Secondary Mania Following Traumatic Brain Injury

Ricardo E. Jorge, M.D., Robert G. Robinson, M.D., Sergio E. Starkstein, M.D., Ph.D., Stephan V. Arndt, Ph.D., Alfred W. Forrester, M.D., and Fred H. Geisler, M.D.

Objective: In this study patients were examined during the first year after traumatic brain injury to determine the presence of secondary mania. Method: A consecutive series of 66 patients with closed-head injury were evaluated in the hospital and at 3-, 6-, and 12-month follow-ups. The patients were examined with a semistructured psychiatric interview and scales for measurement of impairment in activities of daily living, intellectual function, and social functioning. Patients fulfilling the DSM-III-R criteria for mania were compared to patients with major depression and to patients without affective disturbances in regard to their background characteristics, impairment variables, and lesion locations. Results: Six patients (9%) met the criteria for mania at some point during follow-up. The presence of temporal basal polar lesions was significantly associated with secondary mania even when the effect of other lesion locations was taken into account. Secondary mania was not found to be associated with the severity of brain injury, degree of physical or cognitive impairment, level of social functioning, or previous family or personal history of psychiatric disorder. The duration of mania, however, appeared to be brief, lasting approximately 2 months. Conclusions: The 9% frequency of secondary mania in these patients with traumatic brain injury is significantly greater than that seen in other brain-injured populations (e.g., patients with stroke). The major correlate was the presence of a temporal basal polar lesion.

(Am J Psychiatry 1993; 150:916–921)

Traumatic brain injury is a major health concern in the United States. It is the most frequent type of brain injury and cause of death in persons under age 45. During the past 2 years we have been studying the prevalence, duration, pathogenesis, and clinical correlates of depression following traumatic brain injury (1–3). Mania, however, is another mood disorder that occurs after traumatic brain injury. Secondary manic and hypomanic states have been associated with several organic conditions, including uremia (4), thyroid disease (5, 6), vitamin B₁₂ deficiency (7), electrical trauma (8), hyperbaric diving (9), and open-heart surgery (10). Mania has also been associated with brain tumors (11, 12), CNS infections (13), stroke (12, 14–16), and traumatic brain injury (17–19).

Shukla et al. (17) reported on 20 patients who developed manic syndromes after closed-head trauma. They found a significant association between mania and the presence of posttraumatic seizures, predominantly of the partial-complex (temporal lobe epilepsy) type. We have previously reported on two groups of patients with secondary mania whose brain injury was related to cerebrovascular disorder, trauma, or neoplasm (12, 18, 20). Among these patients with secondary mania, there was a significantly greater frequency of lesions involving the right hemisphere, particularly in specific limbic-related areas, such as the temporal basal polar or orbitofrontal cortex.

In this study we analyzed the prevalence, clinical characteristics, and clinical correlates of manic syndromes diagnosed in the first year after traumatic brain injury.

METHOD

Subjects

The study group consisted of 66 consecutive patients admitted to the Shock Trauma Center of the Maryland Institute of Emergency Medical Services System with acute closed-head injury. The inclusion
criteria required that patients be over age 18 and not have injuries in multiple body systems (e.g., multiple fractures, collapsed lungs, severe abdominal organ damage), which would have increased the magnitude and diversity of their impairment and influenced mood. We excluded patients with a decreased level of consciousness (those who were comatose, stuporous, or comatose) or substantial aphasia, i.e., patients who were not able to complete part 1 of the Token Test (21).

Patients with a DSM-III-R diagnosis of delirium and patients with an affective disorder at the time of the traumatic brain injury (e.g., a patient whose head injury was the result of a suicide attempt) were also excluded. Information about the existence of previous mood disorder and about abuse of alcohol or other substances in the family or the patient was specifically requested of each patient and of the relatives who were present at the time of interview. A previous personal or family psychiatric disorder was considered present if the patient or relative appeared to meet the DSM-III-R criteria for that disorder some time in the past.

Severity of brain injury was determined by using the 24-hour Glasgow coma score (1984; mild=12-15, moderate=8-11, severe=3-7). In addition, patients who had scores in the 12-15 range but who received intracranial surgical procedures or had focal lesions greater than 25 cc were considered to have moderate head injuries. Most of the patients (68%, N=45) were categorized as having moderate head injuries.

