Two-Year Longitudinal Study of Post-Stroke Mood Disorders: Dynamic Changes in Correlates of Depression at One and Two Years

Rajesh M. Parikh, John R. Lipsey, Robert G. Robinson, and Thomas R. Price

As part of a prospective study of 103 stroke patients, we have analyzed the relation between depression and associated variables at 3 months, 6 months, 1 year, and 2 years after stroke. At all intervals up to and including 1 year poststroke, patients with left hemisphere strokes showed a strong relation between severity of depression and distance of the lesion on computed tomography scan from the frontal pole. At 2 years poststroke, this relation was no longer significant. The correlation between depression and impairment in activities of daily living peaked at 6 months and thereafter fell but remained significant at 1 and 2 years poststroke. The correlation between depression and cognitive impairment and between depression and social functioning fluctuated — with most correlations at 1 and 2 years follow-up nonsignificant. Although the conclusions that can be drawn from this study are limited by the fact that less than half of the original patients were followed up at each time, these declining correlations between depression and associated variables at 1 and 2 years follow-up may reflect the natural course of major depression which spontaneously remits between 1 and 2 years after stroke. The persisting significant association of impairment in activities of daily living with depression may reflect the effect of severe depression in sustaining and possibly retarding recovery from physical impairment. (Stroke 1987;18:579-584)

During the past few years, we have reported our findings from a prospective 2-year longitudinal study of mood disorders in 103 acute stroke patients.1-9 Our studies have demonstrated the importance of intrahemispheric as well as interhemispheric lesion location in the generation of poststroke depression.5-9 Patients with left anterior strokes were significantly more depressed than patients with lesions of any other location, and severity of depression was significantly correlated with proximity of the lesion to the frontal pole.6-5 This finding has held up not only in patients with single stroke lesions localized using computed tomography (CT) scans but also in patients who had lesions restricted to subcortical structures, bilateral brain injury, and patients who were left-handed.2,9,10

In addition to identifying the importance of lesion location in the production of poststroke mood disorders we found that during the acute stroke period several other variables were significantly correlated with severity of depression, including severity of impairment in activities of daily living, degree of cognitive impairment, the quality of available social supports, and the patient’s age.1,6-8,11 Although the strengths of these correlations were not as strong as the relation between depression and lesion location, each of these variables nevertheless accounted for approximately 5-10% of the variance in depression scores.

At 3 and 6 months follow-up, there were dynamic changes in the relation between depression and some of these associated variables.6 For instance, although the correlation between severity of depression and lesion location did not change significantly, the correlation between functional physical impairment and severity of depression increased steadily over the 6 month follow-up. In a subsequent study, we found that these increased correlations between impairment and depression were not the result of patients developing reactive depressions (to impairment) several months after the stroke, but were the result of an interaction between impairment and longstanding depression.12 That is, impairment did not cause depression, but once depression occurred, those who were the most depressed stayed the most impaired at 6 months after the stroke.

We have begun analyzing the data from this group of stroke patients at 1 and 2 years follow-up. In the present study, we examined the factors associated with poststroke depression and assessed changes in the strength of these relations over the 2 years of follow-up.

Subjects and Methods

The stroke population was selected from inpatients at the University of Maryland Hospital who were included in the NINCDS Pilot Stroke Data Bank and who had a thromboembolic stroke or an intracerebral
hemorrhage.\textsuperscript{13} We have described this acute stroke population of 103 patients.\textsuperscript{1} Patients interviewed at follow-up were predominantly those whose outpatient medical care was provided in the hospital's stroke clinic or neurology clinic. Eighty-six patients were interviewed again at least once during this 2-year follow-up study; 40 patients were interviewed at 3 months, 50 at 6 months, 38 at 1 year, and 48 at 2 years, while 22 patients were interviewed at all 4 times. Twenty-three of the 103 patients died during the course of the study.

**Neurologic and Psychiatric Evaluation**

Neurological evaluations in-hospital and at follow-up were done by the attending neurologist. The standardized examination and rating criteria from the Pilot Stroke Data Bank\textsuperscript{13} were used for the neurologic examination and diagnosis.

