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Mild traumatic brain injury: a neuropsychiatric approach to diagnosis, evaluation, and treatment

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Abstract: Traumatic brain injury (TBI) is a common occurrence in the United States, with an estimated incidence exceeding 1 million injuries per year. Cognitive, emotional, behavioral, and physical impairments are common sequelae of TBI and may, in a significant minority of patients, persist well into the late period following injury. The etiology of these symptoms in individuals with mild TBI is controversial, with hypotheses of postconcussive symptom formation variously ascribing greater or lesser weight to neural damage, pre- and/or post-injury psychological or psychiatric factors, somatization, malingering, or some combination of these. Some of these hypotheses reflect biases common to medicolegal or compensation-related contexts, whereas others are derived from recent neuroimaging and electrophysiology studies. Studies of the latter sort suggest that many of the typical postconcussive symptoms are associated with neurobiological dysfunction in one or more areas of the central nervous system. Whether these symptoms constitute a postconcussive syndrome per se is debatable. Instead, it may be more accurate to describe them as commonly co-occurring symptoms rather than as a syndromal sequela of TBI. The present review addresses these issues including the epidemiology and course of recovery from mild TBI and the validity of the postconcussive syndrome. Suggestions regarding the assessment and treatment of individuals with post-concussive symptoms are offered.

Keywords: traumatic brain injury, postconcussive syndrome, neuroimaging, electroencephalography, diagnosis, treatment

Introduction

Each year in the United States, 235 000 people experience a traumatic brain injury (TBI) that requires hospitalization, and as many as 1.1 million additional individuals experience a TBI for which they are evaluated and released from an emergency department (National Center for Injury Prevention and Control 2004). TBI is bimodally distributed by age, with the highest rates of injury occurring in those aged 15–24 years and those older than 65 years (Kraus and Nourjah 1988). The majority of TBI results from motor vehicle accidents, assaults, and falls (Kraus and Nourjah 1988), the first of these two causes being more frequent in younger and urban dwelling persons and the third being more common among the elderly. Among persons that experience a TBI requiring hospitalization, 50 000 die as a result of their injuries, and an additional 80 000 develop partial or total permanent disabilities (National Center for Injury Prevention and Control 2004). Approximately 5.3 million Americans are presently living with chronic disabilities due to TBI, and the annual cost of TBI in the United States exceeds \$48 billion (Kraus and Sorenson 1994; National Center for Injury Prevention and Control 2004).

Although many physicians are familiar with severe TBI and its management, mild TBI comprises 70%–80% of all such injuries (Kraus and Nourjah 1988; Jennett 1996, 1998). The deficits produced by mild TBI are frequently more subtle, less

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often recognized, and more contentiously debated than are those resulting from severe TBI (MacKenzie et al 1989; Williams et al 1990; Katz and DeLuca 1992; Dikmen et al 2001). Given the large number of persons that experience mild TBI each year, it is indeed fortunate that the majority of these individuals recover fully within the first year following TBI. However, a nontrivial minority of persons with mild TBI, with estimates ranging between 1% and 20% (Katz and DeLuca 1992; Dikmen et al 2001), will develop persistent cognitive, emotional, behavioral, and physical impairments that extend well into the late (>1 year) period following TBI.

Typical acute and/or chronic postconcussive symptoms include physical problems such as headache, dizziness, and visual disturbances; cognitive impairments such as attention, memory, and executive dysfunction; and emotional or behavioral problems such as irritability, anxiety, depression, affective lability, apathy, and/or impulsivity. The development of these symptoms is predicated on a complex set of factors including neural injury produced by mild TBI, expectational sets on the part of patients and clinicians, pre-existing and/or comorbid post-traumatic psychiatric disorders, and occasionally on conscious and/or unconscious efforts to obtain primary and secondary gains (MacMillan et al 2002; Wood 2004).

The cognitive, emotional, behavioral, and physical impairments experienced by mild TBI survivors produce substantial disability and costs (Levin, Mattis, et al 1987; Kraus and Nourjah 1988; Montgomery et al 1991; Katz and DeLuca 1992). Clinicians working with this population should be familiar with recent advances in the basic and clinical neuroscience of mild TBI in order to understand accurately the symptoms with which their patients present and also the treatments available for these symptoms.

In the service of this goal, the present article reviews the clinical features of mild TBI, recent neuroscience findings relevant to understanding this condition, and the validity of the postconcussive syndrome. This review was predicated on initial searches of the medical literature in PubMed and MEDLINE using the terms “traumatic brain injury”, “brain injury”, “closed head injury”, “craniocerebral trauma”, and “concussion”. These searches were subsequently limited to studies of humans and were anchored to the topic areas into which this review is organized (ie, definition of mild TBI, neurobiology, neuroimaging, electrophysiology, post-concussive syndrome, evaluation, and treatment, with the last of these categories including cognitive impairment, emotional disturbances, and somatic symptoms). Where

information in the peer-reviewed literature was lacking and/or where useful summaries of that literature sufficed for the purpose of this review, information published in major textbooks in the field was included. Data from these reviews were synthesized to formulate a neuropsychiatric approach to the issue of mild TBI, and to develop the suggestions offered herein regarding the assessment and treatment of individuals with postconcussive symptoms following mild TBI.

Mild traumatic brain injury

Defining mild TBI

Traumatic brain injury is best defined as the result of the application of either external physical force or rapid acceleration/deceleration forces (eg, mechanical trauma, not anoxia/hypoxia, tumor, stroke) that disrupts brain function as manifested by immediately apparent impairments in cognitive and/or physical function. It is important to note that it is the application of such forces to the brain, rather than to the head per se, that produces a TBI. In other words, not all head injuries produce brain injuries, and some brain injuries (particularly those resulting from acceleration/deceleration forces) may occur without apparent head injury.

