ORIGINAL ARTICLE

Major Depression Following Traumatic Brain Injury

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Background: Major depression is a frequent psychiatric complication among patients with traumatic brain injury (TBI). To our knowledge, however, the clinical correlates of major depression have not been extensively studied.

Objective: To determine the clinical, neuropsychological, and structural neuroimaging correlates of major depression occurring after TBI.

Design: Prospective, case-controlled, surveillance study conducted during the first year after the traumatic episode occurred.

Settings: University hospital level I trauma center and a specialized rehabilitation unit.

Methods: The study group consisted of 91 patients with TBI. In addition, 27 patients with multiple traumas but without evidence of central nervous system injury constituted the control group. The patients' conditions were evaluated at baseline and at 3, 6, and 12 months after the traumatic episode. Psychiatric diagnosis was made using a structured clinical interview and *DSM-IV* criteria. Neuropsychological testing and quantitative magnetic resonance imaging were performed at the 3-month follow-up visit.

Results: Major depressive disorder was observed in 30 (33%) of 91 patients during the first year after sustaining a TBI. Major depressive disorder was significantly more frequent among patients with TBI than among the controls. Patients with TBI who had major depression were more likely to have a personal history of mood and anxiety disorders than patients who did not have major depression. Patients with major depression exhibited comorbid anxiety (76.7%) and aggressive behavior (56.7%). Patients with major depression had significantly greater impairment in executive functions than their nondepressed counterparts. Major depression was also associated with poorer social functioning at the 6-and 12-month follow-up, as well as significantly reduced left prefrontal gray matter volumes, particularly in the ventrolateral and dorsolateral regions.

Conclusions: Major depression is a frequent complication of TBI that hinders a patient's recovery. It is associated with executive dysfunction, negative affect, and prominent anxiety symptoms. The neuropathological changes produced by TBI may lead to deactivation of lateral and dorsal prefrontal cortices and increased activation of ventral limbic and paralimbic structures including the amygdala.

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Mood and anxiety disorders seem to be frequent psychiatric complications among patients who have a traumatic brain injury (TBI).[1-6] We have published our findings for a group of 66 patients with acute TBI who were followed up for more than 1 year.[7] During this period, 28 patients (42.4%) received a diagnosis of major depression as diagnosed using a semistructured interview (Present State Examination) and *DSM-III-R* diagnostic criteria. Hibbard et al[8] used a structured interview and *DSM-IV* criteria to identify Axis I psychopathological abnormalities in 100 adults with TBI who were evaluated, on average, 8 years after the traumatic episode. The prevalence of major depression in this series was 61%.

More recently, Kreutzer et al[9] studied the prevalence of major depressive disorder among a sample of 722 outpatients with TBI, evaluated an average of 2½ years following TBI. Defined using *DSM-IV* criteria, major depression was diagnosed in 303 patients (41.9%). Seel et al[10] used the same method to assess the prevalence of depression among 666 outpatients enrolled at 17 US centers affiliated with the Traumatic Brain Injury Model Systems Program. Patients had moderate or severe head injuries and were evaluated 10 to 126 months after the injury occurred.

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The prevalence of major depression in this sample was 27%.[10]

A recent community study suggested an association between a history of TBI and an increased lifetime prevalence of major depression.[11] Holsinger et al[11] found that the lifetime prevalence of major depression among men who sustained a head injury during World War II was 18.5% vs 13.4% for a comparable group who did not. In addition, current rates of depression were higher in patients who sustained a brain injury 50 years ago or longer, suggesting that patients with a head injury have recurrent depressive disorder throughout their lifetime at a significantly higher frequency than comparable patients without a head injury. Furthermore, Koponen et al[12] assessed the frequency of Axis I and Axis II disorders in a group of 60 patients followed up for 30 years after the TBI occurred. These patients were particularly vulnerable to develop depressive disorders, showing a lifetime prevalence of major depression of 26.7%.

Patients with depression and cerebrovascular disease show prominent executive dysfunction, particularly those patients with late-onset depressive disorders and ischemic deep white matter and basal ganglia lesions.[13,14] Although executive function deficits have been consistently described in patients with TBI,[15,16] to our knowledge, the relationship between mood disorders and executive dysfunction has not been previously described.

