Post-Stroke Depressive Disorders: A Follow-up Study of 103 Patients

ROBERT G. ROBINSON, M.D., AND THOMAS R. PRICE, M.D.*

SUMMARY One hundred three patients attending a stroke clinic were evaluated for post-stroke depressive disorders using repeated quantitative assessment of psychopathology during a 12 month period. Almost one-third of these patients were depressed at the time of the initial assessment and two-thirds of these depressed patients who were re-evaluated remained depressed for 7 to 8 months. The prevalence and severity of depressive disorders was significantly elevated in those patients who were between 6 months and 2 years post-stroke. Demographic variables however did not distinguish depressed and non-depressed patients, nor did type of neurological symptoms, degree of impairment in activities of daily living or global cognitive impairment. However, patients with left hemisphere brain injury were significantly more depressed than patients with right hemisphere or brain stem infarctions. Based on this work and previous studies, we have suggested a profile for patients who are at high risk for developing post-stroke depressive disorders: patients with left hemisphere frontal lobe infarctions who are within 2 years of the stroke. In spite of the fact that these depressions were clinically significant, none of the patients were presently receiving treatment. Effective treatment methods for these patients need to be developed.

FOR YEARS, CLINICIANS have recognized that depression sometimes lasting for many months may accompany brain injury.1-2 Frequently, however, recognition of these depressive disorders is not followed by treatment attempts.2 Fiebel, Berk, and Joynt2 reported that although one-third of 113 post-stroke patients who were followed for 6 months reported depression, only 1 patient received antidepressant medication and only 1 patient was referred for psychiatric treatment. These authors referred to the lack of treatment for emotional problems as one of the "unmet" needs of the stroke patient.

There are probably several reasons why these depressions have gone at times unrecognized and frequently untreated. First, post-stroke depression is generally thought to be an understandable and perhaps an inevitable psychological reaction to the loss or disability.3 A second reason that post-stroke depression may not have received much therapeutic attention is that, although we4 and other workers5 have proposed neural mechanisms which may be involved in emotional reactions after brain injury, there has been little direct neurochemical or neurophysiological evidence to suggest a particular abnormality which might be rectified by pharmacological or physical treatment.

Perhaps another reason for our therapeutic neglect, however, is the fact that we have not identified characteristics of a high risk group for post-stroke depression and determined whether there is a predictable syndromic course to these disorders. This kind of information might make clinicians more aware of the need to treat these depressive disorders and demonstrate both predictable patterns of prognostic significance and a baseline from which to measure therapeutic success or failure. In an effort to establish whether there is a predictable course to post-stroke depressive disorders and what characteristics may be associated with a high risk group, we have examined an unselected group of outpatients attending a stroke clinic and followed them during a 12 month period.

Methods

Patients attending the University of Maryland Hospital stroke clinic were randomly selected for interview. There were 154 patients registered in this clinic, 113 were evaluated over a 1½ year period with 2 to 3 interviews being conducted each week. Ten of these patients were subsequently excluded because their strokes were not clearly documented in the hospital record. Referrals to this clinic are obtained from the inpatient medical and neurological services of the University of Maryland Hospital, and from private practitioners. No stroke patient wishing treatment is excluded from the clinic and there is no selection bias or age limitation except that the referrals tend to be from lower socioeconomic classes who do not have other sources of private medical care. Some of these patients had been attending the clinic for 15 years while others were new referrals with strokes within 6 months prior to the initial evaluation.

The vast majority of these patients were living at home and were ambulatory. Two patients from nursing homes who were confined to wheelchairs were also seen in the clinic. Informed consent was obtained after the nature of the study had been fully explained. Each patient was taken into a private room where the General Health Questionnaire (GHQ),6 was administered. The questionnaire was administered to all patients by an examiner who was blind to the patients diagnosis (except for obvious neurological symptoms), time since stroke, or any hypothesis being tested. The examinations were all done in the late morning. The GHQ was designed to assess psychopathology in a general medical population and its reliability and validity have been established in previous studies.6-7 The patient is asked to respond to 28 questions and rate their feelings using four categories. For example: "I'm
feeling perfectly well and in good health’’ a) better than usual, b) same as usual, c) worse than usual, d) much worse than usual; ‘Felt that life isn’t worth living’’ a) not at all, b) no more than usual, c) rather more than usual, d) much more than usual.