Follow-up evaluations were carried out at 3, 6, and 12 months after trauma. Informed consent was obtained from all patients. The percentage of patients lost to follow-up was 18% at 3 months and 35% at both 6 and 12 months. There were 56 patients (85%) who had at least one follow-up visit and 52 patients (79%) who completed at least three of the four evaluations.

Psychiatric Examination

A structured psychiatric interview was conducted by using a modified version of the Present State Examination (PSE) (22). The instrument was modified to elicit symptoms related to mood and anxiety disorders. Quantitative depression ratings were obtained by using the Hamilton Rating Scale for Depression (23).

Cognitive function was measured with the Mini-Mental State (24). Impairment in activities of daily living was measured by using the Johns Hopkins Functioning Inventory (25). Quantitative assessments of social functioning were made by using the Social Functioning Exam (26) and the Social Ties Checklist (26). Affective disturbances were diagnosed according to the DSM-III-R criteria for major affective disorder, manic episode, and the DSM-III-R criteria for major and minor (dysthymic) depression.

Neuroimaging

Computerized tomographic (CT) scans were obtained at the time of admission. Follow-up scans were usually obtained 1 or 2 weeks later. All scans were done on a GE 1010 scanner with standard 10-mm axial cuts parallel to the canthomeatal line. Traumatic brain injury was classified according to the guidelines proposed by the Traumatic Coma Data Bank of the National Institute of Neurological and Communicative Disorders and Stroke (27). The classification is based on CT findings and distinguishes between diffuse and mass (focal) lesions. Diffuse injury was subdivided into four groups on the basis of the radiological evidence regarding 1) the absence or presence of substantially increased intracranial pressure (i.e., compressed and meningeal cisterns, midline shift greater than 5 mm) and 2) lesion size less than or greater than 25 cc. Mass (focal) lesions were subdivided into those that required surgical evacuation and high- or mixed-density lesions larger than 25 cc that were not surgically evacuated. All lesion locations were transposed to templates by using the procedure described by Levine and Grek (28). All scans were independently read by two neurologists (S.E.S., R.E.J.) who were blind to the results of the psychiatric examination. The interrater reliability (kappa values) for the different neuroradiological variables ranged from 0.81 to 1.00.

Statistical Analysis

The values for several of the rating scales and other variables exhibited nonnormal distributions. For consistency, we used nonparametric procedures throughout our analyses. For instance, when we compared the manic and depressed groups for differences in the demographic variables (e.g., socioeconomic status, sex), we used chi-square tests. When 25% of the expected values were less than 5, we used Fisher's exact tests, two-tailed. When we analyzed the six psychiatric rating scales, we were interested in obtaining an overall multivariate test of significance in order to 1) account for the intercorrelations among the rating scales and 2) control the overall probability of obtaining a significant result by chance (alpha error). This was accomplished with a nonparametric analog of multivariate analysis of variance based on ranks (29). The overall test of significance was taken as the test for the full model including all six scales. Logistic regression was used to test for an association between mania diagnosis and lesions location. Again, an overall test was used to control for alpha inflation and interrelations among the lesion locations. Thus, we estimated the regression coefficient for a specific lesion location while accounting for the effect of other lesion locations. After the significant likelihood ratio test for the full model was determined, backwards selection was used to exclude variables that were not significant at the 0.05 level.

RESULTS

Diagnosis

Of the 66 patients examined, six patients met the DSM-III-R criteria for major affective disorder, manic episode, at some point during the 1-year follow-up. These patients constitute our secondary mania group. One of them had a bipolar disorder. Similarly, 27 patients were diagnosed with major depression at some point during follow-up. Twenty-six patients did not have an affective disturbance.

The psychiatric symptoms found among the patients with secondary mania are shown in table 1. Of the six patients who met the criteria for such a diagnosis, four acknowledged the presence of an elevated mood; in the other two the euphoric mood disturbance was noted by the examining psychiatrist. In all cases, the mood change was felt to be persistent during the preceding 2 weeks.

