

Chapter 44

TRAUMATIC BRAIN INJURY

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INTRODUCTION

Traumatic brain injury (TBI) has been called the signature injury of modern warfare. A Rand Corporation (Arlington, VA) survey published in 2008 estimated that as many as 19.5% of those who deployed to Iraq or Afghanistan sustained a TBI.¹ The Defense Centers of Excellence (DCoE) for Psychological Health and Traumatic Brain Injury estimate that 1.7 million people a year suffer a TBI. The DCoE also reports that in 2013 almost 25,000 military members were diagnosed with a new TBI.² Importantly, TBI is not an injury pattern that will stop as US forces withdraw from Afghanistan. New TBI cases occur frequently in military training or sports and recreational activities. Moreover, exist-

ing TBI cases can cause chronic difficulties and disabilities. Long-term effects of TBI include pathological changes closely related to neurodegenerative disease, frank dementia, and long-term inflammatory changes throughout the brain that might result in even more disease processes.³⁻⁵ The frequency and significance of TBI have resulted in tremendous attention from the scientific community, as well as the lay public. A PubMed search of the term *traumatic brain injury* elicits more than 65,000 results. A similar Internet search produces almost 20 million hits. TBI is an increasingly diagnosed disorder with potentially long-term societal consequences.

TRAUMATIC BRAIN INJURY DEFINITION

Providing a proper and consistent definition of TBI remains challenging. Almost every organization has its own definition and, in many cases, has already revised its original definition at least once. Even the *International Classification of Diseases*, Tenth Revision (ICD-10) struggles to define the condition and lists dozens of ways to code the disorder.⁶

Standard nomenclature is no better, often using terms such as concussion, brain injury, head injury, and diffuse axonal injury synonymously. For this chapter, we will use the definition adopted by Military Health Affairs in 2007.²

The definition uses the following criteria: an event, an alteration or loss of consciousness, and a sign or

symptom.

The list of signs or symptoms is lengthy and primarily neurosensory in nature, but includes dizziness, sensory deficits (hearing or visual loss), headaches, memory loss, and a variety of other disorders. Overall, this definition is the most functional and works well in most cases. In summary, an individual experiences an event, feels the event, and suffers consequences from the event. Although the authors will use this definition to frame this chapter, the ongoing variability in defining TBI continues to impede progress in outcome reporting, describes research results, and reviews epidemiological determinations in particular.

TRAUMATIC BRAIN INJURY CAUSES

There are a variety of TBI causes. The Centers for Disease Control and Prevention (Atlanta, Georgia) ranks the causes of TBI in the following order:

- falls,
- motor vehicle events,
- struck by or striking an object, and
- assaults.⁷

Although this epidemiological examination is accurate, it centers on the incident involved in creating the TBI rather than the mechanism. Ultimately, TBI is caused by one of three basic etiologies:

1. *blunt head trauma*—where an outside object strikes the head or the head strikes an outside

object,

2. *blast injury*—where a blast pressure wave passes through the brain, and
3. *whiplash*—where the brain is shaken within the head.

With regard to the military, virtually every operational and training event, as well as most recreational activities, present the risk of TBI. When examining young individuals outside of the military, motor vehicle accidents and sports injuries remain the dominant causes of TBI. In contrast, blast injury is the most common cause in the military. Other common causes of TBI in military populations include hitting the head in an operational environment, motor vehicle accidents, and sports injuries.

CLASSES OF TRAUMATIC BRAIN INJURY

Much like the overall definition, a variety of TBI classification systems exist. The most commonly used scale divides TBI into three categories: (1) mild, (2) moderate, and (3) severe. Those definitions rely on the initial Glasgow Coma Scale score and the subsequent hospital events as described in Table 44-1. The symptoms and management of moderate and severe TBI differ dramatically when compared to those associated with mild TBI (mTBI). Because of the management and treatment differences and because mTBI is significantly more common, the remainder of this chapter focuses primarily on mTBI. In the civilian sector, the Centers for Disease Control and Prevention reports that mTBI accounts for 75% of all TBIs.⁸ In the military, the relative incidence of mTBI, as compared to moderate and severe TBI, is even greater and accounts for approximately 90% of all cases. mTBI remains the most common diagnosis in Iraq following blast exposure.⁹