The overall score is obtained by counting one point for each c or d category response and adding the total points. Overall scores of 5 or more have been found in other studies to represent significant psychopathology and this was used as a cutoff in this study. Following this initial evaluation, when the patient returned to the clinic, the same questionnaire was administered. Some patients who were seen only once every 6 or more months were given one subsequent evaluation, while other patients who were seen at 2 or 3 monthly intervals were reassessed on those occasions until a follow-up period of 12 months was obtained. Once the initial evaluation was done, every attempt was made to follow-up that patient when they returned to the clinic. Of the 103 patients who were initially included in the study, we were able to obtain follow-up evaluations on 83 patients.

In an effort to obtain more information than is available from the GHQ and to establish the validity of this evaluation as a measure of depression in this patient population an indepth interview was conducted in 30 randomly selected patients who had been included in the study. Following the administration of the GHQ, a psychiatrist (RGR) did a clinical examination and administered several quantitative psychopathology scales to each patient. These included: Zung Self Rating Depression Scale, Hamilton Depression Scale, and the Present State Examination. The PSE is a structured psychiatric interview which we modified to include primarily affective and anxiety symptoms. In addition, the Hopkins Functioning Inventory and the Mini Mental State Examination were administered to quantify the degree of impairment in activities of daily living and global cognitive functions for each patient.

The clinical charts of the 103 study patients were reviewed in order to establish the medical history, previous neurological history, clinical diagnosis, medications being taken and symptomatology associated with the most recent stroke, as well as demographic data such as age, sex, race and socioeconomic status.

Results

a. Study Population

The demographic characteristics of the study population are shown in table 1. The mean age of the patients was 63, there were slightly more females than males and most of the patients were black. Only about one-third of the patients were married with the majority being single or widowed and they were predominately from lower socioeconomic classes as measured by the Hollingshead Index of Social Position.

b. Validity and Reliability of the General Health Questionnaire

The total score on the GHQ was highly correlated with scores on the depression rating scales (r = 0.94 with PSE, r = 0.88 with Hamilton and r = 0.86 with Zung) indicating that the GHQ score represents a valid measure of depression in these patients. In order to summarize the data from all three scales into a single quantitative rating, an overall depression score was calculated by translating the score from each scale (PSE, Zung and Hamilton) into a 5 point rating with 5 representing the most severe depression and 0 representing no depression (i.e. Zung score > 80 = 5, Zung score < 40 = 0). The scores from the three scales were summed for each patient (maximum score 15). The correlation between the total score on the GHQ and the overall depression score was r = 0.94.

Reliability of the GHQ in this population was determined by correlating the initial GHQ score with the follow-up score in those patients who were re-examined within a 2 month period. Of the 20 patients in whom this data was available, the test-re-test correlation was r = 0.90. This suggests that the GHQ score was a reliable as well as valid measure of depression in these patients.

c. Frequency of Depressive Disorders

The percentage of patients who were found to be depressed, based on various GHQ cutoff scores are

