidum or caudate) was more common in individuals with major depression.

Left hemispheric lesion prominence in patients with depression after stroke has mostly been shown in studies 3 or more months after stroke, such as in our series. The anatomic correlates of depression after stroke might change over time: the left anterior lesion location might relate to a recent stroke, and this association might be weaker or nonexistent in longer follow-up.45,52

A critical issue in studies of pathoanatomic correlates of depression after stroke is the brain imaging techniques used. Compared with computed tomography (CT), MRI is superior in detecting the site, type, and extent of infarcts, especially in deep gray matter structures. In ad-
In a study matching patients with and without depression for the size and location of their lesion and for age and sex, our study, with no such matching procedures, we did not find a correlation between extent of atrophy (evaluated by comparison to standard images) and depression after stroke.

Our study has several limitations. First, the patient sample is hospital-based and might be biased in patient age, stroke type, and stroke severity. Second, we included patients with any number of infarcts on MRI to mimic a realistic clinical situation. This makes comparison with results of older CT-based studies that include patients with only one infarct difficult. Third, simple ratings of atrophy and WMLs, as well as volume estimates of infarcts, are less precise than using volumetric methods.

In conclusion, lesions affecting the frontosubcortical circuit, especially the caudate, pallidum, and genu of internal capsule, and in particular on the left side, are correlates of depression after stroke. This finding might be important in understanding the pathophysiology of depressive disorders. Furthermore, an infarct located in these critical locations should make the clinician alert in diagnosis and treatment of eventual depression after stroke, an independent correlate of stroke-related independence.

Accepted for publication April 19, 2001.

This study was supported in part by grants from the Medical Council of the Academy of Finland, Helsinki (Drs Mäntylä, Aronen, and Erkinjuntti); the Clinical Research Institute, Helsinki University Central Hospital (Drs Vataja, Pohjasaava, and Mäntylä); The Finnish Alzheimer Foundation for Research, Helsinki (Drs Vataja, Pohjasaava, and Erkinjuntti); and the University of Helsinki (Drs Erkinjuntti and Pohjasaava).

We thank Vesa Kaasela, senior research officer, Statistics Finland, Helsinki, for statistical support and review.

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