The Glasgow Coma Scale (GCS) (Teasdale and Jennett 1974) is the most widely known system for injury severity classification in the acute injury period, and is useful when performed properly in that context. The American Congress of Rehabilitation Medicine (ACRM) (1993) definition of mild traumatic brain injury may be of greater use to clinicians attempting to determine after-the-fact whether an event experienced by an individual is characterized fairly as a mild TBI, particularly when GCS scores are unavailable or invalid. This definition states that any *one* of the following symptoms following external application of force to the brain reflects an injury of severity sufficient to merit classification as a mild TBI: any period of loss of consciousness, any loss of memory for events immediately before (retrograde amnesia) or after (anterograde amnesia) the accident (collectively referred to as the period of post-traumatic amnesia, or PTA), any alteration in mental state at the time of the accident (eg, feeling dazed, disoriented, or confused), or focal neurologic deficit(s) that may or may not be transient. The ACRM definition of mild TBI includes only those injuries in which loss of consciousness is 30 minutes or less, the GCS score at 30 minutes after injury is 13–15, and the duration of PTA is no longer than 24 hours. Injuries exceeding these criteria are considered to be of

more than mild severity. Although these criteria are not without criticism (Ruff and Jurica 1999; Arciniegas and Silver 2001), they are at present the most widely accepted definition of mild TBI. In the absence of another universally accepted minimum criteria set for this condition, the authors recommend using these criteria to determine whether an event experienced by a patient is characterized fairly as a TBI.

Neurobiology of TBI

The biomechanical and cytotoxic consequences of mild TBI may be substantial despite an ostensibly “mild” mechanism of injury. Experimental injury models demonstrate that mild brain injuries are capable of producing diffuse axonal injury, both as a function of biomechanical forces and a host of injury-mediated cytotoxic processes (ie, calcium and magnesium regulation, free radical formation, neurotransmitter excitotoxicity, inflammatory responses, disruption of vascular homeostasis) (Povlishock et al 1979, 1983; Povlishock 1992; Povlishock and Christman 1995). TBI in humans appears similarly capable of producing structural neuronal damage and/or diffuse neuronal dysfunction (Christman et al 1994; Maxwell et al 1997; Povlishock 1992, 2000; Povlishock and Jenkins 1995), and are central – if perhaps transient – neuropathological features of mild TBI in humans (Povlishock 1992; Povlishock and Jenkins 1995). Alterations of neurotransmitter production and/or delivery occur acutely and chronically following TBI and some of these are related to acute and chronic cognitive impairments following TBI (Povlishock 1992; Obrenovitch and Urenjak 1997; Arciniegas 2003). Additionally, neurogenetic factors may influence the extent of neural injury produced by mild TBI. Recent studies suggest that carrier status for the apolipoprotein epsilon-4 (ApoE-4) allele may increase risk for poor outcome following TBI, particularly among persons with more severe TBI or repetitive mild TBI (Jordan et al 1997; Friedman et al 1999; Lichtman et al 2000; Crawford et al 2002; Chiang et al 2003; Nathoo et al 2003). Although the role of the ApoE-4 allele in outcome following mild TBI is less clear (Liberman et al 2002; Chamelian et al 2004), our laboratory observed an increased frequency of the ApoE-4 among persons with persistent cognitive and electrophysiologic abnormalities following mild TBI (Arciniegas et al 2003). We suggest that while the presence of this allele may not influence outcome in unselected groups of persons with mild TBI, it may be overrepresented among persons who fail to make full

recoveries following mild TBI. Whether or to what extent other genetic factors influence outcome following mild TBI is the subject of active investigation.

Although many clinicians believe that mild TBI produces no significant findings on conventional clinical neuroimaging (ie, CT or MRI scanning), this belief is not supported by the literature (Williams et al 1990). In fact, three recent large studies (Borczuk 1995; Miller et al 1997; Haydel et al 2000) representing data from approximately 4000 persons with mild TBI (GCS = 15) demonstrate early abnormalities on computed tomographic (CT) scanning in 5%–10% of these individuals. Studies evaluating CT abnormalities among persons with GCS scores of 13 or 14 suggest a rate of 20%–35% (Harad and Kerstein 1992; Shackford et al 1992; Stein and Ross 1992; Schynoll et al 1993). Importantly, neuroimaging abnormalities among persons with mild TBI are associated with post-traumatic cognitive sequelae comparable to those experienced by persons with GCS-defined moderate TBI; accordingly, persons with neuroimaging abnormalities in the context of GCS-defined mild TBI are sometimes regarded as having “complicated mild TBI” (Williams et al 1990; van der Naalt et al 1999).

Studies using data acquisition and interpretation methods more sensitive than those afforded by conventional clinical neuroimaging consistently demonstrate significant post-traumatic cerebral structural abnormalities, including cortical and subcortical atrophy, ventricular dilation, and white matter injury (Bigler et al 1992; Wood and Bigler 1995; Anderson et al 1996; Arciniegas et al 2001; Bigler 2001, 2003). While these studies vary in their methodology, they all suggest that TBI, including mild TBI, is associated with measurable reductions in the volumes of several cerebral structures needed to maintain normal cognition and behavior. Functional MRI (fMRI) studies demonstrate that mild TBI produces abnormal allocation of memory processing resources in the acute post-injury period even among persons whose objective neuropsychological performance appears relatively normal (McAllister et al 1999, 2001). Such abnormalities may underlie the subjective experience of difficulty with memory even where neuropsychological performance is within the normal range (McAllister et al 1999). Studies using proton (Garnett, Blamire, Corkill, et al 2000; Garnett, Blamire, Rajagopalan, et al 2000) or phosphorus (Garnett et al 2001) magnetic resonance spectroscopy (MRS) demonstrate cerebral white matter abnormalities and metabolic abnormalities, respectively, that are not otherwise apparent on conventional

clinical neuroimaging. These imaging modalities reflect more accurately the size or extent of damaged tissue than either conventional CT or MRI, and abnormalities on MRS are related to neuropsychological impairments in the late period following TBI (Brooks et al 2000). Single photon computed tomography (SPECT) studies (Choksey et al 1991; Roper et al 1991; Jacobs et al 1994; Mitchener et al 1997) and positron emission tomography (PET) studies (Humayun et al 1989; Ruff et al 1994; Gross et al 1996) also suggest that TBI may produce disturbances in brain function even where such injuries do not produce structural abnormalities visible on conventional neuroimaging (CT or MRI). Although these studies include persons with a range of TBI severity, they suggest that these neuroimaging techniques may afford insights into the neurobiological consequences of TBI, including those among persons with mild TBI and postconcussive symptoms, which are not amenable to detection using conventional structural neuroimaging studies.