Table 1 Comparison of Total Group, Depressed Group and Non-depressed Group

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Total group</th>
<th>Depressed</th>
<th>Non-depressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>103</td>
<td>30</td>
<td>73</td>
</tr>
<tr>
<td>Age (mean ± sd)</td>
<td>63 ± 11</td>
<td>63 ± 11</td>
<td>63 ± 11</td>
</tr>
<tr>
<td>Sex ratio (% M)</td>
<td>44%</td>
<td>47%</td>
<td>42%</td>
</tr>
<tr>
<td>Race (% Black)</td>
<td>87%</td>
<td>87%</td>
<td>88%</td>
</tr>
<tr>
<td>Marital status (% Married)</td>
<td>38%</td>
<td>36%</td>
<td>38%</td>
</tr>
<tr>
<td>(% Widowed)</td>
<td>29%</td>
<td>23%</td>
<td>31%</td>
</tr>
<tr>
<td>Social position (Hollingshead)</td>
<td>6.3 ± 1.1</td>
<td>6.4 ± 0.7</td>
<td>6.2 ± 1.2</td>
</tr>
<tr>
<td>Personal history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous medical (Hospitalized with life threatening event)</td>
<td>28%</td>
<td>30%</td>
<td>27%</td>
</tr>
<tr>
<td>Previous CNS INJ (Stroke, trauma, infection)</td>
<td>26%</td>
<td>30%</td>
<td>25%</td>
</tr>
<tr>
<td>Neurological symptoms (At time of index stroke % with symptoms)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>83%</td>
<td>87%</td>
<td>82%</td>
</tr>
<tr>
<td>Hemisensory loss</td>
<td>31%</td>
<td>30%</td>
<td>31%</td>
</tr>
<tr>
<td>Homonymous hemianopsia</td>
<td>20</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>Aphasiasa</td>
<td>15</td>
<td>17</td>
<td>14</td>
</tr>
<tr>
<td>Cranial nerve signs</td>
<td>13</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>6</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>
shown in Table 2. Using a cutoff score of 5, 30 of the 103 patients (approximately 30%) were significantly depressed at the initial interview.

d. Relationship Between Depression, Physical, Cognitive, or Demographic Variables

Among the 30 patients who were given indepth interviews, there was no significant correlation between their activities of daily living score and their overall depression score \( r = 0.16 \). There was also no relationship between the overall depression score and the Mini Mental State Examination score \( r = -0.18 \). Using the entire study population, the group of 30 depressed patients were compared with the 73 remaining non-depressed patients in their demographic characteristics and previous history. There was no difference between these two groups on any of the demographic or personal history characteristics that were examined (Table 1.).

In addition, a review of patients medications indicated that no one was receiving reserpine which is known to be associated with development of depressive disorders. 14

e. Time Course of Depressive Disorders

Of the 30 patients who were found to be depressed at the time of the interview, 23 were followed up on one or more occasions during a one year period. Figure 1 shows the percent who remained depressed at various time points. There seemed to be a natural course of 7 to 8 months to the depressive disorders. Although all 23 patients were not seen at each of these follow-up intervals, all 23 were re-evaluated at least once after 6 months or more of follow-up and approximately two-thirds of those available for follow-up after 7 to 8 months remained depressed. However, by 9 months follow-up only 16% remained depressed and none evaluated at 12 months after the initial interview were depressed (Fig. 1).

f. Prevalence of Depression at Various Years After the Stroke

Patients were divided into groups depending upon the amount of time that had elapsed since their stroke. Figure 2 shows the mean GHQ scores for groups of patients at various time periods following a stroke. Both the severity and prevalence of depression was significantly increased for those patients who were between 6 months and 2 years following a stroke (Table 3); between 3 years and 9 years post-stroke, the prevalence and severity was low; and although it did not reach the level of significance \((p < .1)\), there was a suggestion that the prevalence and severity of depression may increase again after 10 or more years post-stroke (Table 3, Fig. 2).