Each of the six patients met the DSM-III-R criteria for mania at only one evaluation (five patients at the 3-month follow-up and one patient at the 6-month follow-up). Thus, the manic episodes were short-lived; their estimated duration was 2.0 months. The presence of an abnormally elevated mood, however, was observed in all six patients in at least two of the four evaluations. The mean estimated duration of elevated mood was 5.7 months.

In addition, three of the six patients with secondary

| TABLE 1. Psychiatric Symptoms of Six Patients With Mania Secondary to Traumatic Brain Injury |
|-----------------------------------------------|---------------------|
| Symptom                                      | Number of Patients |
| Expansive mood                               | 6                   |
| Irritability                                 | 5                   |
| Increased motor activity                      | 5                   |
| Increased verbal activity                     | 5                   |
| Thought disorder                             | 3                   |
| Increased sexual interest                     | 3                   |
| Disruptive-aggressive behavior                | 2                   |
| Decreased need for sleep                      | 1                   |
| Grandiose delusions                          | 1                   |
| Autonomic symptoms                           | 1                   |
TABLE 2. Characteristics of 66 Patients With Traumatic Brain Injury Who Did or Did Not Have a Secondary Affective Disorder

<table>
<thead>
<tr>
<th>Secondary Affective Disorder</th>
<th>Mania (N=6)</th>
<th>Major Depression (N=27)</th>
<th>None (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Socioeconomic class IV or V</td>
<td>5</td>
<td>83</td>
<td>21</td>
</tr>
<tr>
<td>White race</td>
<td>5</td>
<td>83</td>
<td>18</td>
</tr>
<tr>
<td>Male sex</td>
<td>6</td>
<td>100</td>
<td>21</td>
</tr>
<tr>
<td>Family history of mood disorders</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Personal history</td>
<td>1</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>Alcohol or drug abuse</td>
<td>0</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Degree of head injury</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Severe</td>
<td>5</td>
<td>83</td>
<td>15</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>17</td>
<td>4</td>
</tr>
</tbody>
</table>

aχ²=17.5, df=2, p=0.0002.

mania developed brief episodes of violent behavior at some point during follow-up. Aggressive behavior was significantly more frequent in the secondary mania group than in the other two groups (χ²=9.9, df=2, p=0.007).

At the time the diagnosis of mania was established, two patients were receiving a benzodiazepine (lorazepam) and one patient was receiving a neuroleptic (haloperidol). Thus, three patients may have been receiving treatment for their manic symptoms. The duration of mania did not appear to be significantly different in the patients who were treated and those who were not treated. In addition, one patient was given an anticonvulsant (phenytoin) for seizure prophylaxis and one patient received triazolam for sleep disturbances.

Background Characteristics

We compared the secondary mania patients (N=6) with the major depression patients (N=27) and the patients who did not develop an affective disturbance (N=26) during the 1-year follow-up period. The mean ages of the three groups were 30.3 (SD=18.4), 27.7 (SD=6.1), and 29.6 (SD=10.0) years, respectively, and their mean education levels were 12.8 (SD=2.3), 11.5 (SD=2.9), and 12.5 (SD=2.6) years. Other background characteristics, family and personal history of psychiatric and substance use disorders, and degree of head injury are shown in table 2. The only significant between-group difference was in personal history of psychiatric disorder, which was significantly more frequent among the major depression group. The patients with secondary mania did not have a higher frequency of personal history of psychiatric disorder than the group without affective disturbance.

Psychiatric Findings

We compared the scores on the Hamilton depression scale, PSE, Mini-Mental State, Johns Hopkins Functioning Inventory, Social Ties Checklist, and Social Functioning Exam of the patients with a secondary mood disorder and the patients who did not have a disorder of mood (table 3). The scores for the patients with a secondary mood disorder were obtained at the time of the affective disorder diagnosis, and the scores for the patients without a mood disorder were the means of the ranked scores obtained at each of the four evaluations.

A one-way multivariate analysis of variance of the six ranked variables showed a significant overall difference among the three groups (Wilks's lambda=0.195, F=7.1, df=12, 102, p=0.0001). Univariate results showed significant between-group differences in the scores on the Hamilton depression scale, PSE, and Social Functioning Exam (table 3). Post hoc analysis of these results revealed that the major depression group had significantly higher scores on the Hamilton depression scale, PSE, and Social Functioning Exam than the group without affective disorder. The patients with major depression also had a higher mean Hamilton depression score than did the group with secondary mania. In addition, the patients with secondary mania had a significantly higher PSE score than did the group without affective disorder, but these two groups did not differ in social functioning level.