Major depressive disorder is a syndrome of variable causes and probably different underlying pathophysiological abnormalities. Neuroimaging studies in patients with primary depression have found structural and metabolic abnormalities in regions of the prefrontal cortex, including dorsolateral prefrontal,[17-21] anterior cingulate,[22-26] and orbitofrontal cortices.[27,28] Furthermore, recent neuropathological studies demonstrated that compared with control subjects, patients with familial unipolar and bipolar depression show a reduction in both the density and number of glial cells in subgenual cortex[23] as well as the density and size of neurons and glial cells in the orbital and dorsolateral aspects of the prefrontal cortex.[23,29-31]

In the present study, we assessed the frequency of comorbid conditions such as anxiety disorders and aggressive behavior that would provide further insight to the clinical phenomenology and the biological mechanisms leading to the onset of major depression among patients with TBI. The relationship between major depressive disorder and cognitive disturbance was analyzed using an extensive neuropsychological battery of tests. Finally, the association of major depression with the type, extent, and location of brain damage was evaluated using more sensitive neuroimaging methods. We hypothesized that frontal lobe dysfunction, particularly in the left hemisphere, would be associated with major depression.

METHODS

STUDY POPULATION

The study group consisted of 91 consecutive patients with closed head injury admitted to the University of Iowa Hospitals and Clinics, Iowa City (n=60) or the Iowa Methodist Medical Center, Des Moines (n=31). Patients with penetrating head injuries or those with clinical or radiological findings suggesting spinal cord injury were excluded from the study. Patients with severe comprehension deficits (ie, those who were unable to complete part II of the Token Test[32]) that precluded a thorough neuropsychiatric evaluation were also excluded from the study. In addition, 27 patients with multiple traumas but without clinical or radiological evidence of central nervous system involvement constituted our control group. Sixty-eight (74.7%) of the 91 patients with TBI were injured in a motor vehicle collision, 16 patients (17.6%) by a fall, 3 patients (3.3%) by assault, and 4 patients (4.4%) by other mechanisms (eg, sport-related injuries). All 118 subjects gave written informed consent for participation in this study.

Both patients with TBI and the controls were followed up at 3, 6, and 12 months. The mean (SD) time of follow-up was not significantly different between the TBI and the general trauma groups (9.38 [4.2] months and 9.26 [3.9] months, respectively). We compared the demographic and clinical characteristics of the patients who completed the study with those who dropped out of the study. Patients who dropped out were significantly younger (mean [SD], 27.2 [7.0] years) than patients who remained in the study (38.2 [12.5] years) ($F_{[1,90]}=7.3$, $P<.009$). Otherwise, there were no significant differences between the groups for sex, race, socioeconomic or employment status, marital status, or educational level. In addition, there were no significant differences between those who dropped out and those who completed the study in the severity of the TBI, degree of functional or cognitive impairment, premorbid social functioning, frequency of psychiatric disorders, or frequency of alcohol or other substance abuse.

TBI SEVERITY

Severity of the TBI was assessed using the 24-hour Glasgow Coma Scale (GCS)[33] score. According to this measurement, GCS scores between 13 and 15 defined mild head injury; between 9 and 12, moderate head injury; and between 3 and 8, severe head injury. Patients with a GCS score in the 12- to 15-point range but who underwent intracranial surgical procedures or were seen with focal lesions greater than 15 mL, however, were considered to have had a moderate head injury.[34] The overall severity of the traumatic injury was assessed using the Abbreviated Injury Scale.[21]

PSYCHIATRIC ASSESSMENT

All patients were assessed by a psychiatrist (R.E.J. or R.G.R.) using 2 semistructured interviews, a modified version of the Present State Examination,[35] designed to elicit symptoms of mood and anxiety disorder, and the Structured Clinical Interview for *DSM-IV* diagnoses.[36,37] Severity of depressive and anxiety symptoms were assessed using the Hamilton Depression Rating Scale[38] and the Hamilton Anxiety Scale,[39] respectively. Aggressive behavior was assessed using the Overt Aggression Scale.[40]

Family history of psychiatric disorders was assessed for first-degree relatives using the family history method using Research Diagnostic Criteria.[41] The Mini-Mental State Examination[42] was used as a global measure of cognitive functioning. Impairment in activities of daily living was assessed using the Functional Independence Measure.[43] Psychosocial adjustment was quantitatively assessed using the Social Functioning Examination and Social Ties Checklist.[44] The Social Functioning Examination is a semistructured interview assessing different aspects of psychosocial adjustment such as quality and satisfaction of interpersonal relationships, performance of home

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Table 1. Demographic and Background Characteristics of 118 Patients With TBI*