Psychiatric examination included 3 standardized quantitative measures of affective state: the Hamilton Depression Scale (HDS),\textsuperscript{14} the Zung Depression Scale (ZDS),\textsuperscript{15} and the modified version of the Present State Exam (PSE).\textsuperscript{16} All 3 scales and their reliability and validity in a stroke population have been described in detail.\textsuperscript{1,4,7,18}

**Physical and Intellectual Impairment and Social Functioning**

Quantitative evaluations of cognitive, physical, and social functioning were made in conjunction with the psychiatric assessment. The Mini-Mental State Exam (MMSE),\textsuperscript{19} the Johns Hopkins Functioning Inventory (JHFI),\textsuperscript{20} the Social Functioning Exam (SFE),\textsuperscript{21,22} and the Social Ties Checklist (STC)\textsuperscript{21,22} have all been described.\textsuperscript{1,4,7,18}

**CT Scan Analysis**

All CT scans were analyzed by an attending neuroradiologist who was blind to the psychiatric assessment. Lesion size, calculated using a computer program and an electronic cursor, was determined by dividing the maximal lesion cross-sectional area by the largest cross-sectional area of total brain in a CT slice passing through the maximal cross section of the lateral ventricles, as described in a previous publication.\textsuperscript{23}

The distance of the lesion from the frontal pole was determined by measuring the distance of the anterior border of the lesion from the frontal pole and dividing by the overall anteroposterior (A-P) distance in that brain slice. This measurement was made in all slices where the lesion was visible, and a mean distance was calculated. Lesions were considered anterior if their rostral border was anterior to 40% of the A-P distance, and posterior if their rostral border was posterior to this demarcation. This anterior–posterior dichotomy has been previously described.\textsuperscript{2,4}

**Statistical Analysis**

Intergroup comparisons were made using analysis of variance and appropriate post hoc tests. \( \chi^2 \) statistics were used to compare nonparametric between-group measures. The relations between different measures made during the same examination were calculated using Pearson correlation coefficients.

**Results**

The 86 patients seen at least once during the 2-year study were predominantly black patients in the lower socioeconomic class, most of whom were married and many of whom had a previous life-threatening medical illness (Table 1). As reported,\textsuperscript{4} there was no significant difference in the demographic factors of the patients who were followed up compared with the patients who were not followed up.

The neurologic diagnoses and findings from the follow-up group are shown in Table 2.

**In-Hospital Evaluation**

Although we have published our findings for in-hospital evaluation,\textsuperscript{1,6} we recalculated these data based on the 86 patients seen at any time during the 2-year follow-up. Our earlier data included only the 61 patients seen at 3 or 6 months follow-up. Of the 86 patients seen at least once during the 2-year follow-up, 54 had positive CT scans. Of these, 28 had single left hemisphere lesions (17 anterior, 11 posterior), 17 had single right hemisphere lesions (9 anterior, 8 posterior), and 9 had bilateral lesions. For the 28 patients with single left hemisphere lesions, the correlation coefficient between the distance of the lesion from the frontal pole and severity of in-hospital depression (mean of the 3 depression scales) was \( r = -0.41, p < 0.05 \) (Figure 1). The significant negative correlation indicates greater depression associated with lesions that were closer to the left frontal pole and corroborates similar observations in other groups of stroke patients.\textsuperscript{1,4,9,10,17}

For these 86 patients seen in the hospital, the mean correlation coefficients between the depression scores (measured by PSE, HDS, and ZDS) and activities of daily living (measured by JHFI), cognitive function (measured by MMSE), social functioning (measured by SFE), and social ties (measured by STC) are shown in Figure 1. During acute hospitalization, the most

<table>
<thead>
<tr>
<th>Table 1. Description of Follow-up Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seen at least once during follow-up (( n = 86 ))</td>
</tr>
<tr>
<td>Age (mean ( \pm ) SD)</td>
</tr>
<tr>
<td>Race (% black)</td>
</tr>
<tr>
<td>Sex (% male)</td>
</tr>
<tr>
<td>Marital status</td>
</tr>
<tr>
<td>(% Married)</td>
</tr>
<tr>
<td>(% Widowed)</td>
</tr>
<tr>
<td>Socioeconomic status\textsuperscript{24}</td>
</tr>
<tr>
<td>(% Class I–III)</td>
</tr>
<tr>
<td>(% Class IV–V)</td>
</tr>
<tr>
<td>Living situation (% living alone)</td>
</tr>
<tr>
<td>History of prior stroke(s)</td>
</tr>
</tbody>
</table>
Table 2. Neurologic Diagnosis and Findings in 86 Follow-up Patients

<table>
<thead>
<tr>
<th>Diagnosis*</th>
<th>Left hemisphere (n = 37)</th>
<th>Right hemisphere (n = 23)</th>
<th>Bilateral (n = 9)</th>
<th>Brainstem (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolic</td>
<td>32</td>
<td>22</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Neurologic examination findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis/monoparesis (moderate–severe)</td>
<td>15</td>
<td>11</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Touch-pain deficit (moderate–severe)</td>
<td>14</td>
<td>12</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Visual neglect</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Aphasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Broca’s</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Wernicke’s</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Neurologic diagnosis made by computed tomography scan analysis and/or clinical symptoms.

