Mood and Anxiety Disorders Following Traumatic Brain Injury

June 01, 2008 | Anxiety [1], Comorbidity In Psychiatry [2], Mood Disorders [3], Generalized Anxiety [4], Major Depressive Disorder [5], Military Mental Health [6], Trauma And Violence [7], Alcohol Abuse [8], Amnesia [9], Cognitive Behavioral Therapy [10] By Ricardo E. Jorge, MD [11]

Traumatic brain injury (TBI) is the major cause of death and disability among young adults. In spite of preventive measures, the incidence of a TBI associated with motor vehicle accidents, falls, assault, and high-contact sports continues to be alarmingly high and constitutes a major public health concern. In addition, the recent military operations in Iraq and Afghanistan have resulted in a large number of persons with blast injuries and brain trauma. Taking into account that cognitive and behavioral changes have a decisive influence in the recovery and community reintegration of patients with a TBI, there is a renewed interest in developing systematic studies of the frequency, mechanism, and treatment of the psychopathological alterations observed among these patients.

Nonmilitary TBI

Each year, an estimated 1.5 million Americans sustain a TBI that requires hospitalization. As a result of these injuries, 80,000 to 90,000 patients experience long-term disability.1 There is consensus that cognitive, emotional, and behavioral problems constitute the major source of disability for TBI patients.

The neuropsychiatric consequences of a TBI can be studied from a dimensional perspective using neuropsychological tests and behavioral scales that have been extensively validated in acute-care settings and rehabilitation services.2-5 Cognitive and behavioral morbidity can also be assessed from a categorical, disease-based perspective, which assumes that psychiatric disorders, although diagnosed through a recognized constellation of symptoms, have an identifiable biological substrate, a distinct clinical prognosis, and an expected treatment response.6 Fann and colleagues7 examined the risk of psychiatric illness after a TBI in an adult health maintenance organization population. They compared the frequency of psychiatric disorders among 939 patients with a TBI and 2817 controls. The prevalence of any psychiatric illness in the first year was 49% following a moderate to severe TBI, 34% following a mild TBI, and 18% in the control group. Among study participants without a history of psychiatric illness, those with moderate to severe TBI were 4 times (95% confidence interval [CI], 2.4 to 6.8) more likely to sustain any psychiatric illness in the 6 months following a TBI than those without a TBI. The risk was 2.8-fold higher (95% CI, 2.1 to 3.7) in patients with a mild TBI compared with study participants who did not have a TBI.7 Mood disorders are the most frequent psychiatric illness observed among patients with a TBI.8-10 Hibbard and colleagues11 used a structured interview and DSM-IV criteria to identify Axis I psychopathology in 100 adults with a TBI who were evaluated, on average, 8 years after trauma. The prevalence of major depression in this population was 61%. More recently, Kreutzer and colleagues12 studied the prevalence of major depressive disorder in a sample of 722 outpatients with a TBI, evaluated an average of 2.5 years following brain injury. Major depression, defined using DSM-IV criteria, was diagnosed in 303 patients (42%). Findings from a prospective study indicate that the frequency of mood disorders was significantly greater in patients with a TBI than in a control group of patients who had had an orthopedic trauma. A mood disorder developed at some time during the first year after injury in 46 of 92 patients with a TBI (51%), compared with 6 of 27 patients (22%) with multiple traumatic injuries but without CNS involvement. In addition, the frequency of major depressive disorder was significantly greater in patients with TBI than in the control group.13 Thus,
mood disorders were significantly more frequent in patients with a TBI than in patients with similar background characteristics who underwent similar levels of stress (eg, motor vehicle accidents) but who did not sustain brain injury. This suggests that structural brain damage associated with a TBI constitutes an important contributing factor to the development of affective disorders. Furthermore, patients who experience major depression following a TBI frequently show structural and/or functional alterations in the prefrontal cortex as evidenced by abnormal performance on neuropsychological tests or by abnormal neuroimaging findings.\textsuperscript{13-15} Emotional processing and mood regulation involves the complex interaction between prefrontal regions (eg, anterior cingulate gyrus, orbitofrontal cortex) and limbic structures (eg, amygdala, hippocampus, ventral striatum). Different forms of traumatic lesions such as diffuse axonal injury and cerebral contusions may result in disruption of these neural circuits and, consequently, in affective disturbance. Furthermore, these changes may persist and evolve with time. A significant proportion of patients in whom mood disorders develop following a TBI will progress to a more chronic and recurrent form of these psychiatric conditions, spanning many years. Thus, the prevalence of psychiatric disorders continues to be significantly higher in TBI patients than in control groups many years after the traumatic injury.\textsuperscript{16-18}