Variable	Patients With TBI (n = 91)	Controls Subjects (n = 27)
Age, mean (SD), y	36.4 (15.7)	35.7 (14.1)
Male sex	59.3	74.1
White patients	94.5	92.6
Abbreviated Injury Scale, mean (SD), score	16.8 (7.4)	15.5 (6.4)
Functional Independence Measure, mean (SD), score	62.7 (10.1)	60.2 (10.5)
Social Functioning Examination, mean (SD), score	0.175 (0.141)	0.128 (0.069)
History of alcohol or other drug abuse	22.5	25.9
History of depressive disorders	19.8	14.8
History of anxiety disorders	8.8	7.4

Abbreviation: TBI, traumatic brain injury.
*Data are given as the mean (percentage of patients) unless otherwise indicated.

and family responsibilities, work experience, social activities, economic practices, stability of family income, living environment, spiritual beliefs, and use of community resources. Scores range from 0.0 to 1.0 with the higher scores indicating greater impairment. The Social Ties Checklist is a 10-item questionnaire that determines the number of social connections (eg, frequency of seeing friends or membership in clubs, churches, or other organizations) available to the patient. Scores range from 0 to 10 with the higher scores indicating fewer social connections. Initial Social Ties Checklist scores assessed social support networks prior to the traumatic episode. The reliability and validity of each of these instruments has previously been demonstrated in populations with brain injuries.[45]

NEUROIMAGING

Computed tomographic scans and occasionally magnetic resonance (MR) imaging were obtained as part of the standard clinical evaluation in the emergency and neurosurgery departments of the participating institutions. The nature, extent, and location of traumatic lesions were classified in accord with the Traumatic Coma Data Bank criteria and registered using the appropriate forms.[46] A neurologist trained in the assessment of structural neuroimaging scans, who was blind to the results of the psychiatric examination, read all of the scans.

In addition a research MR image was obtained in patients with TBI at the time of the 3-month evaluation using a 1.5-T scanner (GE Sigma, Milwaukee, Wis) at the radiology department of the University of Iowa. The tools of a locally developed software package, BRAINS (Department of Psychiatry, University of Iowa, Iowa City), were used to generate volumetric data. This software permits cross-modality image registration, automated tissue classification, automated regional identification, cortical surface generation, volume and surface measurement, 3-dimensional visualization of surfaces, and multiplanar telegraphing. The validity and reproducibility of morphometric analysis using the aforementioned software has been reported in previous studies.[47-54]

To quantify gray matter volume of the frontal lobe, an MR image–based parcellation method was used.[55] This method subdivides the frontal lobe into 11 functionally relevant subregions on the basis of individual gyral and sulcal topography. Morphometric tracings were performed by a research assistant who was extensively trained in this technique and who was blind to the psychiatric diagnosis and group assignment of the participants.

NEUROPSYCHOLOGICAL EVALUATION

Participants underwent neuropsychological assessment evaluated by an experienced neuropsychologist (D.M.) at the 3-month follow-up visit. Analyses included in this article focused on memory and frontal-executive functioning, as assessed by the following 8 tests: Rey Auditory Verbal Learning Test[56] (delayed recall trial); Rey Complex Figure Test[56] (delayed recall trial); Trail Making Test[57] (A and B/A ratio); Multilingual Aphasia Examination[58] (controlled oral word association); Stroop Color-Word Interference Test[59]; Wisconsin Card-Sorting Test (the number of categories achieved and the number of perseverative errors).[60]

STATISTICAL ANALYSIS

Comparison of the groups used simple χ^2 analyses when the expected frequencies were sufficiently large and the Fisher exact test when the χ^2 test was inappropriate. Because some of our continuous measures were clearly nonnormally distributed, we chose the Mann-Whitney test for comparing the groups. To remain consistent, the Mann-Whitney test was used for all such comparisons. Data are given as mean (SD).

RESULTS

CHARACTERIZATION OF THE TBI GROUP

According to their initial GCS scores and initial computed tomographic data, of the 91 patients who sustained a TBI, 40 patients (44.3%) had a mild TBI, 30 patients (32.5%) had a moderate TBI, and 21 patients (23.2%) had a severe TBI. Although their GCS scores fell within the mild range, 10 patients were classified as having a moderate TBI because they required a surgical evacuation procedure and/or they were initially seen with focal lesions larger than 15 mL. In accord with the Traumatic Coma Data Bank Classification, 66 (72.1%) of the 91 patients had diffuse lesions and 25 patients (27.9%) had a mass or focal pattern of injury.