Conventional EEG may be abnormal in as many as 10% of persons with mild TBI (Arciniegas et al 2004). Findings on conventional EEG in this population most often include mild disorganization of the background rhythms and/or a mild excess of slow wave frequencies. Topographic brain electrical activity mapping (BEAM) and quantitative EEG (or QEEG) may demonstrate frontal and frontotemporal abnormalities not evident on conventional EEG (Thatcher et al 1989, 1998a, 1998b). When present, these abnormalities are similar in type and location, although of lesser severity, to those seen following severe TBI (Thatcher et al 2001). Evoked potential and/or event-related potential (EP and ERP, respectively) studies of persons with mild TBI also demonstrate abnormal brain function (Gaetz et al 2000; Gaetz and Weinberg 2000). The most robust correlations between specific EP/ERP findings and clinical postconcussive symptoms emerge when the electrophysiologic procedures index dysfunction within the neural systems related to those serving the cognitive and behavioral functions in which the person is experiencing impairment (Pratap-Chand et al 1988; Arciniegas et al 1999, 2001; Arciniegas, Olincy et al 2000; Arciniegas and Topkoff 2004). For example, persons with persistent attention and memory impairments following mild TBI have been shown to demonstrate abnormalities in the hippocampally-mediated P50 evoked response (Arciniegas et al 1999, 2001; Arciniegas, Olincy, et al 2000; Arciniegas and Topkoff 2004) and the frontocentral P300 response (Pratap-Chand et al 1988). These abnormalities are strongly associated with the

function cortical areas involved in the generation of attention and memory. Electrophysiologic abnormalities of these types among persons with post-traumatic attention and memory impairments offers additional support to the hypothesis that mild TBI does in some cases give rise to neurophysiologically-based persistent cognitive impairments.

The findings from neuropathological, neurophysiological, neuroimaging, and electrophysiologic studies of persons with mild TBI suggest that the traditional view of these injuries as neurobiologically trivial requires serious reconsideration. These studies support an approach to the evaluation of persons with mild TBI that emphasizes the recognition, identification, and evaluation of the neurobiologic underpinnings of his or her postconcussive symptoms. It is, however, important to be clear that the findings from the neuroimaging and electrophysiologic measures discussed in this section are, in most cases, not specific to mild TBI; instead, they are most accurately understood as reflecting neurobiological changes produced by any condition that adversely affects the brain structures and functions that these measures index. Accordingly, it is imperative that clinicians bear in mind the differential diagnosis of such findings if any of these measures are employed in the clinical evaluation of persons with suspected mild TBI. In fact, we suggest that it is premature to advocate routine use of advanced structural or functional neuroimaging studies and/or unconventional electrophysiologic studies in the evaluation of persons with persistent postconcussive symptoms. Nonetheless, clinicians should be mindful of the literature reviewed here before dismissing a patient's symptoms as "psychological" when conventional neuroimaging and electrophysiologic studies are unrevealing.

The postconcussive syndrome

There are important conceptual differences between mild TBI, postconcussive symptoms, and the postconcussive syndrome about which clinicians should be aware. Strictly applied, the term "mild TBI" refers only to the initial injury severity and should not be interpreted unequivocally as suggesting mild outcome severity. Although both the postconcussive syndrome and postconcussive symptoms are most often discussed in the context of mild TBI, these terms and their clinical referents are not synonymous with mild TBI: mild TBI describes a type of injury whereas postconcussive symptoms or syndrome describe a set

of problems resulting from TBI, including mild TBI (Arciniegas and Silver 2001).

Postconcussive symptoms may develop following a TBI of any severity, and are generally grouped into three categories: cognitive, physical, and emotional/behavioral. The term “postconcussive syndrome” (or postconcussional disorder in the nosology of the DSM-IV [APA 1994]) generally denotes the development of a constellation of physical, cognitive, and emotional/behavioral postconcussive symptoms.

However, it is not clear there is a postconcussive syndrome per se. Syndromes generally refer to conditions in which there is both consistent symptom linkage and also coupling of symptom resolution. Symptom linkage suggests that the presence of symptom A predicts the presence of symptoms B, C, and so on. Coupling of symptom resolution, whether over time or in response to treatment, suggests that the resolution of symptom A predicts resolution of symptom B, C, and so on.

The studies of symptom occurrence and resolution following mild TBI noted above do not offer strong support for linkage between the types of symptoms experienced by these persons. In other words, postconcussive symptoms do not appear to cluster together in an invariable, or even in a consistently predictable, fashion. The presence of somatic symptoms is not linked predictably to the presence of neuropsychiatric (ie, cognitive, emotional, or behavioral) symptoms, and the neuropsychiatric sequelae of TBI are not linked consistently to one another. This lack of symptom linkage may reflect the complex effects of injury (focal, diffuse, or both) on the brain and also the interaction between each individual’s injury and his or her pre- or post-injury psychosocial factors (Alexander 1995; King 1996).

Additionally, there is little evidence of coupling of symptom resolution following TBI. Few persons with multiple postconcussive symptoms immediately after TBI experience persistence of the entire set of their symptoms over time, and instead maintain only a few, if any, of them into the late post-injury period. Which of these initial symptoms are maintained is also not reliably predictable based on their early occurrence after TBI. Furthermore, neither common clinical experience nor the medication studies performed in this population to date (for a review, see Arciniegas, Topkoff, et al 2000) support the concept of a coupled response of postconcussive symptoms to treatment. Instead, multiple and varied treatments are generally required for the multiple and varied symptoms of these individuals.

Both the lack of linkage between postconcussive symptoms and the lack of coupling of symptom resolution (spontaneously or in response to treatment) argues against the concept of a postconcussive syndrome in the conventional sense of the term “syndrome”. Accordingly, the problems experienced by persons with mild TBI are more accurately understood as “postconcussive symptoms” rather than as a “postconcussive syndrome” per se. Using this conceptual framework to understand the sequelae of mild TBI facilitates consideration of each person’s postconcussive symptoms as reflecting dysfunction of the brain areas to which such symptoms are referable. Concurrently, consideration of associated psychological or social (including medicolegal) stressors is required to understand the development and persistence of those symptoms, particularly when those symptoms fail to conform to our current understanding of brain-behavior relationships.