g. Relationship Between Depression and Location of Lesion

Because CT scans were not available in every case, patients were divided into right hemisphere, left hemisphere and brain stem strokes based on the clinical localization of the stroke. Any patient who was left handed or who had a previous history of brain injury (eg. stroke or trauma) was excluded (40 of the 103 were excluded). The right hemisphere stroke group \((N = 37)\) included 8 patients with a clinical diagnosis of subcortical lesions of the internal capsule, basal ganglia, or thalamus, one patient with a diagnosis of a lacunar infarct and one patient with an intracerebral bleed. The left hemisphere stroke group \((N = 47)\) included 6 patients with subcortical infarcts, 4 with lacunar infarcts, and 2 with intracerebral bleeds. One patient with a brain stem infarct \((N = 19)\) was diagnosed as having a bleed. Patients demographic characteristics and personal history (using categories shown on Table 1) were compared amongst these three groups. There were no significant differences with the exception that the sex ratio of the brain stem lesion patients was predominately male (13 males versus 6 females) while in the right and left hemisphere stroke patients the ratio was slightly greater for females (left hemisphere, 17 males to 28 females, right hemisphere, 15 males to 24 females). We also compared right and left hemisphere lesioned patients on their neurological symptoms. There were no significant differences in the number of patients with hemiparesis, hemisensory loss or visual field loss. Aphasia was found in 15 patients

<table>
<thead>
<tr>
<th>GHQ score</th>
<th>% depressed at initial evaluation</th>
<th>% remaining depressed for at least 6 months</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>29% (30/103)</td>
<td>68%</td>
</tr>
<tr>
<td>6</td>
<td>23% (24/103)</td>
<td>60%</td>
</tr>
<tr>
<td>8</td>
<td>17% (17/103)</td>
<td>46%</td>
</tr>
</tbody>
</table>

TABLE 2 Frequency of Depression Related to Cutoff Score on GHQ

**Figure 1.** The percent of patients who were found to be depressed at the initial interview, who continued to be depressed at various time intervals following the initial interview. The number of patients evaluated at each time period is indicated on the figure.
with left hemisphere lesions and one left-hander with a right hemisphere lesion. As shown on table 1 there were no significant differences in the number of depressed or non-depressed patients with this symptom. The severity and frequency of depression in these groups is shown in table 4. Patients with left hemisphere lesions were significantly more depressed and at 6 months or more of follow-up almost 80% of them remained depressed. The severity and prevalence of depression was lowest in patients with right hemisphere lesions while brain stem lesioned patients were between these two extremes. Because of the small number of patients who were found to be depressed in the right hemisphere and brain stem lesioned groups, it is difficult to say whether the length of depression is really different than that found in patients with left hemisphere lesions and conclusions must be tentative in these groups. However, it is clear that patients with left hemisphere lesions were significantly more frequently and more severely depressed than patients with right hemisphere or brain stem strokes and their depressions were sustained in the majority of cases for more than 6 months.

h. Relationship Between Depression and Time Since Stroke

Analysis of the relationship between depression and time since stroke for the various lesion locations, revealed that the left hemisphere group from ½ to 2 years post-stroke was significantly more depressed than the other left hemisphere stroke patients who were at different post-stroke time periods (table 3). The other groups did not show this marked increase in depression at ½ to 2 years (table 3).

i. Clinical Description of Depressive Disorders

Although we are in the process of preparing a detailed description of the psychopathology associated with left or right hemisphere brain injury (Robinson,
Discussion

We have studied an unselected group of stroke out-patients and found depressive disorders to be present in about 30% of them. In addition, we have demonstrated that the General Health Questionnaire is a reliable and valid measure of depression in these patients. These depressive disorders do not appear to be related to the overall physical or cognitive impairments of the patients nor to any demographic characteristics, previous medical history, or neurological symptoms incurred from the stroke.