TBI AND CONTROL GROUP COMPARISONS

The demographic and background characteristics of the TBI and control groups are given in **Table 1**. There were no significant differences between the TBI and control groups for age, sex, race, or socioeconomic status. There were no significant between-group differences in Abbreviated Injury Scale and Functional Independence Measure scores. Thus, compared with patients with TBI, the controls had experienced comparable traumatic injuries and had a similar degree of functional impairment. In addition, there were no significant differences between the control and TBI groups in the frequency of personal history of psychiatric disorders or personal history of substance abuse.

MOOD DISORDERS FREQUENCY

Mood disorders were significantly more frequent among patients with TBI. Of 91 patients with TBI, 47 patients

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(51.6%) developed a mood disorder at some time during the first year after injury compared with 6 (22.2%) of 27 patients with multiple traumatic injuries but without central nervous system involvement (χ^2_1=7.3, P=.006). Of the 91 patients, 47 patients met *DSM-IV* criteria for mood disorder due to TBI, 30 patients (33%) presented with major depressive features, 9 patients (9.9%) had depression without major depressive features, while the remaining 8 patients (8.8%) had manic or mixed features. Of the 27 controls, 2 patients (7.4%) had major depressive disorder and 4 patients (14.8%) had depression without major depressive features. The frequency of major depressive disorder was significantly greater in the patients with TBI (P=.008, Fisher exact test). Of the 91 patients with TBI we have excluded 17 patients who developed mania or subsyndromal depression; thus, the final number of participants included in the study were 74 (ie, 30 patients with major depressive features and 44 nondepressed patients).

Patients with a mood disorder due to TBI with major depressive features will be the subject of the present article and will be compared with those patients who did not develop mood disorders during the first year after the TBI occurred. We have previously shown that patients with posttraumatic manic and hypomanic syndromes have different clinical correlates than those with major depressive disorder.[61] It is conceivable that post-TBI manic syndromes have different pathophysiological mechanisms. These syndromes will be the focus of an independent study. On the other hand, in contrast with what has been demonstrated in other depressed populations such as geriatric patients, there is no empirical evidence validating minor or subsyndromal depressions occurring after TBI as a helpful construct with distinct clinical implications. For example, we did not find an effect of minor depression on the long-term outcome of patients with TBI.[62] In addition, there is a high degree of overlap of minor depression with other prevalent conditions such as adjustment disorders and postconcussive syndromes. In fact, the frequency of minor depression was not significantly different among our patients with either TBI or general trauma. On the other hand, major depressive disorder has been more extensively validated in different TBI samples, and the specificity and sensitivity of *DSM*-based criteria adequately demonstrated.

PHENOMENOLOGICAL FEATURES OF MAJOR DEPRESSION DUE TO TBI

Major depressive disorder following TBI was significantly associated with the presence of anxiety disorders. Of 30 patients with major depressive disorder, 23 (76.7%) met diagnostic criteria for a comorbid anxiety disorder compared with 9 (20.4%) of 44 patients who did not develop a mood disorder but met criteria for an anxiety disorder during the first year following TBI (χ^2_1=24.3, P<.001). Of these 23 patients who had major depression and a coexisting anxiety disorder, 14 patients presented with generalized anxiety features, 2 patients had generalized anxiety and panic attacks, and 7 patients met diagnostic criteria for posttraumatic stress disorder.

Major depression was also associated with the occurrence of aggressive behavior that was categorized using the Overt Aggression Scale. Of the 30 patients with major depression, 17 patients (56.7%) demonstrated significant aggressive behavior (Overt Aggression Scale scores >3 or a score of 3 with physically aggressive behavior against self or others) compared with 10 of 44 patients who showed the same level of aggression without mood disorder during the first year after the TBI (χ^2_1=8.9, P=.003).

LONGITUDINAL COURSE OF MAJOR DEPRESSION AND RESPONSE TO ANTIDEPRESSANT THERAPY

Of the 30 patients who developed major depression, 15 patients (50%) received the diagnosis at the initial evaluation, 9 patients (30%) received the diagnosis at the 3-month follow-up, and 6 patients (20%) received the diagnosis at the 6-month follow-up. Thus, half of the patients developed major depression during the subacute period following TBI. We obtained follow-up data in 24 (80%) of the 30 patients with major depression during the first year after the TBI occurred. The average time of follow-up was 10.5 months (range, 3-12 months) with 20 patients (67%) completing the 12-month follow-up evaluation. Primary physicians prescribed antidepressants in 8 (33%) of 24 patients. Among the 16 patients who did not receive antidepressant therapy, major depressive disorder had a mean duration of 5.8 (2.7) months. The mean for duration of depression among patients treated with antidepressants was 4.7 (2.7) months, respectively.