Evaluation and treatment of mild TBI

Evaluation

The complexity and multiplicity of postconcussive symptoms, the subtlety of the neurobiological consequences of TBI, and the inescapability of psychosocial influences on outcome following TBI necessitate an approach to the treatment of persons with mild brain injury that begins with a thorough neuropsychiatric evaluation. Care should be taken to characterize clearly the initial injury using the criteria offered by the ACRM described in the preceding sections of this review: establishing whether an event that is characterized fairly as a mild TBI indeed occurred is the first and most critical step in the evaluation of persons with possible postconcussive symptoms. It is sometimes difficult to obtain reliable information regarding the occurrence and duration of loss of consciousness, PTA, alteration of mental status, and focal neurologic deficits from the individual with a possible TBI. Individuals will often misinterpret a period of PTA as a loss of consciousness: if events cannot be remembered, the erroneous assumption that one was unconsciousness during those events may be made. Similarly, the very nature of an alteration in consciousness may preclude accurate self-observation during that period, thereby rendering any history obtained from the individual him- or herself regarding the immediate injury period as difficult-to-interpret at best. Accordingly, the ACRM criteria should be used to probe for the possible occurrence of an injury that produced alterations in cerebral function

sufficient to meet the threshold of mild TBI; positive responses should prompt efforts to obtain collateral information from medical records and other reliable information sources regarding the initial injury, particularly if the clinician will be required to participate in the medicolegal matters in which persons with TBI are sometimes involved.

It is particularly important to define clearly the patient's postconcussive symptoms, as well as the course and resolution (or lack thereof) of those symptoms since the time of injury. As noted in the preceding section of this article, postconcussive symptoms often do not conform in either presentation or resolution to the traditional concept of a syndrome. Nonetheless, many clinicians will attempt to make a diagnosis of a postconcussive syndrome using either the DSM-IV or ICD-10 definitions of this condition. Unfortunately, these are not equivalent definitions (Boake et al 2004), with the ICD-10 criteria for this condition being more liberal than those of the DSM-IV by virtue of the ICD-10's lack of a criterion defining the clinical significance of the postconcussive symptoms. It is also worth noting that the DSM-IV states explicitly that its proposed criteria for "postconcussional disorder" are not intended for application to clinical practice but are instead intended to serve only as a proposed set of criteria for further study. Accordingly, it is our position that clinicians will serve better the persons with TBI for whom they provide care by emphasizing a thorough evaluation of specific postconcussive symptoms rather than by attempting to establish whether or not those symptoms and related disability conform to either the DSM-IV or ICD-10 definitions of postconcussional disorder or postconcussive syndrome, respectively.

The clinical presentation is expected to include at least some elements of the classic constellation of postconcussive symptoms and gradual, although sometimes incomplete, symptomatic improvement over time. In the immediate post-injury period, 80%–100% of persons with mild brain injury will describe one or more symptoms reasonably attributable to their injury, most commonly including headache, slowed thinking, and/or impaired attention and memory (Levin, Mattis, et al 1987; Stuss 1995; Dikmen et al 2001; McMillan and Herbert 2004). About 50% of persons with mild TBI demonstrate gradual, although sometimes incomplete, recovery by three months post-injury (Dikmen et al 1986). About 40% of persons with mild TBI experience the persistence of postconcussive symptoms three to six months post-injury (Ingebrigtsen et al 1998; McCullagh et al 2001), and 1%–20% continue to experience one or more

postconcussive symptoms thereafter (Leininger et al 1990; Levin and Eisenberg 1991; Beetar et al 1996; Deb et al 1999). Physical or cognitive symptoms with initial onset weeks or months after TBI, symptoms that progressively worsen over the months or years after injury, or symptoms that are grossly out of proportion to the injury history and objective (ie, neuropsychological, neuroimaging, or electrophysiologic) testing may require explanations other than TBI. Such histories should prompt consideration of other potential contributors to the patient's presentation, including other neurological conditions, psychiatric disturbances (ie, depression, anxiety, post-traumatic stress disorder, pain, sleep disturbance), adverse medication effects, psychosocial or medicolegal stressors, or some combination of these.

Clarifying pre-injury developmental, medical, neurological, psychiatric, substance, academic, and employment histories is essential, particularly as regards conditions that may influence recovery following mild TBI. Prior TBI may be present in as many as 30% of these individuals (Rimel et al 1981) and the presence of such may also offer explanation for relatively poor recovery following an apparently mild TBI. Substance abuse and/or intoxication at the time of injury is important to note, as the association of substance abuse with brain injury and relatively poor psychological and functional outcome after TBI is well described (Bigler et al 1996; Kolakowsky-Hayner et al 1999; Bombardier et al 2002; MacMillan et al 2002; Ashman et al 2004). Depression, anxiety disorders, post-traumatic stress disorder, and sleep disturbances may develop after TBI, and premorbid disorders of these types may be exacerbated by mild TBI. In the context of TBI, these disorders may present atypically with respect to conventional symptom clusters and diagnostic boundaries. Consequently, clinicians should be flexible with respect to the diagnosis and treatment of these conditions in the brain-injured patient. Conversely, psychiatric and substance disorders, cranial and cervical trauma, and other primary neurological and somatic disorders may produce symptoms that overlap with those commonly produced by TBI. As noted earlier, interpreting these symptoms accurately requires that clinicians ascertain the occurrence of a definable TBI and assess their relationship to and consistency with the natural course of symptom development and resolution following TBI.

A thorough physical and neuropsychiatric examination is an essential part of the evaluation of the brain-injured individual. The physical examination should include a detailed neurological examination, including assessment for

primitive reflexes (“frontal release signs”) and other neurological “soft-signs” that may reflect subtle neurological dysfunction not evidenced by routine (“elemental”) neurological examination. Neuropsychiatric assessment should include a thorough general mental status examination as well as a detailed cognitive examination; the latter examination should emphasize timed tests of attention and information processing, memory encoding and retrieval, and executive function. Clinicians should be aware that the Mini-Mental State Examination (MMSE) (Folstein et al 1975) is not generally regarded by brain injury specialists as an adequate tool with which to screen for the types of cognitive impairment produced by mild TBI. The anatomy of TBI, whether of mild or greater severity, predicts greater impairments in frontally-mediated cognitive functions rather than in the medial temporal and bitemporoparietal cognitive functions assessed by the MMSE (Brooks et al 1999). Accordingly, bedside measures with greater sensitivity to deficits in frontally-mediated cognition such as the Frontal Assessment Battery (Dubois et al 2000) or the Behavioral Dyscontrol Scale (Kaye et al 1990; Grigsby et al 1992) may improve detection of functionally-relevant cognitive impairments among persons with mild TBI (Leahy et al 2003; Suchy et al 2003). Clinicians unfamiliar with the administration and interpretation of bedside measures that assess frontally-mediated cognition should consider referring the person with brain injury and cognitive symptoms for formal neuropsychological testing. Quantification of postconcussive symptoms using standardized scales developed for this purpose (Levin, High, et al 1987; Crawford et al 1996; Kreutzer et al 1999) also may guide usefully the diagnosis and treatment of persons with postconcussive symptoms.