A recent community study suggests an association between a history of a TBI and an increased lifetime prevalence of major depression.\textsuperscript{17} The investigators found that the lifetime prevalence of major depression among men who had sustained a TBI during the Second World War was 18.5\% versus 13.4\% for a comparable group without a TBI. Koponen and colleagues\textsuperscript{18} assessed the frequency of Axis I and Axis II disorders in a group of 60 patients 30 years after sustaining a TBI. The patients showed a lifetime prevalence of major depression of 26.7\%. Overall, these findings suggest that patients with a TBI have recurrent depressive disorder throughout their lifetime at a significantly higher frequency than comparable patients without a TBI. When present, affective disturbances have a large impact on family relationships, social integration, and return to productive activity. Anxiety disorders occur in a significant proportion of patients with a TBI and frequently coexist with depressive disorders (Table 1).\textsuperscript{18,19} There is a significant degree of comorbidity between mood and anxiety disorders among patients with a TBI. For example, about two-thirds of patients in whom major depression develops also meet diagnostic criteria for generalized anxiety disorder.\textsuperscript{13} Posttraumatic stress disorder (PTSD) is another frequent psychiatric complication in patients with traumatic injuries.\textsuperscript{20} Whether unconsciousness and posttraumatic amnesia associated with a TBI would preclude the onset of PTSD in patients who have had a life-threatening experience, such as a motor vehicle accident or physical assault, has been widely debated. In fact, PTSD has been described in patients with a TBI of different degrees of severity, even among those patients who have partial or fragmentary recollection of the contingencies of the traumatic episode.\textsuperscript{21-23} Recently, Glaesser and colleagues\textsuperscript{24} assessed the occurrence of PTSD in a group of 46 patients with a TBI who were admitted to an acute neurorehabilitation clinic. They concluded that a TBI and PTSD are not mutually exclusive. However, PTSD was unlikely to develop in victims of accidents if trauma had resulted in a prolonged period of unconsciousness. Bryant and colleagues\textsuperscript{25} analyzed the relationship between resting heart rates at 1 week and 1 month following a severe TBI and a PTSD diagnosis assessed 6 months after the injury. In these trials, PTSD developed in 16 of 68 (23\%) severely injured patients. Compared with patients in whom PTSD did not develop, the patients had significantly higher heart rates at 1 week but not at 1 month after trauma. These findings suggest that fear conditioning can occur independently of the level of awareness and contribute to the onset of PTSD. These investigators also reported that patients who had PTSD at 6 months following a severe TBI had significantly poorer functional and vocational outcomes than did patients who did not have PTSD.\textsuperscript{26}

**Military TBI**

TBI has been described as the "signature wound" of Operation Iraqi Freedom and Operation Enduring Freedom in Afghanistan. Modern body armor has greatly reduced the frequency of severe injuries to the thoracic and abdominal regions. Consequently, injuries to the head and the extremities are the predominant wounds encountered in contemporary battlefields. The use of Kevlar helmets has significantly reduced the frequency of penetrating head injuries, making closed head injury (eg, from blasts, motor vehicle accidents, or falls) the most frequent form of TBI observed in current military operations.\textsuperscript{27} According to military records, blast injuries constitute the most frequent type of injury observed, accounting for approximately two-thirds of war-zone evacuations.\textsuperscript{27} A recent study reported that 88\% of soldiers treated at a medical unit in Iraq were injured by improvised explosive devices or
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The vast majority of injuries (97%) observed among the troops of a Marine unit in Iraq were produced by improvised explosive devices or mines. In addition, it has been estimated that 59% of soldiers with blast injuries have sustained a TBI. As of March 2006, 28% of all injured troops in these conflicts had a TBI, with blast being the cause in most cases (88%).

The troops in Iraq and Afghanistan are different from other military groups and from civilian populations at risk for a TBI. In contrast to other conflicts (eg, the Vietnam War), deployed military forces in Iraq are all-volunteer, professional troops. A recent study reported on the demographic characteristics of a large cohort of soldiers in Iraq. About 90% of the troops were men in their 20s; 56.4% were white, 16.2% were black, 14.7% were Hispanic American, 2.6% were Asian American, and 10.1% were other. About half (45.4%) were married and most had a high school education (mean [SD], 12.5 [1.3] years). Overall, military samples were found to have better psychosocial adjustment than civilians with a TBI. Within the military cohort, 6% reported past psychiatric disorders, and 4.2% reported past alcohol use disorders. The rates for alcohol abuse were significantly lower than the ones observed in civilian samples.

