Comparison of Spontaneously Recovered Versus Nonrecovered Patients
With Poststroke Depression

Sergio E. Starkstein, MD, Robert G. Robinson, MD, and Thomas R. Price, MD

We followed 16 patients who developed depression immediately after a stroke for 6 months. By that time, six patients showed no depression (recovered group), while 10 patients were still depressed (nonrecovered group). There were no significant differences in demographic variables and social functioning between the groups, but the nonrecovered group showed less improvement in cognitive function and more physical impairments. Patients in the nonrecovered group had mainly cortical lesions, while those in the recovered group had mainly subcortical and posterior circulation strokes. (Stroke 1988;19:1491-1496)

Affective disturbance has been recognized for many years to be a common sequela of cerebral infarction.1 Recent empirical studies have demonstrated that the frequency of depression is approximately 50% among hospitalized poststroke populations2-5 and approximately 30% among outpatient stroke populations.6

We7-9 have consistently found a strong relation between lesion location and poststroke major depression. Major depression is significantly more frequent among patients with left anterior lesions than among patients with lesions in any other location.7 In a recent study, we8,9 found that patients with single lesions restricted to the left frontal cortex (without involvement of deep gray nuclei) had the same high frequency of depression as patients with strokes restricted to the left basal ganglia regions. Moreover, we8,9 found that patients with left frontal cortical or basal ganglia lesions (mainly on the head of the caudate) had a significantly higher frequency of major depression than patients with right cortical, right basal ganglia, or left or right thalamic stroke lesions.

Spontaneous recovery from depression following stroke is potentially an important phenomenon because it may provide insight into both the mechanisms of recovery (e.g., nerve regeneration, adoption of function by uninjured brain areas) as well as into the different etiologies of depression. In a recent longitudinal study, we10 found that the duration of poststroke depression was approximately 1 year for major depression and >2 years for most minor depressions. We11 also reported, however, that some patients recover from their poststroke depression within 6 months. To understand why some patients recover rapidly while others have sustained depressions, we compared patients who spontaneously recovered from poststroke depression within 6 months with those who did not.

Subjects and Methods

We selected patients from consecutive admissions to the University of Maryland Hospital for treatment of acute stroke. Detailed psychiatric examinations were performed on all patients, excluding only those who had severe comprehension deficits (i.e., moderate or severe Wernicke's or global aphasia) or markedly decreased levels of consciousness. We included patients with nonfluent aphasias who were able to give yes-no answers.

We examined a series of 16 consecutive patients who had in-hospital diagnoses of major or minor depression 6 months after their stroke. By this time, six patients were not depressed (recovered group), while 10 patients still showed (major) depression (nonrecovered group). No patient had received antidepressant drugs or any other psychiatric treatment and none had suffered a second stroke.
The neurologic examination and diagnosis for all patients was performed using the criteria established by the National Institute of Neurological and Communicative Disorders and Stroke's Stroke Data Bank. All neurologic evaluations and computed tomogram (CT scan) readings were performed by one of us who was blinded to the findings of the psychopathological examination. After giving informed consent, patients were administered a series of standardized instruments that quantitatively measure mood, cognitive function, and physical impairment. We have shown that these instruments give reliable and valid measurements in this stroke population. To evaluate mood, the Hamilton Depression Scale (HDS) was scored by the interviewer, as was the modified Present State Exam (PSE), a semistructured psychiatric interview that elicits symptoms related to depression and anxiety, described previously. Cognitive function was assessed using the Mini Mental State Exam (MMSE), an eleven-item examination that has been found to be reliable and valid in assessing a limited range of cognitive functions in stroke patients. Physical impairment was measured using the Johns Hopkins Functioning Inventory (JHFI), a ten-item scale that evaluates the degree of independence in activities of daily living. In conjunction with the psychiatric examination, social function was assessed quantitatively using the Social Functioning Exam (SFE).

Using the symptoms elicited by the PSE, depression was diagnosed using DSM-III symptom criteria for either major or dysthymic (minor) depression. We separated poststroke depressions into diagnostic categories of major and minor depression rather than using the DSM-III category of organic affective disorder because previous studies have supported this division and have provided some validation for making specific diagnoses in brain-injured subjects. For example, only major depression is strongly associated with lesion location; patients with major and minor depression have different longitudinal evolutions, and patients with major but not minor depression demonstrate a dementia of depression (pseudodementia) and have a positive dexamethasone suppression test response (i.e., failure to suppress serum cortisol following dexamethasone administration).