TABLE 44-1

TRAUMATIC BRAIN INJURY CLASSIFICATION SYSTEM

Type of Traumatic Brain Injury	Criteria
Mild	GCS score of >12 No CT abnormalities No operative interventions Hospital stay <48 hours (for the head injury)
Moderate	GCS score of 9–12 alone OR GCS score of >9 with CT abnormalities or operative interventions Hospital stay >48 hours (from the head injury)
Severe	GCS score of <9

CT: computed tomography; GCS: Glasgow Coma Scale

SYMPTOMS OF TRAUMATIC BRAIN INJURY

The most common symptoms of mTBI are neurosensory. In general, patients with mTBI report some or all of the following complaints: dizziness, headache, hearing loss, tinnitus, short-term memory loss, sleep difficulty, and a variety of eye complaints. Hoffer and colleagues¹⁰ studied a set of these symptoms divided into time epochs following injury: *acute* (<72 hours postinjury), *subacute* (7–30 days postinjury), and *chronic* (>30 days postinjury). This group found that dizziness was the most common symptom at every time point, followed closely by headache, with both occurring in >75% of chronic patients. Virtually all (98%) individuals reported dizziness when seen acutely after blast exposure.

Dizziness is one of the dominant symptoms of mTBI and is observed in >80% of all individuals with blast exposure.^{10–13} A number of groups have worked to develop an objective assessment of dizziness after mTBI. Scherer and colleagues^{12,14} examined vestibuloocular reflex (VOR) responses in a variety of mTBI patients and found them to be significantly more impaired when compared against normal controls. Akin and Murnane¹⁵ examined otolithic abnormalities in a group of individuals with mTBI and found that 84% of mTBI patients had an abnormality. A number of groups examined

incidence by mechanism and found that the rate of vestibular disorders were significant, independent of the mechanism of injury.^{16–18}

Headaches, along with dizziness, are the most common symptom associated with mTBI. They are classified descriptively as secondary headaches by the International Headache Society (IHS; London, UK). An *acute posttraumatic headache* (IHS 5.1.2; ICD-10 G44.880) begins within 7 days of injury. A diagnosis of *chronic posttraumatic headache* (IHS 5.2.2; ICD-10 G44.31) ensues if the acute headache persists for >3 months. Published articles summarize the extensive examination of the prevalence of these diagnoses in military personnel serving in Southwest Asia and in civilian populations.^{19–27} The reported symptoms fall along a continuum between tension-type headache and migraine, and may vary over time.^{22,28}

The spectrum of tension-type and migraine-type posttraumatic headaches and polysensory symptoms in blast-related mTBI likely results from a sequence of long-term responses to acute injury in brain pathways that have been implicated in migraines, including vestibular migraine. Recently published reviews provide a detailed discussion of the migraine mechanisms and likely loci of action of therapeutic agents.^{29–31}

Similar mechanisms have been implicated in the tension-type headache with chronic tension-type and migraine headaches displaying similar therapeutic responses.^{28,32–35}

Basic and clinical research indicate that blast-related mTBI should be considered a chronic consequence of intracranial wound healing and plastic neuronal responses.³⁶ In animal models, low-level blast-wave exposure produces intracranial microvascular injury to cerebral veins and the inner ear, which includes microthrombi, microhemorrhage, increased blood–brain barrier permeability, and altered brain anisotropy.^{37–51} The ensuing wound healing, repair, and inflammatory responses can persist into a chronic timeframe. Even very low-level exposures can produce acute changes in regional brain ganglioside and ceramide turnover, resulting in short- to intermediate-term changes in neuronal membrane composition.⁵² Identifying these small changes clinically with imaging methods remains a challenge.

A diagram of the sequence of cellular events that likely contributes to chronic posttraumatic headache is shown in Figure 44-1. As in other soft tissues, animal data indicate that shockwave exposure generates microvascular effects that include microthrombus formation in small cerebral blood vessels and injury

to small veins (including bridging veins) in both the subarachnoid and subdural spaces. The effects on the latter veins may include local plasma extravasation and local ruptures that seal rapidly, leaving very small hemorrhages. These injuries recruit short- and long-term wound healing processes, indicated by sequences of modified expression of proinflammatory, immune response, and vascular remodeling mRNAs to facilitate processes that include lymphocyte docking, transmural lymphocyte migration, microglial and macrophage responses, and local angiogenesis and angiostasis.