Severe impairments in functional physical activity or cognition were associated with the most severe depressions. Additionally, patients with poorer social supports were more depressed than those with better social supports. These associations with depression were less strong than that between lesion location and depression and were in agreement with our earlier reported findings.1,6

DEPRESSION SCORES AND OTHER VARIABLES

Figure 1. Correlation coefficients between depression scores and other variables at different times during the 2-year study period. All correlations above the cross-hatched area are significant at p < 0.05 except those marked †, which are indicative of a trend (p < 0.1). The diminished number of patients with positive computed tomography scans at 1 year explains the low level of significance despite the high degree of correlation. Spontaneous remission of depression between 1 and 2 years follow-up may explain the decline in strength of correlation between depression and associated variables during this period. L. Ant. Les. Loc., left anterior lesion location; JHFI, Johns Hopkins Functioning Inventory; MMSE, Mini-Mental State Exam; SFE, Social Functioning Exam; STC, Social Ties Checklist.
Table 3. Correlation Coefficients Between CT Scan Measurement In-Hospital and Depression at Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Left hemisphere A–P location*</th>
<th>Right hemisphere A–P location</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 mos†</td>
<td>1 yr</td>
</tr>
<tr>
<td></td>
<td>(n=9)</td>
<td>(n=6)</td>
</tr>
<tr>
<td>PSE</td>
<td>−0.78†</td>
<td>−0.83‡</td>
</tr>
<tr>
<td>HDS</td>
<td>−0.69‡</td>
<td>−0.78§</td>
</tr>
<tr>
<td>ZDS</td>
<td>−0.72‡</td>
<td>−0.66</td>
</tr>
<tr>
<td>Mean correlation</td>
<td>−0.73‡</td>
<td>−0.76§</td>
</tr>
</tbody>
</table>

CT, computed tomography; PSE, Present State Exam; HDS, Hamilton Depression Scale; ZDS, Zung Depression Scale; A–P, anteroposterior.

*Includes patients with left anterior lesions only.
†Previously published findings.
‡Trend, p<0.10.
§P<0.01.

1-Year Follow-Up

Of the 38 patients seen at 1 year, 14 had positive CT scans showing single lesions, and of these, 9 had left hemisphere lesions and 5 had right-sided lesions. As at 6 months, the correlation between proximity of the lesion to the left frontal pole and severity of depression was high for left anterior lesions (Table 3, Figure 1). The mean correlation coefficient between the 3 depression scales and lesion location was r = 0.76; this just failed to reach significance due to the small number of positive CT scans.

The strength of the correlation between JHFI and the 3 scales measuring depression was highly significant although between 6 months and 1 year follow-up the mean r had dropped from 0.59 to 0.50 (Figure 1). However, the strengths of the relations between MMSE and the 3 scales measuring depression, between STC and the depression scales, and between SFE and the depression scales had weakened considerably and were no longer significant (Figure 1). Thus, by 1 year after stroke, the correlation between depression and associated variables (except lesion location and physical impairment) had dropped significantly.

2-Year Follow-Up

Of the 48 patients seen at 2 years, 21 had positive CT scans showing single lesions, 14 on the left and 7 on the right side. By this time, there were no significant correlations between left anterior lesion location and severity of depression (Table 3, Figure 1).

Correlations between severity of depression and other associated variables were also not significant except for functional physical impairment (measured by JHFI) and social functioning (measured by SFE) (Figure 1). The strength of the relation between JHFI and the depression scales had decreased from the level at 1 year follow-up but remained significant for all depression scales. The correlations between depression scores and social functioning had increased between 1 and 2 years follow-up (Figure 1).

Thus, at 2 years after stroke, the trend toward weakening of the relations between depression scores and associated variables, which was seen at 1 year, generally continued. Physical impairment and social functioning, however, did show significant relations with depression.

Correlation Between the 3 Scales Measuring Depression

As seen in Figure 2, the correlations between the 3 depression scales remained highly significant at all times, establishing their concurrent validity in longitudinally assessing depression in a stroke population.

Discussion

This study has demonstrated dynamic changes in the relations between poststroke mood disorders and associated variables over a 2-year follow-up. Left hemisphere lesion location had the strongest correlation with severity of depression for the first year after stroke. By 2 years follow-up, however, lesion location was no longer an important predictor of depression in this stroke population.