CORRELATES OF MAJOR DEPRESSION AMONG PATIENTS WITH TBI

Relationship of Major Depression With Background Variables

There were no significant differences between the patients with major depression and those who did not have major depression for age, sex, race, socioeconomic status, marital status, educational level, or annual income. However, the number of patients who were unemployed at the time of TBI was significantly greater for the patients with major depression (P=.004, Fisher exact test) (**Table 2**).

Relationship of Major Depression With History of Psychiatric Illness

The frequency of previous psychiatric disorders is summarized in **Table 3**. When compared with nondepressed patients, patients with TBI who developed major depression had a significantly higher frequency of personal history of mood disorders (P=.01, Fisher exact test) and personal history of anxiety disorders (P=.05, Fisher exact test).

There were no significant differences between those who were depressed and those who were not in the frequency of previous or concurrent alcohol or other drug abuse. Furthermore, a history of alcohol and/or other drug abuse was not significantly more frequent in the group

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Table 2. Background Characteristics

Variable	Patients With TBI and Major Depression (n = 30)	Patients With TBI Without Major Depression (n = 44)
Age, mean (SD), y*	39.5 (13.9)	35.6 (15.4)
Male sex, %	44.8	58.1
White patients, %	96.5	95.4
Socioeconomic status, % of patients in Hollingshead classes IV and V†	69.2	51.3
Marital status, % married	40.7	27.3
Educational level, mean (SD), y	13.1 (2.6)	13.0 (2.2)
Annual income, % of patients earning <$20 000	45.8	24.1
Unemployed at the time TBI, % of patients*	25.9	2.4

Abbreviation: TBI, traumatic brain injury.
*$P = .005$.
†Hollingshead classes range from I (the lowest) to V (the highest).

Table 3. History of Psychiatric Illness*

Variable	Patients With TBI and Major Depression (n = 30)	Patients With TBI Without Major Depression (n = 44)
History of mood disorders†	36.7	11.4
History of anxiety disorders‡	20.0	4.6
History of alcohol abuse	20.0	15.9
History of other drug abuse	20.0	6.8
Concurrent alcohol abuse	6.7	2.3
Concurrent other drug abuse	6.7	2.3

Abbreviation: TBI, traumatic brain injury.
*Data are given as percentages.
†$P<.01$.
‡$P<.05$.

with major depression ($\chi^2_1=0.64$, $P=.42$). Interestingly, we did not observe a significant association between having a personal history of mood or anxiety disorders and posttraumatic depressive disorders among the controls (ie, patients without central nervous system injury). Finally, the frequency of psychiatric disorders in first-degree relatives of patients with TBI was not significantly different between the those with and those without major depression.

Relationship of Major Depression With Impairment Variables

These findings are summarized in **Table 4**. There were no significant differences between those with and those without major depression in activities of daily living impairment as measured by Functional Independence Measure scores or in global measures of cognitive function such as Mini-Mental State Examination scores. Initial Social Ties Checklist scores were not significantly different between these groups. On the other hand, compared with patients who did not develop depression, patients with major depression had significantly

Table 4. Baseline Impairment Variables*

Variable	Patients With TBI and Major Depression (n = 30)	Patients With TBI Without Major Depression (n = 44)
Glasgow Coma Scale score	12.3 (2.2)	11.6 (3.1)
Severity of TBI, % of patients		
Mild	46.7	47.5
Moderate	40.0	25.0
Severe	13.3	27.3
Abbreviated Injury Scale score	16.7 (5.7)	18 (8.1)
Functional Independence Measure score	62.6 (10.7)	62.5 (9.9)
Mini-Mental Status Examination score	27.7 (1.5)	27.7 (2.7)
Social Ties Checklist score	3.8 (1.8)	3.3 (1.9)

Abbreviation: TBI, traumatic brain injury.
*Data are given as the mean (SD) unless otherwise indicated.

higher Social Functioning Examination scores at the 6-month follow-up ($\chi^2_1=11.4$, $P<.001$, Mann-Whitney test) and at the 12-month follow-up ($\chi^2_1=4.6$, $P=0.03$, Mann-Whitney test). These findings are consistent with poorer psychosocial outcome in the group with major depression.

Relationship of Major Depression With Neuropsychological Variables

We analyzed memory and executive functioning among patients who had major depression at the time of the neuropsychological evaluation (ie, 3-month follow-up visit). The results are given in **Table 5**. Compared with the nondepressed group, those who were depressed had lower scores on all 8 tests. Because the 2 groups differed significantly in age, we transformed these variables into ranks and tested the between-groups differences using analysis of covariance, covarying for age. There were significant differences in the Wisconsin Card-Sorting Test number of perseverative errors ($F_{1,4}=4.76$, $P=.03$) and Trail Making Test B/A ratio ($F_{1,51}=5.82$, $P=.02$).