Neuroimaging and electrophysiological assessments may also provide corroborative evidence of injury type and severity. The results of such neuroimaging and neurodiagnostic studies must be interpreted in light of their sensitivity to the effects of mild TBI and with respect to the timing of their acquisition in relation to the injury. These studies are rarely diagnostic, but may provide useful evidence in support of a history of traumatic brain injury, and may offer explanation for the specific types of postconcussive symptoms experienced by a person with mild TBI (Smith et al 1995; Hofman et al 2001; Davalos and Bennett 2002; Hillary et al 2002). However, advanced neuroimaging and neurodiagnostic studies are not recommended for routine use in the evaluation of persons with mild TBI. Instead, their use should be reserved for the

evaluation of persons with TBI in whom standard clinical evaluations have not yielded adequate explanation for presenting symptoms. Whether conventional or advanced neuroimaging and neurodiagnostic methods are employed, clinicians should remain mindful that the absence of evidence of TBI on conventional neuroimaging does not constitute evidence of an absence of TBI. If the history and clinical presentation support a diagnosis of mild TBI and the onset and pattern of postconcussive symptoms is, in the judgment of the evaluating physician, consistent with that diagnosis then the lack of neuroimaging and/or electrophysiologic abnormalities may be understood as reflecting the relative insensitivity of such studies to the types of abnormalities produced by mild TBI.

Clinicians are encouraged to undertake a thorough neuropsychiatric evaluation of the sort described above before establishing a diagnosis of mild TBI, and are particularly encouraged to do so before excluding such a diagnosis from consideration. It is important to reiterate that while somatization and malingering do occur among persons with mild TBI (Slick et al 1994; Paniak et al 2002; Langeluddecke and Lucas 2003), these are relatively uncommon, if not frankly rare, conditions even in the context of medicolegal proceedings (Iverson and Binder 2000). The initiation of compensation claims should not be misunderstood as arising solely from the pursuit of primary or secondary gains (eg, money, role change, or other external incentives). Such claims more often reflect the occurrence and persistence of postconcussive symptoms and related disabilities arising as a result of TBI, although they may be complicated by injury-related exacerbation of pre-injury psychological or neuropsychiatric problems, the pursuit of primary or secondary gains, or a complex interaction between these factors (Binder 1986; Feinstein et al 2001). Without question, malingering and somatization should not be the first or the default diagnoses when individuals present with difficult-to-diagnose symptoms following TBI and/or are involved in litigation related to their injuries. Attribution of symptoms to malingering should be avoided unless: (1) the patient demonstrates incontrovertible evidence of such on multiple neuropsychological measures designed for the specific identification of this problem (ie, demonstrates a pattern of response bias that can only be explained as an attempt to “fake bad” on cognitive testing); and (2) there is clear demonstration of function in everyday life that is inconsistent with reported symptoms and/or disabilities and that cannot be accounted for by other neuropsychiatric factors.

Treatment

Treatment should be predicated upon the type of thorough neuropsychiatric evaluation described in the preceding section. The presence of comorbid psychiatric problems such as a major depressive episode, anxiety disorders (including post-traumatic stress disorder), or substance abuse – whether or not these are regarded as etiologically related to the mild TBI – should be treated aggressively using appropriate psychotherapeutic and pharmacologic interventions. It is important to be aware that even when psychiatric, neurological (eg, seizure), or other bodily injury issues (eg, pain) are present, one cannot assume that all of the individual's postconcussive symptoms are fully or best accounted for by these conditions. Therefore, assessment for residual (or uncoupled) postconcussive symptoms should be ongoing during treatment of post-traumatic psychiatric, neurological, and physical conditions. The persistence of some postconcussive symptoms despite the effective treatment for others does not necessarily suggest treatment failure, but may instead indicate the need for additional therapies targeting specific residual postconcussive symptoms.

Education early after a mild TBI includes the symptoms it produces, the usual time course for resolution of these symptoms, and the potential for long-term difficulties, which may decrease the likelihood of developing persistent postconcussive symptoms (Paniak et al 1998; Wade et al 2001). These interventions are most effective when offered not only to the person with mild TBI but also to that person's family, friends, employers, insurers, and/or significant others. Education of this sort is particularly important in the context of mild TBI: the often apparently "mild" mechanism of injury and the affected person's otherwise healthy appearance may lead some patients and families to minimize or disregard entirely the relationship between the injury, subsequent symptoms, and functional impairments. The clinician should offer validation of the person's experience of symptoms, regardless of their cause, without fostering illness behaviors. This validation is best coupled with the development of individualized and realistic goals for return to major activities and employment. The development of such goals should involve key stakeholders in the brain-injured person's life (eg, patient, significant others, employers, payors), and recovery goals should not be offered in a proscriptive, "one size fits all" manner.

Nonpharmacologic rehabilitative therapies are useful in the treatment of cognitive and physical symptoms following mild TBI. Although cognitive rehabilitation is a subject of

some controversy, the American Congress of Rehabilitation Medicine promulgated guidelines and recommendations for cognitive rehabilitation strategies based on a review of the treatment literature in this area (Cicerone et al 2000). While there are relatively few randomized controlled trials of these treatments in the TBI population, there is evidence suggesting that when properly applied they may be of benefit for the treatment of memory, attention, executive function, and communication deficits among reasonably high-functioning and well motivated persons with TBI.

At present, no medication has received approval from the United States Food and Drug Administration (FDA) for the treatment of any neuropsychiatric consequence of TBI. The lack of FDA approved treatments in this population is, in the opinion of the authors, a reflection of medicoeconomic issues rather than of the science relevant to the development of such treatments. However, given the absence of FDA approved pharmacotherapies for neuropsychiatric problems after TBI, clinicians should be mindful that all treatments for the neuropsychiatric sequelae of TBI must be regarded as "off-label". Where possible, clinicians should predicate the treatments they offer on the published literature specific to the neuropsychiatry of TBI. Unfortunately, randomized, double-blind, placebo-controlled, trials are uncommon in this literature and the vast majority of the treatment literature for the neuropsychiatric sequelae of TBI consists of open-label case series or single case reports (Arciniegas, Topkoff, et al 2000). In the absence of published studies with which to guide treatment, the selection of pharmacologic agents is generally modeled after the approach used to select such agents for patients with cognitive, emotional, or somatic symptoms arising from other neurological or primary psychiatric conditions.