Statistical analysis was carried out using means and standard deviations, t tests (with 14 degrees of freedom), χ² tests with Yates’ modification for expected cell sizes of <5 (with 1 degree of freedom), repeated-measures analysis of variance (ANOVA), and Pearson correlation coefficients.

Results

Demographic Variables

Patients were mainly black women in their 40s and 50s who belonged to the lower socioeconomic classes (Table 1). No significant between-group differences were found in any demographic variable examined. One patient in the recovered group had a history of depression, whereas two patients (one in the recovered and one in the nonrecovered group) had a history of mild anxiety.

Neurologic Examination and Lesion Location

The frequencies of various neurologic findings in the recovered and nonrecovered groups were motor deficits, 50% and 90% (χ² with Yates’ correction = 1.44, p = 0.21); sensory deficits, 20% and 50% (χ² = 1.77, p = 0.18); aphasia, 17% and 30% (χ² = 0.56, p = 0.45); visual field deficits, 33% and 20% (χ² = 0.35, p = 0.55); cerebellar signs, 17% and 0% (χ² = 1.77,
TABLE 2. Neurologic Findings, Psychiatric History, Type of Depression, and Computed Tomography Findings in 16 Patients With Poststroke Depression

<table>
<thead>
<tr>
<th>Pt</th>
<th>Neurologic findings</th>
<th>Psychiatric history</th>
<th>Depression type</th>
<th>CT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>R homonymous hemianopia, nystagmus</td>
<td>Negative</td>
<td>Major</td>
<td>B occipital cerebellum</td>
</tr>
<tr>
<td>2</td>
<td>R homonymous hemianopia</td>
<td>Negative</td>
<td>Major</td>
<td>L occipital</td>
</tr>
<tr>
<td>3</td>
<td>L hemiparesis, dysarthria, constructional apraxia</td>
<td>Negative</td>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R hemiparesis, nonfluent aphasia, mild sensory deficit</td>
<td>Anxiety</td>
<td>Major</td>
<td>L caudate</td>
</tr>
<tr>
<td>5</td>
<td>R hemiparesis</td>
<td>Depression</td>
<td>Major</td>
<td>L caudate</td>
</tr>
<tr>
<td>6</td>
<td>Dysarthria, nystagmus, dysmetria, gait ataxia</td>
<td>Negative</td>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Nonrecovered</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>L hemiparesis, dysarthria</td>
<td>Anxiety</td>
<td>Major</td>
<td>L frontal opercular</td>
</tr>
<tr>
<td>2</td>
<td>R hemiparesis, nonfluent aphasia</td>
<td>Negative</td>
<td>Major</td>
<td>L frontal opercular</td>
</tr>
<tr>
<td>3</td>
<td>R hemiparesis, R hemisensory deficit, R homonymous hemianopia, anomaia</td>
<td>Negative</td>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>R hemiparesis, R hemisensory deficit</td>
<td>Negative</td>
<td>Major</td>
<td>Multiple</td>
</tr>
<tr>
<td>5</td>
<td>R hemiparesis, R hemisensory deficit</td>
<td>Negative</td>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Nonfluent aphasia</td>
<td>Negative</td>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>R hemiplegia, R homonymous hemianopia</td>
<td>Negative</td>
<td>Major</td>
<td>L frontotemporoparietal</td>
</tr>
<tr>
<td>8</td>
<td>R hemiparesis</td>
<td>Negative</td>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>R hemiparesis, dysarthria, R hemisensory deficit</td>
<td>Negative</td>
<td>Minor</td>
<td>Multiple</td>
</tr>
<tr>
<td>10</td>
<td>R hemiparesis, R hemisensory deficit, buccofacial apraxia</td>
<td>Negative</td>
<td>Major</td>
<td>L frontal opercular</td>
</tr>
</tbody>
</table>

Pt, patient number; CT, computed tomography; R, right; L, left; B, bilateral.

$p=0.18$; and cranial nerve involvement, 17% and 0% ($\chi^2=1.77$, $p=0.18$).