Patients with TBI who had a personal history of depressive disorders who were not depressed at the time of the neuropsychological evaluation did not differ from patients with TBI without a psychiatric history in memory and executive functioning tests, suggesting that the neuropsychological deficits observed among patients with major depression were not the result of a chronic mood disorder that preexisted brain trauma and the current depressive episode.

Relationship With Neurological and Radiological Findings

The frequency of mild, moderate, and severe TBIs was not significantly different between those with and those without major depression. There were no significant intergroup differences in GCS scores or in Abbreviated Injury Scale scores (Table 4). Thus, severity of trauma was similar in both groups.

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Table 5. Neuropsychological Scores and Effect Sizes*

Variable	Patients With TBI and Major Depression	Patients With TBI Without Major Depression	Effect Size (Cohen *d*)†
RAVLT score	8.33 (2.77)	9.93 (3.14)	.52
Rey Complex Figure score	14.50 (8.10)	17.64 (5.31)	.52
WCST, score			
Perseverative errors	13.92 (11.09)‡	7.95 (5.17)‡	**.82**
Categories achieved	2.25 (1.60)	3.33 (1.49)	**.69**
Trail Making Test A score, seconds to completion	37.08 (15.18)	31.90 (15.24)	.34
Trail Making Test, B/A ratio	3.44 (1.60)‡	2.49 (.80)‡	**.87**
Stroop Color-Word Interference Test score	31.83 (10.30)	38.05 (9.92)	.61
Multilingual Asphasia Examination score	34.08 (12.06)	36.29 (12.73)	.18

Abbreviations: RAVLT, Rey Auditory Verbal Learning Test; TBI, traumatic brain injury; WCST, Wisconsin Card-Sorting Test.

*Data are given as the mean (SD). For a more detailed explanation of the tests used, see the "Neuropsychological Evaluation" subsection of the "Methods" section.

†Boldfaced values indicate a large effect size.

‡$P<.05$ controlling for age. All values are raw scores. The score of 12 was for patients with TBI and major depression; the score of 40 to 42 was for patients with TBI without major depression.

Table 6. Regional Frontal Gray Matter Volumes*

Variable	Patients With TBI Without Major Depression (n = 17)	Patients With TBI and Major Depression (n = 17)
L orbitofrontal cortex	2.1 (0.25)	2.1 (0.25)
L medial frontal cortex	1.5 (0.24)	1.6 (0.37)
L lateral frontal cortex†	5.6 (0.7)	4.5 (0.9)
L superior frontal gyrus	2.2 (0.4)	1.9 (0.3)
L middle frontal gyrus	2.2 (0.5)	1.7 (0.7)
L inferior frontal gyrus‡	1.2 (0.2)	0.9 (0.2)
R orbitofrontal cortex	2.1 (0.20)	2.1 (0.46)
R medial frontal cortex	1.6 (0.30)	1.7 (0.43)
R lateral frontal cortex	5.4 (0.7)	4.9 (1.2)
R superior frontal gyrus	2.1 (0.3)	1.9 (0.3)
R middle frontal gyrus	2.2 (0.6)	2.0 (0.8)
R inferior frontal gyrus	1.1 (0.2)	1.0 (0.3)

Abbreviation: TBI, traumatic brain injury.

*Data are given as the gray matter volume (percentage of gray matter volume).

†$P<.001$.

‡$P<.009$.

VOLUMETRIC ANALYSIS

A research MR image taken at the 3-month follow-up visit provided the data necessary to conduct a volumetric analysis of frontal lobe regions. A group of 17 patients with major depressive disorder was compared with 17 patients who did not develop a mood disorder during the first year of follow-up. The groups were matched for age (±2 years), sex, and severity of TBI. Those with and those without major depression were not significantly different with regard to the frequency of diffuse or focal patterns of brain injury, the location of the lesion, or the volume of focal (mass) lesions. In addition, there were no significant intergroup differences in the frequency of previous or current alcohol or other drug abuse, which has been associated with volumetric changes. We also compared these 34 patients with the remaining 57 patients with TBI who were excluded from the volumetric analysis. There were no significant differences between the groups in demographic variables, severity of TBI, as well as in the cognitive, activities of daily living, or psychosocial impairment variables. Thus, these groups were essentially comparable.