Neuroradiological Findings

Nature of the lesion. We compared the CT findings for the six patients with secondary mania with the find-
ings for the other 60 patients in the study. There were no significant differences in the frequency of diffuse or focal CT patterns of brain injury or in the frequency of extraparenchymal hemorrhages (i.e., epidural, subdural, or subarachnoid hemorrhages), intracerebral hemorrhages, contusions, hydrocephalus, or brain atrophy.

We also compared the secondary mania, major depression, and no-affective-disturbance groups. There were no significant between-group differences in the nature of their lesions.

**Lesion location.** We then analyzed the relationship between lesion location and the presence of secondary mania by using a logistic regression model. The model included the following location variables: left (left hemisphere lesions only), right (right hemisphere lesions only), bilateral (bilateral hemispheric lesions), cortical (lesions involving cerebral cortex plus adjacent subcortical white matter), subcortical (lesions involving deep white matter, basal ganglia, brainstem, and cerebellum), frontal (right, left, or bilateral frontal lesions excluding orbitofrontal involvement), orbitofrontal (lesions involving the orbital surface of the frontal lobe), temporal (right, left, or bilateral temporal lesions excluding temporal basopolar involvement), temporal basopolar (lesions involving the temporopolar cortex and the anterobasal areas of the temporal lobe), and parietal-occipital.

We first compared the manic group (N=6) with the rest of the traumatic brain injury patients (N=60). There was an overall significant association between lesion location and the development of secondary mania ($\chi^2=28.2, df=12, p=0.005$). A backward selection procedure was performed in order to remove the nonsignificant variables ($p>0.05$). This procedure selected temporal basal polar location as the only location significantly associated with mania (Wald $\chi^2=12.0, df=1, p=0.0005$).

We then compared the manic group (N=6) with the major depression (N=27) group. There was also an overall significant association between lesion location and the development of secondary mania ($\chi^2=23.2, df=12, p=0.03$), and, once again, the presence of temporal basal polar lesions was associated with a greater risk of developing mania (Wald $\chi^2=8.72, df=1, p=0.003$).

**DISCUSSION**

In this study we examined the prevalence and clinical correlates of mania in 66 patients followed for 1 year after closed-head injury. Six patients (9%) met the DSM-III-R criteria for major affective disorder, manic episode. The estimated duration of the manic episodes was 2 months. However, an elevated mood was present in these patients for approximately 6 months. Secondary mania was not found to be associated with the severity of brain injury, degree of physical or cognitive impairment, level of social functioning, or previous family or personal history of psychiatric disorder. The presence of temporal basal polar lesions, however, was strongly associated with secondary mania.

Before a further discussion of these findings, we must acknowledge several methodological limitations. The patients included in this study did not have significant non-CNS injury. They were primarily young white men who had a history of alcohol or drug abuse and were from lower socioeconomic classes. Therefore, these findings may not be applicable to all patients with traumatic brain injury. The closed-head injuries produced multifocal brain damage, and it would be misleading to assume that the only areas which were injured were the ones visible on CT scan. Moreover, neuropathological evidence of diffuse axonal injury has been consistently found in both clinical and experimental studies of closed-head injury. Evaluation of its severity must be done on clinical grounds in patients with acute traumatic brain injury. Since the Glasgow coma scores, Johns Hopkins Functioning Inventory scores, Mini-Mental State scores, frequencies of diffuse and focal patterns of injury, and distributions of mild, moderate, and severe head injuries were not significantly different between groups, the presence of a systematic error is unlikely to explain our findings.