Four of the six recovered patients had positive CT scans (Table 2), with lesions in the left caudate in two, in the left occipital lobe in one, and in the cerebellum and left and right occipital lobes in one (Figure 1). The other two patients in the recovered group had negative CT scans; one patient had cerebellar signs and the other had clinical symptoms compatible with a right middle cerebral artery (MCA) stroke.

Five of the 10 nonrecovered patients had positive CT scans; three had lesions involving the left frontal operculum, and the other two had multiple infarcts. Based on clinical data alone, four of the five had lesions in the left MCA territory (two had aphasia), while the fifth patient had a right MCA territory lesion; further localization was not possible.

In summary, the nonrecovered group showed mainly cortical lesions in the MCA territory (frontotemporoparietal operculum and insular cortex); no patient in this group had purely subcortical damage or lesions in the posterior circulation territory. On the other hand, patients in the recovered group had predominantly subcortical lesions (mainly in the left caudate) and lesions in the posterior circulation territory (occipital lobes, cerebellum, and brainstem). This cortical vs. subcortical/posterior circulation distribution of lesions was significantly different between groups ($\chi^2$ with Yates' correction $=8.33$, $p<0.01$).

Mood, Cognitive Function, Physical Impairment, and Social Function

In-hospital PSE scores were not significantly different between groups. Six months after the stroke, mean PSE scores were significantly lower ($p<0.002$) in the recovered than in the nonrecovered group. One-way repeated-measures ANOVA showed a significant group effect ($p<0.05$) as well as a significant group $\times$ time interaction ($p<0.01$). Similar results were obtained for HDS scores, the recovered group scoring significantly lower ($p<0.02$) than the nonrecovered group at 6 months; there was a significant group effect ($p<0.05$) by repeated-measures ANOVA.

On the MMSE, ANOVA revealed a significant effect for time ($p<0.01$) but not for group or the group $\times$ time interaction. Mean JHFI scores were significantly different between groups for both the in-hospital ($p<0.005$) and the 6-month evaluations ($p<0.02$). There were significant effects for both group ($p<0.01$) and time ($p<0.01$).

There were no significant differences between groups for SFE scores.

Mood was not significantly correlated with physical impairments either in the hospital or 6 months after the stroke (PSE vs. JHFI $r=0.01$ and $r=0.36$, respectively; HDS vs. JHFI $r=0.21$ and $r=0.48$, respectively). The correlation between in-hospital JHFI score and 6-month PSE score was also not significant ($r=0.44$).
Discussion

Our study has demonstrated that two perhaps related factors differed significantly between the recovered and nonrecovered groups at the 6-month follow-up. Those patients who recovered from poststroke major depression had mainly subcortical or posterior circulation strokes and fewer physical impairments, while patients who failed to recover had mainly cortical lesions and a significantly greater degree of functional physical impairment.

Our study has several limitations that should be pointed out. We included only a few patients in both groups. Thus, our preliminary findings need to be replicated using a larger population. However, spontaneous recovery from poststroke major depression before the natural course of approximately 12 months is relatively rare; to find these six cases, we examined more than 100 acute stroke patients and produced some interesting findings in this study.

No significant between-group differences were found in age, socioeconomic or marital status, years of education, social functioning, or family or personal history of psychiatric disorders. While these demographic variables did not seem to play a major role in the longitudinal evolution of poststroke depression, our small sample size may have decreased the power of the statistical tests to detect differences. Nonetheless, lesion location and score on the JHFI emerged as the most important factors predicting longitudinal recovery from poststroke depression. Several hypotheses may account for these findings.

First, the most obvious explanation is that the patients with the least severe deficits improve in their mood as their minor physical impairments abate. The problem with this explanation in our study, however, is that for the overall group of 16 patients, the severity of depression (PSE score) both in the hospital and 6 months after the stroke did not correlate significantly with the severity of physical impairment (JHFI score). Moreover, there was no significant correlation between JHFI score in the hospital and PSE score 6 months after the stroke. Also, the course of improvement in JHFI score for the recovered group was not significantly different from that of the nonrecovered group (i.e., repeated-measures ANOVA for JHFI score showed no significant group \times time interaction). Both in the hospital and 6 months after the stroke, however, the