There were no significant differences between those with and those without depression in total brain volume, total gray matter volume, or total white matter volume. Temporal, parietal, and occipital lobe gray matter volumes (standardized to percentages of total gray matter volume) were also similar between the 2 groups. However, patients with major depression had significantly decreased frontal gray matter volumes compared with those in the nondepressed group ($\chi^2_1=10.5$, $P=.001$, Mann-Whitney test). Furthermore, patients with major depression had significantly smaller left frontal gray matter volumes than the those in the nondepressed group ($\chi^2_1=7.1$, $P=.008$, Mann-Whitney test).

Using a previously validated parcellation method,[55] we identified 3 frontal areas that have previously been associated with mood regulation and the pathophysiology of mood disorders. These were the orbitofrontal cortex (ie, orbitofrontal cortex and straight gyrus), the medial-frontal cortex (ie, anterior cingular gyrus and caudal medial frontal cortex), and the lateral prefrontal cortex (ie, superior middle and inferior frontal gyri). The superior, middle, and inferior frontal gyri include the dorsolateral and ventrolateral prefrontal cortex that are otherwise difficult to measure in a reliable way because of the lack of consistent anatomical landmarks. The results of this analysis are summarized in **Table 6**. Regional gray matter volumes have been normalized as percentages of the total gray matter volume.

Compared with those in the nondepressed group, patients with major depression showed significantly decreased left lateral frontal cortex volumes ($\chi^2_1=9.7$, $P=.001$, Mann-Whitney test). This difference was owing to significantly smaller left inferior frontal gyrus volumes ($\chi^2_1=6.8$, $P=.009$, Mann-Whitney test) as well as smaller left superior frontal gyrus volumes ($\chi^2_1=3.8$, $P=.05$, Mann-Whitney test) and left middle frontal gyrus volumes ($\chi^2_1=3.2$, $P=.08$, Mann-Whitney test). Although right lateral frontal volumes were smaller among those with major depression, this difference did not reach statistical significance. There were no significant differences between the 2 groups in orbitofrontal or medial prefrontal volumes.

COMMENT

To our knowledge, this is the first prospective study analyzing the clinical, neuropsychological, and neuroimaging correlates of major depressive disorder following TBI using a complete neuropsychological battery and a re-

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fined structural MR imaging analysis. The principal findings of this study may be summarized as follows: major depressive disorder was observed in 30 (33%) of 91 patients during the first year after TBI. Major depressive disorder was significantly more frequent among patients with TBI than among patients with traumatic injuries of comparable severity but without involvement of the central nervous system. Compared with the group of patients who did not develop a mood disorder, those with major depression were more likely to have a personal history of mood and anxiety disorders. Most of the patients with major depression exhibited comorbid anxiety disorders and aggressive behavior. Patients with major depression showed significantly greater impairment in problem-solving ability and cognitive flexibility than their nondepressed counterparts. Major depression was also associated with poorer social functioning at the 6- and 12-month follow-up visits, as well as significantly reduced left prefrontal gray matter volumes, particularly the ventrolateral and dorsolateral regions.

Before discussing the implications of this study, we should acknowledge its methodological limitations. First, most of our patients were young males of caucasian origin, reflecting the demographic characteristics of Iowa. Thus, our findings may not pertain to other groups of patients with TBI. Although we made a special effort to obtain complete longitudinal data, 16 (21.6%) of 74 patients included in the present analysis were unavailable for follow-up. Similar or greater attrition rates are common in the vast majority of longitudinal studies of patients with TBI. As aforementioned, the clinical and demographic characteristics of patients who dropped out were essentially similar to those of patients who completed the study. Thus, we believe that attrition had only a limited effect on the findings that were addressed earlier. Given these limitations, what are the most important implications of the present study?

Major depressive disorder as well as total mood disorders were significantly more frequent in patients who sustained TBIs than in patients with similar background characteristics who underwent similar levels of stress (eg, motor vehicle collisions) but who did not sustain brain injury. This suggests that neuropathological processes associated with TBI constitute an important contributing factor to the development of these mood disorders.

The reported frequency of major depression (33%) is consistent with the findings of 2 recent large cross-sectional studies of patients with TBI.[9,10] These patients, however, were assessed later during the course of recovery.