Functional physical impairment (measured by JHFI) maintained a significant correlation with depression scores over the 2-year study period. The high degree of correlation between the 3 depression scales over time (p.s.e., h.d.s., and z.d.s.) supports their continued concurrent validity in assessing depression in this patient population.

![Correlation coefficients between depression rating scales over the 2-year study period. The high degree of correlation between the 3 depression scales over time (p.s.e., h.d.s., and z.d.s.) supports their continued concurrent validity in assessing depression in this patient population. p.s.e., Present State Exam; h.d.s., Hamilton Depression Scale; z.d.s., Zung Depression Scale.](attachment:correlation-coefficients.png)
throughout the entire study period. Although left hemisphere lesion location accounted for most of the variance in depression for the first year, by 2 years follow-up functional physical impairment had become the variable with the strongest correlation with depression.

Cognitive impairment (measured by MMSE) was significantly correlated with depression for the first 6 months after stroke but then waned in importance. Social dysfunction (measured by STC and SFE) had a variable relation with depression. STC correlated significantly with depression only at 6 months and at other times bore little, if any, relation to mood. SFE was significantly correlated with mood at all points except 1 year; however, only at 2 years after stroke did it account for more of the variation in depression than lesion location or as much as functional impairment.

Our study was conducted in a predominantly black population of the lower socioeconomic class. Moreover, we were able to evaluate only patients without severe aphasia or comprehension deficits. The conclusions that can be drawn from this study are limited by the fact that <50% of the original group were re-evaluated at any one time. We followed patients who were physically able to return to the outpatient clinic for ongoing evaluation. Patients who needed institutional care or patients who died did not contribute to our follow-up data. The above factors could have contributed to the outcome of our study, which therefore may not be applicable to all stroke patient populations.

Our initial inpatient sample, however, was comprised of a consecutive series of stroke admissions (excluding only those patients who could not be reliably evaluated due to severe comprehension deficits), and by 2 years follow-up we reevaluated 60% of the surviving patients.

Not all patients with clearly evident clinical stroke had positive brain CT scans at the time of our study. Small or developing lesions may have been missed on CT scan, and this may have limited the strength of our analysis of lesion location vs. mood disturbance. We did, however, document an ongoing important interaction between left hemisphere lesion location and depression, and this corroborates the findings in our previous studies of an important relation between mood disorders and lesion location.1,2,4,6,9,10,17,22

Although left hemisphere lesion location accounted for more of the variation in depression than any other variable, this association was sustained for only 1 year. In a separate study, we found that major, but not minor, depressions were significantly improved between 1 and 2 years follow-up.35 This spontaneous remission of major depression between 1 and 2 years follow-up probably led to the decline in the association between lesion location and severity of depression.

We have previously suggested that depletions of biogenic amine neurotransmitters or alterations in their postsynaptic receptor sensitivities may play an important role in the development of poststroke depressive disorders in humans.26,27 This suggestion has been based on our laboratory finding that small frontal cortical lesions in rats provoke widespread depletions of biogenic amine concentrations in the injured as well as the uninjured hemisphere.28,29 and a preliminary positron emission tomography (PET) scan study demonstrating asymmetrical increased ipsilateral cortical serotonin receptor sensitivity among patients with right compared with left hemisphere stroke.30 These neurophysiologic changes may persist for only 1 year in humans and thus account for the time-limited effects of lesion location on mood demonstrated in this longitudinal study.

The major new finding of this investigation is the persistent significant association of functional impairment with depression throughout the study period. This might suggest either that patients who are physically impaired remain depressed or that patients who are depressed remain physically impaired. The finding of a significant association between depression and physical impairment at 2 years after stroke may have important implications for the rehabilitation of stroke victims. In a recent study12 comparing acute-onset vs. delayed-onset depression following stroke, we have shown that impairment does not provoke reactive psychological depression in stroke patients but, instead, that severe depression seems to sustain severe impairment. Thus, antidepressant medication that we18 and others32 have demonstrated to be effective in the treatment of poststroke depression may be beneficial not only for the patients' mood but also for their rehabilitation and functional recovery.

Whatever the effect of depression on physical recovery from stroke, the present study reiterates the importance of depression as an important clinical entity among stroke patients. Our work as well as that of other investigators3334 has demonstrated the high prevalence of depression in stroke populations and the fact that these depressions are not simply an understandable reaction to the impairment.

Acknowledgments

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**Key Words** stroke • outcome • brain injury • prognosis • longitudinal • depression
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