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Recovered</th>
<th>Non-recovered</th>
<th>Recovered</th>
<th>Non-recovered</th>
<th>Group</th>
<th>Time</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=10)</td>
<td>(n=6)</td>
<td>(n=10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDS</td>
<td>14.2±5.5</td>
<td>16.3±6.7</td>
<td>9.5±3.4</td>
<td>17.0±4.8</td>
<td>3.29</td>
<td>&lt;0.02</td>
<td>5.36 &lt;0.05</td>
</tr>
<tr>
<td>PSE</td>
<td>21.8±7.7</td>
<td>21.4±7.8</td>
<td>8.8±5.3</td>
<td>21.8±7.7</td>
<td>4.01</td>
<td>&lt;0.002</td>
<td>6.82 &lt;0.05</td>
</tr>
<tr>
<td>Cognitive function</td>
<td>24.5±5.5</td>
<td>19.0±7.5</td>
<td>26.8±4.1</td>
<td>21.4±7.4</td>
<td>2.54</td>
<td>NS</td>
<td>10.14 &lt;0.01</td>
</tr>
<tr>
<td>MMSE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JHFI</td>
<td>2.0±2.7</td>
<td>12.0±8.2</td>
<td>0.5±1.2</td>
<td>6.0±4.7</td>
<td>2.75</td>
<td>&lt;0.005</td>
<td>8.70 &lt;0.01</td>
</tr>
<tr>
<td>Social function</td>
<td>330±323</td>
<td>216±146</td>
<td>284±204</td>
<td>363±196</td>
<td>0.3</td>
<td>NS</td>
<td>0.59 NS</td>
</tr>
<tr>
<td>SFE</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Data are mean±SD; 14 degrees of freedom for $t$; 1 and 14 degrees of freedom for $F$; NS, not significant. HDS, Hamilton rating scale for depression; PSE, Present State Exam; MMSE, Mini Mental State Exam; JHFI, Johns Hopkins Functioning Inventory; SFE, Social Functioning Exam.
nonrecovered group was significantly more impaired (had a higher JHFI score) than the recovered group.

Another interesting explanation for our findings is that the presence of major depression may have sustained a greater functional impairment in the nonrecovered group. We23,24 have shown that physical impairment does not seem to cause depression, but once depression occurs the most depressed patients remain the most impaired. Sinory et al23 have recently reported that immediately after stroke, depressed patients had a significantly lower functional status than nondepressed patients; moreover, while nondepressed patients showed a slight increase or no change in functional status over time, depressed patients showed important reductions in functional status during the first months following stroke. Thus, although we do not exclude the possibility that the degree of physical impairment contributed to the natural course of depression following stroke, the available data suggest that depression itself may lead to greater impairment in the activities of daily living than the physical impairment attributable to the lesion alone.

On the other hand, the significantly milder physical impairment in the recovered group may have resulted from the patients' having subcortical or posterior circulation lesions, and their spontaneous recovery may have been due to the location of their lesions.

If lesion location plays an important role in the longitudinal evolution of poststroke depression, how might this finding (i.e., faster recovery from poststroke depression in patients with subcortical or posterior circulation stroke lesions) be construed? In previous publications we8,9 have suggested that neurophysiological changes provoked by left frontal or left basal ganglia lesions may play a role in the etiology of poststroke depression. Abnormalities in biogenic amine systems have been implicated in the neurophysiological changes provoked by left frontal lesions.25 Cortical lesions may produce irreversible damage to terminal biogenic fields, thereby affecting neuronal compensation (e.g., sprouting and up-regulation of receptors) and causing long-lasting depressions; subcortical lesions, which may affect cortical structures only transiently, do not interfere with neuronal compensation and may cause only transient depressions. Thus, the shorter evolution of poststroke depression after subcortical or posterior circulation lesions may depend on the transient nature of impairment to cortical structures and more rapid biochemical compensation.

Although other explanations might be proposed for this phenomenon of spontaneous recovery, our study represents another step in the process of identifying clinical manifestations and pathologic correlates of poststroke depression, which may reflect different mechanisms for the cause of or recovery from these disorders.

References
20. Robinson RG, Bolduc PL, Starr LB, Price TR: Social functioning assessment in stroke patients: Responses of patients and other informants and relationship of initial

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