The generalizability of these findings, however, may be limited by the population studied and the experimental design. First, this was an outpatient population of stroke patients and may not reflect findings in those with more severe impairments needing chronic institutional care. However, our previous work with chronically institutionalized patients showed about the same percent of patients with left hemisphere lesions who were depressed as we found in the present study. Second, because patients were evaluated only at the times they attended the clinic, the intervals between follow-ups were not identical. Some patients were seen more frequently than others, although all those available for follow-up were seen at least once during a one year period. Third, we were not able to obtain follow-up evaluations in all patients, approximately 20% either dropped out of the clinic or did not return for follow-up evaluation during the time that this study was being conducted. Thus, it might be speculated that this 20% who were not followed-up may represent a distinct subgroup of patients with a different prognosis. However of this 20% of patients who were not followed-up, 7 were depressed at the initial interview which represents about 30% of the non-followed-up group. This percentage is not significantly different than what would be expected by random distribution, suggesting that those who were not followed-up may not have been significantly different than the follow-up group. Fourth, the patients studied were predominantly lower socioeconomic class, black and not married. The findings in a different socioeconomic group may not have been the same. Fifth, we did not have CT scans on all of these patients and the location of their lesion was based on the clinical diagnosis. Sixth, we did not see the patients from the beginning of their depressive disorders. We identified depressed patients by cross sectional evaluation when they happened to be attending the clinic. Thus, we probably found patients at various time points in their depressive disorders and the estimate of 7 to 8 months for the natural history of these disorders may be an underestimate.

Given these caveats, there were, however, some interesting results. First, of all, although depressive disorders were quite common, at the time of evaluation none of these patients was receiving psychiatric treatment and, in spite of the fact that two of them had previously been tried on tricyclic antidepressants, none were presently receiving them. The treating physicians were aware that some of these patients were depressed but not all of them. The high prevalence of depression and lack of treatment efforts in this group was surprising to us and we certainly confirmed the findings of Fiebel, Berk, and Joynt that post-stroke depressions frequently remain untreated. In addition, the length of these depressions was also surprising. As previously mentioned, we may have underestimated the length of these depressions but even with that limitation, these depressions lasted 7 to 8 months. This is comparable to the time period for major depressive episodes in patients with functional affective disorders. Another important finding is that the depressive disorders were significantly more common during the period from 6 months to 2 years after stroke. Between 2 and 9 years post-stroke, the frequency was reduced, but after 10 or more years following the stroke the percent of depressed patients may increase again. These early and late types of depressions may arise from different mechanisms, however, further studies will be needed in this period of very chronic illness. Another significant finding was that there was no cor-

| Table 4 Frequency of Depression Related to Area of Brain Lesion* |
|-----------------|-----------------|-----------------|
|                 | Mean GHQ score + sd | % depressed at initial visit | % remaining depressed at least 6 months |
| Left hemisphere | 5.7 ± 5.0‡ | 49% (17/35) | 78% (7/9) |
| Right hemisphere | 1.8 ± 3.5 | 7% (2/27) | 100% (2/2) |
| Brain stem      | 2.8 ± 3.5 | 36% (4/11) | 0% (0/3) |

*Patients with previous brain injury or left handedness were excluded. Eleven patients were left handed, had left hemisphere strokes and 1 was depressed, 7 had right hemisphere strokes and 3 were depressed.

†The distribution of depression for different lesion locations is significantly different than a random distribution (χ² = 11.4 p < 0.005).

‡Left and right hemisphere mean GHQ scores are significantly different by t test t = 3.45, p = 0.002. Left and brain stem GHQ scores are significantly different one tailed t = 1.78, p < 0.05.

Kubos, Starr and Price, in prep.), a clinical description of the types of depressions seen in post-stroke patients seems appropriate. Approximately 33% to 40% of the patients who are labeled as depressed in this study would meet the DSM-III criteria for a major depressive disorder. In our study in preparation we found that 7 of 18 depressed patients (7 of 28 total patients) with left hemisphere infarcts had major depressions while only 1 of 4 depressed patients (1 of 20 total patients) with a right hemisphere infarct had a major depression. The other 60% to 67% of the depressed patients would meet the criteria for a minor depression (dysthymic disorder) except the depression has not lasted 2 years. The clinical symptoms found in these patients include anxiety, depression, hopelessness, irritability, social withdrawal, sleep disturbance, appetite disturbance with weight loss, decrease in libido, agitation, loss of interest, and loss of energy. Self blame does occur but is not a prominent symptom. Thus these depressions are clinically significant and many of them might be expected to respond to antidepressant medication.
relation between the degree of physical or cognitive impairment and the severity of depression. This result confirms a similar finding in a previously reported group of chronically institutionalized stroke patients. It also provides further evidence that post-stroke mood disorders are not simply a psychological reaction to the impairment.