Consequences of subarachnoid hemorrhage include delayed thromboembolism, transient ischemia, vasospasm, brain oxidative stress, and microcirculatory dysfunction.^{53–55} Blood in the inner ear perilymph, which is confluent with cerebrospinal fluid, can have analogous effects that compromise vestibular and auditory function.⁵⁶ Individual outcomes reflect a complex interaction between these primary effects and the downstream, intrinsic responses to shock-wave exposure. Mechanisms that can contribute to a deleterious outcome include delayed neuronal insult and apoptotic cell death. Mechanisms that mitigate the outcome include cellular repair and plasticity. The practice of precision medicine for chronic headache after blast-related mTBI hinges on developing the

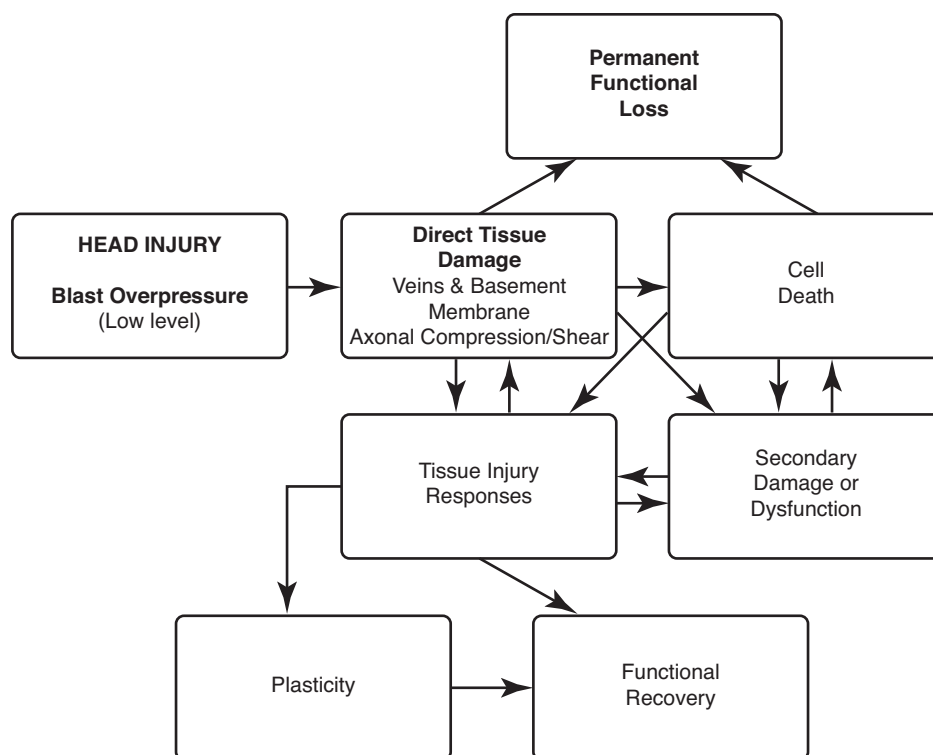


Figure 44-1. Diagram of the sequence of cellular events that likely contribute to chronic posttraumatic headache.

capabilities to identify patient trajectories and apply interventions strategically during the evolution of the chronic disorder.⁵⁷

Current models for migraine generation center on a medullopontine, midbrain, and thalamocortical “migraine circuit” that processes multisensory information and produces headache, premonitory symptoms, sensory hypersensitivity, allodynia, and comorbid anxiety elicited by internal and external triggers.^{29–31} The same structures are implicated in central processes for tension-type headaches, but with the additional peripheral myofacial and muscular contributions.³² Because this central migraine/headache circuit includes interconnected trigeminal nociceptive, vestibular, visceral, auditory, and visual pathway components, external headache trigger circuits include visual, auditory, somatosensory, and chemical (olfactory and gustatory) sensory pathways. Internal triggers include hormonal fluctuations and stress from environmental factors or demands with negative perception.⁵⁸ The internal and external trigger pathways also involve structures such as the hypothalamus, amygdala, locus coeruleus, and dorsal raphe nucleus that show high expression of stress-response receptors and may also show altered functional magnetic resonance imaging activity associated with migraines.^{59–64} These intrinsic components may contribute to stress interactions with development of the signs and symptoms along the spectrum from migraines to tension-type headaches.^{32,58}