When pharmacologic therapies are used, the indications and need for ongoing prescriptions should be reviewed, and efforts should be made to eliminate those not affording clear benefits or that are potentially worsening postconcussive symptoms. Excepting agents for which there are peer-reviewed publications describing safety, tolerability, and effectiveness for postconcussive symptoms, the use of over-the-counter (OTC), herbal, and other supplemental agents in this population should be discouraged. Many of these may adversely affect cognition (particularly OTC "sleeping pills" containing scopolamine) and may negatively interact with prescribed medications (Wong et al 1998; Spinella and Eaton 2002).

Specific target symptoms should be identified before and reassessed assiduously during treatment, and the use of

standardized assessment tools for this purpose is encouraged. A “start low, go slow” approach is prudent, as persons with TBI are particularly susceptible to adverse effects from both a variety of commonly used psychotropic medications and from rapid dose escalation. Nonetheless, it is important to note that some persons with neuropsychiatric problems following TBI will require standard therapeutic doses to achieve substantial relief from those problems. Finally, particular attention should be given to side effects and possible drug–drug interactions when prescribing any combination of medications in this population.

Treatment of postconcussive cognitive impairments

Catecholaminergic and cholinergic dysfunction may be involved in the genesis of attention, memory, and executive function impairments after TBI. Consequently, most of the treatments for these problems are used for the purpose of augmenting the function of these neurotransmitter systems. In the acute rehabilitation setting, methylphenidate may improve attention and hasten the rate of functional recovery during the post-acute recovery period after TBI (Kaelin et al 1996; Plenger et al 1996). Arousal and speed of information processing may be also improved by methylphenidate, even where no significant effects are observed on other aspects of attention or motor performance (Whyte et al 1997). Methylphenidate may also reduce mood disturbances occurring in the context of post-TBI cognitive impairments (Gualtieri and Evans 1988), and has been reported to improve post-TBI aggression even in the absence of observable effects on cognition (Speech et al 1993). The duration of benefit from methylphenidate treatment in this population is not clear, but common clinical experience suggests that appropriately treated individuals may sustain one or several of these benefits during years of treatment, and typically do so without the development of tachyphylaxis or dependence to methylphenidate. Importantly, methylphenidate does not appear to reduce seizure threshold in persons with TBI, including those with active seizure disorders (Wroblewski et al 1992). Accordingly, while the possible occurrence of seizures during treatment with methylphenidate should be included in the process of providing informed consent, it should be communicated as an unlikely possibility.

Case reports and case series suggest that dextro-amphetamine (Evans et al 1987), amantadine (Gualtieri et

al 1989; Nickels et al 1994; Kraus and Maki 1997), bromocriptine (McDowell et al 1998), and L-dopa/carbidopa (Lal et al 1988) also may improve arousal, some aspects of attention, and executive function among persons with post-traumatic impairments in these cognitive domains. The latter three of these medications may also reduce the severity of diminished motivation (apathy) following TBI (Lal et al 1988; Van Reekum et al 1995; McDowell et al 1998), and amantadine may also reduce agitation, aggression, and affective lability (Van Reekum et al 1995).

Cholinesterase inhibitors may improve attention and memory deficits produced by TBI, both in the acute (Bogdanovitch et al 1975; Levin et al 1986) and late post-injury periods (Goldberg et al 1982; Cardenas et al 1994; Eames and Sutton 1995). Among the modern cholinesterase inhibitors, donepezil is the only agent for which there are specific reports of use in the TBI population. Several reports (Taverni et al 1998; Whelan et al 2000; Masanic et al 2001; Kaye et al 2003; Morey et al 2003; Walker et al 2004; Zhang et al 2004) suggest that this medication may be of benefit for the treatment of attention and/or memory impairments in both the acute and late periods following TBI, including mild TBI. Whether or not the other presently-available cholinesterase inhibitors (ie, rivastigmine, galantamine) afford similar benefits is not clear, but anecdotal reports suggest that the benefits attendant to these medications is mostly likely a class effect rather than a medication-specific one.

Cytidine 5'-diphosphocholine (CDP-choline or citicoline) is an essential intermediate in the biosynthetic pathway of phospholipids incorporated into cell membranes, and its orally ingested form appears to activate the biosynthesis of structural phospholipids in neuronal membranes, increase cerebral metabolism, and enhance the activity of dopamine, norepinephrine, and acetylcholine in the brain (Secades and Frontera 1995; Dixon et al 1997). In light of these properties, CDP-choline has been studied as a treatment for post-traumatic cognitive impairments. Calatayud et al (1991), in a single-blind randomized study of 216 patients with severe or moderate TBI during the acute post-injury period, observed improvements in motor, cognitive, and psychiatric function during treatment with CDP-choline, and use of the agent was associated with decreased length of stay in the hospital. Levin (1991), in a double blind, placebo-controlled study of 14 patients to evaluate the efficacy of CDP-choline for treating postconcussional symptoms in the first month after mild to moderate TBI, reported reduced severity of postconcussional

symptoms and improved recognition memory for designs during treatment with this agent. Although these findings are encouraging of CDP-choline's abilities to facilitate recovery during the acute post-injury period in persons with TBI, the lack of rigorous FDA scrutiny of the safety, tolerability, and efficacy of this agent preclude recommending routine use of CDP-choline in this population. However, for patients unwilling or unable to take other prescribed medications, CDP-choline may be a "nutritional supplement" that some patients may find acceptable and of modest benefit.