Although psychiatric disturbance will certainly have a negative impact on the clinical recovery and quality of life of injured veterans, the frequency, phenomenological characteristics, and clinical correlates of mood and anxiety disorders that occur after a TBI have not been thoroughly described among veterans returning from Iraq and Afghanistan. Lew and colleagues reported on 2 cases of veterans with mild head injuries who, although they were initially judged fit to return to light duty, experienced dramatic personality changes 3 to 5 months after the TBI. A comprehensive battery of neuropsychological tests and electrophysiological measures revealed significant impairments on tasks probing complex attentional functions, speed of information processing, and problem-solving ability. Unfortunately, the impact of mood and anxiety disorders on neuropsychological performance was not assessed. The investigators concluded that these 2 cases are paradigmatic of a growing number of veterans referred to their rehabilitation center.

Previous epidemiological studies suggest that there is a high prevalence of mental health disorders among military personnel in Iraq and Afghanistan. A recent study of 103,788 veterans first seen at the Veterans Affairs Health Care System (VA) following active duty in Iraq and Afghanistan reported that about 25% of all veterans received a mental health diagnosis. The median time from service separation to the first VA clinic visit (mostly in primary care settings) was 2.9 months after separation, and the most frequent diagnoses were PTSD (13%) and mood disorders (11%). In another recent study, Hoge and colleagues examined the frequency of mood and anxiety disorders following a mild TBI in 2525 US soldiers returning from Iraq. PTSD was strongly associated with the occurrence of a mild TBI (Table 2). Soldiers with a mild TBI were more likely to have poorer medical outcomes. More important, PTSD and depression were most frequently linked to poor outcomes.

It must be noted that assessment of a mild TBI in the context of military operations is difficult for multiple reasons, including retrospective bias and the fact that alterations of consciousness (a decisive criterion in the traditional definition of a mild TBI) may be part of an acute stress reaction rather than the consequence of a traumatic injury. This may result not only in an overestimation of the number of TBI cases but also in a biased estimate of the strength of the association between a TBI and PTSD, given that acute stress reactions are a significant predictor of later PTSD. However, the stronger relationship of psychiatric illness with a history of loss of consciousness suggests that subtle forms of brain damage may contribute to the genesis of these disorders. Assessment of the type, location, and extent of these brain alterations requires the use of more sensitive neuroimaging techniques such as diffusion tensor imaging, functional MRI, or magnetic resonance spectroscopy.

Cognitive dysfunction is a major contributor to disability following a TBI. Neuropsychological changes following active duty in Iraq and Afghanistan were examined by the Neurocognition Deployment Health Study. The investigators concluded that deployment to Iraq was associated with increased risk of neuropsychological deficits. However, the relationship of these cognitive changes to the presence of mood and anxiety disorders has not been adequately studied and constitutes one of the priorities of research in this field. Is a TBI a significant risk factor for mental health problems following active duty in Iraq or Afghanistan? Are the phenomenological presentation and clinical course of psychiatric disorders that occur after a TBI different from those observed in patients without brain damage? These important clinical questions require more extensive investigation. Furthermore, the physiopathology of blast injuries, particularly in the case of recurrent exposure to blasts, has not been fully elucidated and might be substantially different from the mechanisms described in other forms of TBI. This pathophysiology may be contributing to differences in the clinical presentation of these TBI patients. For example, preliminary studies that compare blast versus nonblast closed head injuries among veterans admitted to the Walter Reed Army Medical Center have suggested differential patterns of injury and recovery.
Center suggest that patients injured in a blast are more likely than those with a nonblast TBI to present with acute stress reaction and PTSD.27

**Conclusions**

TBI has been associated with an increased frequency of psychopathological disorders in both civilian and military populations. Disruption of prefrontal circuits regulating mood and emotional processing is an important causative factor in the genesis of these syndromes. In addition, mood and anxiety disorders account for a significant part of disability resulting from TBI of varying severity. Thus, there is an urgent need to study clinical characteristics, mechanisms, and treatment alternatives for these conditions. In turn, the information obtained from patients with brain injuries may provide further insight into the pathophysiology of these disorders in the population as a whole.

**References:**


34. Hoge CW, Auchterlonie JL, Milliken CS. Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. JAMA.


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