Vestibular migraine is an example of multisensory, mood, and anxiety effects that can be mediated by central migraine headache circuits in individuals with posttraumatic headache.³⁰ Vascular and neuronal consequences of acute focal hemorrhage from small veins can elicit headache and audiovestibular symptoms, both in the inner ear and the central nervous system.^{53–55} Cellular responses can produce chronic effects (see Figure 44-1) in the central migraine circuits and pathways mediating balance function. The comorbidity between balance dysfunction, headache, anxiety, and mood disorders may also reflect these longer term responses and their sequential motor, perceptual, and behavioral consequences.^{29,65–69} These considerations are important in the rehabilitation process for vestibular dysfunction (including mTBI-related balance dysfunction), which follows sequential interventions to improve head, neck, trunk, and whole-body stabilization and locomotion.⁷⁰ Impaired function at each stage can have consequences that affect the perception of balance stability, limit activities of daily life, and contribute to anxiety and mood disorders.

The remaining neurosensory sequelae of mTBI can vary depending on the mechanism and related circumstances of the injury (distance from blast, site

of blow to the head, etc). The reported frequency of hearing loss associated with mTBI is 35% to 80%.^{71–76} Most conductive hearing loss is secondary to damage to the tympanic membrane (TM) alone. Although not completely clear, it appears that approximately 15% to 20% of individuals with mTBI experience a TM perforation. Such perforations typically cause a mild conductive hearing loss that resolves following TM repair.⁷⁶ An unknown, but very small, percentage of individuals experience concomitant damage to middle ear bones from blast injuries that produces more significant hearing loss. Surgery can also correct this hearing loss.

The majority of individuals with mTBI-associated hearing loss experience sensorineural hearing loss. The exact percentage of individuals with SNHL is difficult to determine because many of these individuals have a preexisting, noise-induced hearing loss prior to the mTBI injury. Tinnitus is often coincident with SNHL, but can also occur without any associated hearing loss. The frequency of tinnitus secondary to mTBI has been estimated to be 50% to 75%.^{71–73} As with SNHL, tinnitus rates secondary to mTBI are difficult to determine because of the high incidence in the military population that predates the mTBI. An additional hearing disorder has been recently recognized in the mTBI population: central auditory process disorder (CAPD). It is characterized by the inability to comprehend the meaning of strings of words and can often be present in an individual with normal hearing. The increased frequency of this disorder in mTBI patients has been recognized, but the exact percentage remains difficult to determine. This is because no precise testing paradigm for determining the presence of a CAPD has yet to be clearly established. In addition, the coincident short-term memory loss commonly seen in these patients makes distinguishing a CAPD from memory loss a difficult task.

Cognitive deficits associated with more severe TBI commonly occurs. It is now understood that mTBI can also be associated with a higher incidence of cognitive difficulties.^{77,78} The issue of cognitive and memory deficits after battlefield mTBI is confounded by a variety of factors, including the necessity to wait a period of time for certain cognitive testing to be accurate, the comorbidity of posttraumatic stress disorder in many of these patients, and the need to treat other injuries prior to addressing cognitive rehabilitation therapy. However, Hoffer et al¹¹ demonstrated definitive cognitive deficits in soldiers with mTBI seen within the first 72 hours of a blast. This work clearly demonstrates a direct effect of blast-related mTBI on cognitive function.

BATTLEFIELD ASSESSMENT

One of the most important mTBI-related issues is diagnosis in an austere environment. The diagnosis of moderate and severe TBI is rarely subtle, and requires immediate evacuation to a higher level of care. Similarly, the diagnosis of mTBI can be easily made in tertiary care facilities, as long as those facilities recognize the presence of the entity. The challenge with mTBI is diagnosing the disorder in the theater of operations. There are several key requirements that accompany this challenge:

- individuals with tech-level/corpsman-level training must possess the capability to perform the first-level testing and diagnosis,
- first-level testing cannot rely on large equipment operable only at a fixed base with special personnel,
- first-level testing has to distinguish patients who need evacuation to higher care from

those who can be treated locally, and

- first-level testing must provide clear answers and minimize ambiguity as much as possible.