In clinical practice, some patients respond to psychostimulants, some to cholinesterase inhibitors, some to both, and others to neither class of medication. At present, there are no widely available methods of identifying dopaminergic or cholinergic function for the purpose of predicting treatment response. Hence, treatment selection is best made on the basis of the patient's predominant symptoms and/or comorbid neuropsychiatric symptoms or conditions. Stimulants appear to be the first choice for the pharmacologic treatment of impaired attention with or without comorbid hypoarousal, apathy, fatigue, or depressed mood. The cholinesterase inhibitors may be a better first choice when memory impairments are the predominant clinical problem or when there is concern that use of a stimulant may exacerbate other postconcussive symptoms (eg, sleep disturbance). There is no consensus regarding the treatment of cognitive impairments among persons with TBI and substance use disorders, but most clinicians avoid the traditional psychostimulants (ie, methylphenidate, dextroamphetamine) and instead favor the use of agents with a lower potential for abuse or dependency (ie, amantadine, cholinesterase inhibitors). As noted above, CDP-choline may be an alternative treatment strategy when there is concern regarding the potential for complicating other neuropsychiatric symptoms or conditions. However, the lack of regulated production of this medication requires that additional vigilance for both beneficial and adverse effects be maintained when its use is undertaken.

Treatment of postconcussive emotional disturbances

The treatment of emotional disturbances (eg, depression, anxiety, affective lability, irritability) is similar to the treatment of phenotypically similar problems in the non-injured populations. There are no published randomized, double-blind, placebo-controlled trials of any treatment for depression following TBI. However, the available literature

suggests that the selective serotonin reuptake inhibitors (SSRIs) are likely to be both more effective and better tolerated as first-line treatments for depression and/or affective lability in this population. Although all of the SSRIs may be of use for the treatment of depression, anxiety, and/or irritability following TBI, the authors recommend using agents lacking potent antimuscarinic effects and having relatively short half-lives (ie, sertraline, citalopram, escitalopram).

Depression is a common consequence of TBI, with a frequency of 10%–60% in the first year post-injury (Hibbard et al 1998; Dikmen et al 2004; O'Donnell et al 2004) and up to 17% even 3–5 years post-injury (Dikmen et al 2004). Among the published reports describing the use of sertraline, the study of Fann et al (2000) offers the clearest description of treatment-induced improvements in depressive symptoms following mild TBI. In that study, which was a single-blind trial among persons with major depression 3–24 months after a mild traumatic brain injury, sertraline 25–200 mg resulted in marked reductions in depressive symptoms, self-reported postconcussive symptoms, and self-reported symptomatic distress. In a subsequent report, Fann et al (2001) describe sertraline's additional benefits on cognitive performance and perception of cognitive and other postconcussive symptoms among persons whose depressive symptoms responded to this treatment.

Tricyclic antidepressants may be of benefit for postconcussive depressive symptoms, but may not be as effective in this population as in comparably ill individuals with primary depressive disorders (Saran 1985; Varney et al 1987; Dinan and Mobayed 1992; Wroblewski et al 1996). Additionally, tricyclic antidepressants appear to be associated with an increased risk of adverse effects such as seizures when used in the acute post-injury period (Wroblewski et al 1990). Of note, there are at the time of this writing no reports offering support for the use of newer antidepressants such as venlafaxine, bupropion, mirtazapine, or nefazodone in the treatment of depression after TBI. Although anecdotal reports suggest that these agents may be of benefit for the treatment of postconcussive emotional symptoms, their use should be undertaken with caution given the absence of information regarding the safety, tolerability, and effectiveness in this population.

Affective lability is also common among persons with TBI, with a prevalence of approximately 11% in the first year post-injury (Tateno et al 2004). Breen and Goldman (1997) and Muller et al (1999) report reductions in affective lability produced by brain injury during treatment with

paroxetine. Muller et al (1999) also compared the effectiveness of paroxetine with citalopram for the treatment of affective lability after brain injury (stroke or TBI); while both medications were comparably effective, citalopram was better tolerated. Whether or not the relatively more prominent adverse effects of paroxetine are a function of its antimuscarinic effects is unclear, but this differential in adverse effects merits some consideration when considering the use of paroxetine in this population. As is often seen in the treatment of affective lability in other neurological conditions, the response of affective lability due to TBI is often more rapid (ie, days rather than weeks) than that typically observed for post-traumatic depression. When affective lability is a target of pharmacotherapy, the authors recommend as first-line treatments SSRIs with relatively short half-lives and lacking potent antimuscarinic properties.

Although irritability, paroxysmal aggression, and mania may develop after a mild TBI (Hibbard et al 1998), these problems are relatively uncommon consequences of such injuries, and the optimal treatments for these problems are not clear at present. The limited published case literature and expert opinions suggest that anticonvulsant mood stabilizers are preferable to lithium carbonate for the treatment of these problems (Arciniegas, Topkoff, et al 2000), although lithium carbonate may be of benefit in some persons with such symptoms following TBI (Zwil et al 1993). In general, when severe irritability, paroxysmal aggression, and mania are the predominant features of the clinical presentation in a person with TBI we recommend consultation with a neuropsychiatrist, behavioral neurologist, or neurorehabilitation specialist with expertise in the management of these postconcussive symptoms.

Treatment of postconcussive somatic symptoms

Typical postconcussive somatic symptoms include headache, dizziness, pain, seizures, fatigue, visual disturbance, hyposmia, and hyperacusis. A detailed discussion of the evaluation and treatments for postconcussive somatic symptoms is beyond the scope of this review, but a brief discussion of the treatment of the most common postconcussive somatic symptoms in the context of the neuropsychiatric care of persons with TBI are offered here.

Maintaining effective communication between healthcare providers involved in the provision of treatments for such symptoms is essential for the delivery of a coordinated and effective treatment program. When pharmacotherapies are used, clinicians should be mindful

of the lack of clinical data to guide the treatment of postconcussive somatic symptoms. To date, there are no controlled clinical trials for the treatment of headache, sleep disturbance, or fatigue in this population despite the high frequency of these symptoms following TBI. Consequently, the selection of pharmacotherapies for postconcussive somatic symptoms is generally guided by those selected for persons with phenotypically similar but etiologically distinct conditions. Nonpharmacologic therapies should be used where such are feasible and appropriate.