We were unable to obtain computerized tomography (CT) scans to localize the lesions on all of the patients because, in some, CT scanning was not available at the time they had their strokes, while in others, the CT scan was negative in the acute stroke period. But, given that we were limited to clinical diagnoses to localize the stroke, we did find that depressive disorders were significantly more common in patients with left hemisphere strokes than in those with right hemisphere or brain stem strokes. Other investigators have also reported that depressive symptoms are more common with left hemisphere brain injury than right hemisphere injury. In previous work, we have demonstrated that approximately 60% of patients with chronic left hemisphere brain injury were significantly depressed and that the severity of depression was strongly correlated with the distance from the frontopolar cortex. The results of our present study, using a very different patient population, demonstrate about the same percentage of left hemisphere brain injured patients with depression.

Our laboratory work, has shown that the behavioral and catecholaminergic response in the rat to injury on one side of the brain is significantly different than the response to a similar injury on the other side of the brain. In previous publications, we have suggested that the difference in emotional response to stroke lesions between hemispheres may be a neurophysiological manifestation of different vulnerabilities of the two hemispheres to injury to the catecholamine pathways. There is a significant amount of evidence that catecholamines play a role in several neurological disorders, as well as depressive states. In addition, recent work has shown in humans that the catecholamine pathways may be anatomically asymmetrical. Our present findings i.e. depression is more common after a left hemisphere stroke, as opposed to a right hemisphere stroke, is consistent with this suggestion.

As we pointed out in the beginning of this paper, perhaps one reason that post-stroke depressions have not received much therapeutic attention is our failure to have identified a particularly vulnerable group of patients and to demonstrate a characteristic course to the disorder. Based on the present study it is possible to make tentative statements about which patients may be most inclined to develop depression and to suggest to clinicians a high risk population. Patients who have had a left hemisphere stroke particularly in the frontal areas have a high likelihood of developing depression within the first 2 years after their stroke. Many of these depressions are severe and may at times lead to suicide attempts. They should be expected to last about 7 to 8 months without treatment efforts and the use of tricyclic antidepressants and psychotherapy seems to be warranted. In chronically ill patients who are 10 or more years post-stroke, depressive symptoms may also appear, particularly in patients with left hemisphere brain injury. Families of stroke patients in these high risk categories should be informed about the time periods when patients seem to be the most vulnerable for developing depression and instructed, if depressive symptoms develop, to bring the patient in for evaluation and possible treatment. Although these findings are preliminary and other studies need to be done, we have for the first time characterized the disorder of post-stroke depression by demonstrating its natural course, its most frequent time of onset and which patients seem to be most vulnerable. We hope that this will help to make clinicians more aware of the possibility of stroke patients developing these depressive disorders. The development and careful clinical evaluation of treatment methods is clearly needed for these patients.

Acknowledgments

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References

18. Robinson RG, Coyle JT: The differential effect of right versus left
Predicting Functional Outcome Following Acute Stroke Using a Standard Clinical Examination


SUMMARY In a series of 149 patients admitted to a stroke unit, the outcome of the acute phase of stroke rehabilitation, assessed by the patients' return to independence, was found to be related to the results of standardized weekly clinical examinations of mental, motor, sensory and communication function. The prediction of subsequent independence was estimated just as accurately using the results from three of these tests (upper limb motor function, postural function and proprioception) as when using the entire set of tests. A group of patients with little chance of responding to rehabilitation was identified.

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