The percentage of patients lost at the 6-month and 1-year follow-up interviews was 35%. This reduction in the size of the group affected the power of the statistical analysis. Nevertheless, 56 patients (85%) had at least 1 follow-up visit and 52 patients (79%) completed at least three of the four evaluations. We compared the latter group (follow-up group) with the 14 patients who completed fewer than three follow-up evaluations (dropout group). There were no significant differences between the follow-up and dropout groups in background or psychiatric variables or in the prevalence of depressive disorders. Logistic regression analysis of the lesion location variables, however, showed a significant association between lesion location and dropping out of the study ($\chi^2=25.2, df=12, p=0.01$). The dropout group had significantly higher frequencies of both cortical (Wald $\chi^2=8.5, df=1, p=0.004$) and orbitofrontal (Wald $\chi^2=4.4, df=1, p=0.04$) lesions. Since orbitofrontal lesions have been associated with behavioral disturbances, including mania, the loss of patients with orbitofrontal lesions may have resulted in an underestimation of both the prevalence of secondary mania and the association with orbitofrontal lesion location.

Given these limitations, what are the implications of this study? First, mania following traumatic brain injury appears to be related to the presence of temporal basal polar lesions. This is consistent with our previous finding that mania is associated with anterior-inferior temporal vascular lesions of the right hemisphere (18, 20). We probably did not find an association with right temporal basal polar lesions because traumatic brain injury tends to be multifocal and bilateral. The fact that there were only two patients with unilateral temporal basal polar lesions precluded an adequate analysis of differences between sides.

The temporal basal polar area may serve as the neural substrate for a wide array of sensory-limbic interactions.
and may also be involved in the complex networks that integrate visceral and autonomic output, as well as more complex behavioral patterns, such as exploration, aggression, and appetitive behaviors (30–32). Stevens (33) analyzed the psychiatric outcome of patients who underwent temporal lobectomy as a treatment for intractable seizures. Development of psychosis or worsening of the preoperative psychiatric status was associated with evidence of bilateral brain damage and persistence of EEG abnormalities or seizure activity. She proposed that the pathophysiology of psychoses following temporal lobectomy may be related to the persistence of an epileptic focus that “kindles” abnormal electrical patterns in subcortical projection sites, such as the amygdala or ventral striatum. The presence of an epileptic focus may also elicit suppressive physiological responses (i.e., enhanced surround inhibition) that may be mediated by catecholaminergic inhibitory systems (e.g., dopaminergic) (34).

In the present patient series, secondary manic syndromes were associated with bilateral, asymmetrical, anterior temporal lesions. Although these patients did not develop seizures during follow-up, the buildup of subclinical epileptic activity in the anterior temporal lobes and the putative enhancement of dopaminergic mesocorticolimbic transmission may certainly have had pathophysiological importance.

It is unclear whether some of these patients will ultimately develop seizures (the onset of posttraumatic epilepsy may occur years after traumatic brain injury). Experimental amygdaloïd kindling studies, however, have shown that enduring behavioral abnormalities may be seen in the absence of seizure activity (35).

There are very few reports about the prevalence of manic syndromes following traumatic brain injury. Tennent (36) described two manic patients among a group of 44 head-injured patients. Lishman (37) reported the presence of euphoric mood in 10 of 144 patients with traumatic brain injury. Achte et al. (38) studied a large group of brain-injured war veterans (N=3,552) and found that affective psychoses occurred in 37 patients (1%). Of these patients, only three were diagnosed as manic-depressive. In the present study, however, six (9%) of 66 patients with traumatic brain injury developed symptoms of secondary mania. This is nine times the frequency observed in our group of 300 stroke patients (1%). This difference in the frequency of mania may tentatively be explained by the different pathophysiological mechanisms involved in stroke and traumatic brain injury and by the higher frequency of anterior temporal lesions observed in the patients with closed-head injury.

Given the nature and location of lesions following traumatic brain injury, one might ask why manic syndromes are not even more frequent. Previous studies have suggested that posttraumatic epilepsy (17), subcortical atrophy (as evidenced by increased ventricle-brain ratio), and genetic vulnerability (as evidenced by the presence of a positive family history of mood disorder) (20) are major risk factors for the development of secondary mania. In the present study, however, the patients with secondary mania did not have a higher frequency of family or personal history of mood disorders, and none of them developed seizures during the follow-up period. We did not measure ventricle size in these patients, however, because we lacked an adequate lesion-matched comparison group without mood disorder. Thus, the issue remains unexplained and warrants further research.

REFERENCES

PSE and CATEG0 Program. New York, Cambridge University Press, 1974