Patients with major depression were more likely to have a history of mood and anxiety disorders and it is reasonable to assume that they were more prone to develop psychiatric symptoms and major depression when exposed to significant stress. However, the fact that we did not observe the same effect of psychiatric history among patients without brain injury suggests that this factor might not play a decisive causative role. Interestingly, the frequency of alcohol or other drug abuse was not significantly different between the 2 groups, a fact that suggests that the pathological changes in reward and mood regulation circuits observed in patients with addictive disorders did not convey a significantly higher risk of developing major depressive disorder in this group of patients with TBI. Finally, although it does not exclude the role of genetic factors in the cause of post-TBI depression, a family history of mood or anxiety disorders was not significantly more frequent among patients with major depression.

Although patients with major depression and TBI were not different from those patients with TBI only with regard to global measures of cognitive function such as the Mini-Mental State Examination score, they were significantly impaired in neuropsychological tests assessing executive functioning.

Traumatic brain injury has been consistently associated with damage to the prefrontal cortex, basal ganglia, and the white matter tracts that connect these structures. Executive dysfunction and depression may be related to the same pathophysiological mechanism (ie, the disruption of these fronto-striatal-thalamic circuits). Patients with major depression did not differ from the nondepressed controls with TBI in regard to the severity of TBI or the frequency and overall extent of frontal lobe lesions identified in their initial neuroimaging studies. Certainly, the selective volumetric changes in left prefrontal cortex observed among patients with major depression may contribute to their cognitive deficits. It is conceivable, however, that a mechanism specific for depression (eg, abnormal aminergic modulation of prefrontal structures) may also produce impairment in executive functioning as observed in the present group of patients.

Major depression was associated with reduced gray matter volume in the lateral aspects of the left prefrontal cortex. We have previously reported on the selective involvement of left prefrontal and left basal ganglia lesions in patients with acute major depressive disorder following TBI.[63] Other studies of secondary depressive disorders have also found decreased metabolic rates in inferior frontal regions in patients with Parkinson disease,[64] Huntington disease,[65] and caudate stroke.[18]

It is unclear if the reduced prefrontal volumes observed in patients with major depressive disorder are the result of the pathophysiological mechanisms initiated by TBI or they constitute a preexistent trait associated with an increased risk to develop mood disorders. Brain atrophic changes can be observed among patients with chronic mood disorders.[30,66,67] We analyzed the effect of a history of anxiety or depressive disorders on frontal lobe volumetric measures. There were no significant differences between patients with a history of depressive or anxiety disorders and patients without a history of psychiatric illness in total frontal lobe volume, total frontal gray and white matter volumes, or gray matter volumes of frontal subregions including left inferior frontal gray matter volume. We can also hypothesize that social deprivation and unemployment can be associated with prefrontal cortex changes. However, unemployed patients did not show significant reductions in prefrontal volumes. In fact, patients with and without major depression who were unemployed had higher prefrontal volumes than their employed counterparts. Thus, there is no evidence to support the idea that asymmetric differences in frontal lobe vol-

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ume preexisted the brain injury and we believe that the decreased left frontal lobe volume is the result of resolving traumatic lesions approximately 3 months after the TBI occurred.

Recent experimental studies of TBI suggest that diffuse neuronal damage and cell loss may progress over weeks to months after the initial insult in selectively vulnerable regions of the neocortex, hippocampus, thalamus, and striatum.[68-70] On the other hand, neuroimaging studies of patients with TBI have demonstrated delayed cerebral atrophy on computed tomographic scan and MR imaging,[71-73] as well as altered metabolic patterns consistent with neuronal loss and inflammation as evidenced by proton magnetic resonance spectroscopy.[74,75] Furthermore, behavioral outcome seems to be more strongly correlated with delayed rather than early imaging findings.[76,77]

Whatever the case may be, major depression could result from deactivation of more lateral and dorsal frontal cortex and increased activation in ventral limbic and paralimbic structures including the amygdala.[78-80] The cognitive abnormalities observed in patients with TBI and major depression are consistent with left lateral prefrontal dysfunction. Interestingly, high levels of amygdala activation may be associated with an increased prevalence of anxiety symptoms and negative affect,[81] a pattern of symptoms that closely resembles what we observed in our group of patients with TBI. Moreover, faulty prefrontal modulation of medial limbic structures could explain the impulsive and aggressive behavior observed in these patients.[82,83]

CONCLUSIONS

Major depressive disorder is a frequent complication of TBI that exerts a deleterious effect on the recovery process and psychosocial outcome of patients with brain injuries.[62,84] Biological factors such as the involvement of the prefrontal cortex and probably other limbic and paralimbic structures may play a significant role in the complex pathophysiology of major depression. Future studies need to further characterize these factors to identify patients with TBI who are at high risk of developing major depression and to design appropriate therapeutic interventions.

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