The military has a current tool kit that attempts to meet these aims. Refer to the DCoE web page that documents these procedures and any updates subsequently adopted.⁷⁹ Additionally, studies from theater have suggested that a relatively limited tool kit can provide an accurate diagnosis of mTBI in many individuals and can also assess return-to-duty status.¹¹

This tool kit consists of:

- a test of the vestibuloocular reflex using either head thrust or dynamic visual acuity,
- a simple gait analysis (like the functional gait assessment tool), and
- a simple cognitive test (Trail Making Test A and Trail Making Test B).

A TREATMENT AT THE FRONT AND BEYOND

A mounting body of evidence suggests that the early management of mTBI may yield better outcomes.¹¹ Until very recently, the mainstay of early management consisted of symptom control and bedrest. Although these two measures are effective, they do not go far enough. Just as too much activity after mTBI can be detrimental, too little activity can impair the pace of response. Measured rehabilitation is effective even in the acute phase.¹¹ Perhaps the most promising technique for early management is the use of medicines designed to speed recovery. Although there are many agents postulated to provide benefit, only one agent has been shown to be efficacious. In a double-blind, placebo-controlled trial of mTBI patients in an active combat zone, *N*-acetylcysteine (NAC) was effective at producing 7-day symptom resolution.¹¹ Not only was NAC significantly more effective than placebo on resolving medical symptoms, but it also had a substantial impact on cognitive performance. Work is now under way to examine the longer term benefits of acute NAC treatment and the use of NAC in a variety of other mechanism of head injury.

Long-term management of mTBI involves addressing the sequelae of the injury. The management of hearing loss and balance disorders seen after mTBI

is highlighted elsewhere in this chapter. Management techniques are more beneficial if headache can be controlled. Headache management in mTBI is difficult because of the ambiguity in the literature regarding how to best characterize and treat these headaches. Most investigators have agreed that migraine management strategies may offer the best control for posttraumatic headache.⁸⁰ Unfortunately, these strategies are not universally successful, and it is not uncommon for individuals to undergo trials on a number of agents for headache control.⁸¹ Headache management is made more difficult by the fact that many mTBI patients are on other medicines to treat other mTBI sequelae or comorbid posttraumatic stress disorder.

The symptoms of mTBI change over time, and management may involve deploying the specialties of a variety of different medical and rehabilitation services. Describing this longer term management in detail is beyond the scope of this chapter, but this treatment is critical. Recent evidence suggests that, over time, individuals with mTBI may begin to show neurodegenerative changes.³⁻⁸² Work to prevent these long-term sequelae is essential.

SUMMARY

The last several years have contributed a great deal to the collective understanding of mTBI. In the past, most TBI work focused on moderate and severe cases. With the increased frequency of and attention to mTBI

(both from the military and from professional sports), we have gained a better understanding of the significance, diagnosis, and management of this disorder. As such, there were several distinct lessons learned:

- *mTBI is significant*—The disorder represents the most common injury seen in modern warfare and likely represents one of the most common health issues for our segment of the population.
- *mTBI has multiple sequelae that cross specialties*—Although attention in the past has focused on headaches and memory issues, balance disorders remain among the most common sequelae of mTBI. Other sequelae require the expertise of a variety of medical and rehabilitation disciplines.
- *mTBI requires early treatment*—Research has clearly demonstrated that early management impacts outcomes favorably. Moreover, work has begun to identify the most important and effective early management techniques. A medical countermeasure for acute mTBI has proven beneficial and should be implemented.
- *Long-term management remains complex and requires a significant commitment of personnel and resources*—mTBI does not go away with time. In fact, it can get worse and progress to more serious neurodegenerative conditions. Aggressive management from the acute phase through the chronic phase is critical. As such, the management of war-related mTBI will continue to be an issue for the next several decades.

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