Post-traumatic headache is the most common, and may be the most persistent, post-traumatic somatic symptom (Goldstein 1991; Bell et al 1999; Martelli et al 1999; Ryan and Warden 2003). Although there is considerable debate regarding the classification and treatment of postconcussive headaches (Packard 1999; Zasler 1999), this problem often requires evaluation and treatment in both the acute and late post-injury periods. When present, post-traumatic headache presents a serious confound to the assessment of other postconcussive symptoms, and particularly post-traumatic cognitive impairments (Martelli et al 1999; Nicholson et al 2001). The differential diagnosis of post-traumatic headaches is broad, and includes myofascial pain, cervicodynia, zygapophyseal joint pain, neuritic pain, and craniocervical somatic pain, among other such conditions (Bell et al 1999; Packard 1999). As with most other types of headache, combinations of medication and nonpharmacological interventions are generally required. The phenomenology of post-traumatic headache appears to conform to the diagnostic criteria of the International Headache Society (Packard and Ham 1994, 1997; Packard 2005). Consequently, treatment of post-traumatic migraine or tension headaches generally uses the same set of abortive and prophylactic agents used in the treatment of their idiopathic counterparts. Given the frequency and complexity of post-traumatic headaches and their potential interactive and complicating effects on other postconcussive symptoms, collaboration with a multidisciplinary rehabilitation team including a physiatrist or neurologist with expertise in the evaluation and treatment of postconcussive headaches is strongly encouraged.

Similarly, postconcussive dizziness (Chamelian and Feinstein 2004; Marzo et al 2004), sleep disturbance (Rao and Rollings 2002), and fatigue (Parsons and Ver Beek 1982; Perlis et al 1997), are common, and their occurrence may confound the neuropsychiatric assessment of persons with mild TBI. The use of anticholinergic agents for post-traumatic dizziness is common in clinical practice, but must

be undertaken with vigilance for treatment-emergent cognitive impairment in light of the role of cholinergic deficits in post-traumatic cognitive impairments (Arciniegas 2003). Nonpharmacologic interventions for post-traumatic dizziness may be useful as an alternative to pharmacotherapies (de Kruijk et al 2002), although the effectiveness of such interventions is not fully established.

Treatment of sleep disturbance following TBI is commonly undertaken with trazodone as the first-line pharmacotherapy (Rao and Rollings 2002). Most experts suggest avoiding benzodiazepines for post-traumatic sleep disturbances, where possible, in light of their propensity for reducing arousal, impairing cognition, and exacerbating motor impairments (Bleiberg et al 1993; Buffett-Jerrott and Stewart 2002), and also in light of the small but nontrivial risk of paradoxical agitation associated with their use in neurologically impaired patients (Fouilladieu et al 1985). Behavioral interventions directed at improving sleep hygiene as well as the development of relaxation techniques may also be of use in the treatment of post-traumatic sleep disturbances (Rao and Rollings 2002).

Fatigue may occur independently of other post-traumatic neuropsychiatric disturbances. When treatment of other post-traumatic neuropsychiatric and/or somatic problems does not adequately improve fatigue, specific treatment of this problem may be required. Psychostimulants and amantadine are the most commonly used agents for the treatment of fatigue in persons with TBI, and may be of some benefit toward that end. In our experience, the dose of agents similar to that employed for the treatment of diminished arousal and attention is usually sufficient to treat post-traumatic fatigue. These medications may be of particular benefit in patients with post-traumatic depression in whom fatigue persists despite improvement in mood during treatment with antidepressants.

Modafinil, a medication recently approved for the treatment of excessive daytime somnolence in patients with narcolepsy, also may have a role in treatment of post-TBI fatigue (Elovic 2000). Teitelman (2001) described the use of modafinil among 10 outpatients with nonpenetrating traumatic brain injury and functionally significant excessive daytime sleepiness, and in two patients with somnolence due to sedating psychiatric medications. Doses of modafinil ranged between 100 mg and 400 mg taken once each morning, to which nine of these patients reported improvements in excessive daytime sleepiness. In this open-label case series, Teitelman (2001) also notes that some

patients also reported subjective improvements in attention as well as other cognitive benefits. Although this medication was generally well tolerated, two patients developed increased "emotional instability". Although it is premature to advocate the routine use of modafinil for the treatment of post-traumatic fatigue, this agent may be in some cases be useful for this purpose.

For some persons with TBI, selecting agents whose effects may afford the reduction of several target symptoms may be useful. For example, sleep disturbance, post-traumatic headaches, and chronic cervical (neck) pain might benefit from an anticonvulsant at night, the effects of which may confer some relief from each of these problems, particularly when the patient is also experiencing post-traumatic irritability or aggression. Alternatively, an individual with post-traumatic depression, affective lability, and headache might benefit from treatment with either an SSRI or low-doses of a serotonergically-potent tricyclic antidepressant with relatively limited anticholinergic effects (ie, nortriptyline or desipramine).

To the extent that targeting multiple symptoms with agents affecting multiple symptom domains is feasible and effective, the potentially adverse consequences of polypharmacy in this population may be limited. However, clinicians should bear in mind the issue raised earlier in this paper with respect to uncoupling of postconcussive symptom response to treatment and remain open to carefully employing multiple medications during treatment of postconcussive symptoms. When post-traumatic somatic symptoms such as those described above require treatment, the involvement of a multidisciplinary team, and particularly psychiatrists and/or neurologists with expertise in the evaluation and treatment of these problems, is often necessary and may be highly productive.

Conclusion

Cognitive, emotional, behavioral, and physical impairments are common sequelae of mild TBI and may in a nontrivial minority of persons persist into the late period following injury. Typical postconcussive symptoms include headache, dizziness, and visual disturbances; attention, memory, and other cognitive impairments; irritability, anxiety, depression, and other emotional disturbances; and behavioral problems such as apathy or impulsivity. The evaluation of postconcussive symptoms requires an understanding of the multiple factors relevant to the production and maintenance of symptoms following trauma to the brain. Despite the

skepticism particularly common to discussion of post-concussive symptoms in medicolegal contexts, recent studies suggest that the neurobiological effects of TBI are not trivial and may produce dysfunction in one or more areas of the central nervous system. The characterization of these symptoms as a postconcussive syndrome is dubious, and in the opinion of the authors it is more accurate to describe these symptoms as frequently co-occurring postconcussive symptoms rather than as a postconcussive syndrome.

Treatment of postconcussive symptoms necessitates a thorough and accurate assessment of the factors involved in the genesis and maintenance of the symptoms. Education, nonpharmacologic interventions, and some symptom-targeted pharmacotherapies, as well as encouraging patience during the time required for spontaneous recovery after mild TBI may afford substantial reductions in postconcussive symptoms and improvements in everyday function. An individualized, flexible, and multi-faceted treatment plan involving the principles described herein—best described as a neurobiopsychosocial approach—appears to offer the patient with postconcussive symptoms following mild TBI the best hope for symptomatic and functional recovery.

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