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Traumatic brain injury research opportunities: Results of Department of Veterans Affairs Consensus Conference

Traumatic brain injury (TBI) is one of the foremost medical problems resulting from the wars in Afghanistan and Iraq. In 2006, 13,969 active-duty servicemen and servicewomen with incident TBI were treated in the military medical system; of those, 7.6 percent were hospitalized [1]. While the consequences of moderate to severe TBI capture public and media attention, the majority of brain injuries are mild. Mild TBI (mTBI) represents 85 to 90 percent of civilians with TBI and a large majority with war-related TBI [2–5]. Our current ability to accurately diagnose war-related mTBI is greatly challenged because much of our knowledge of this injury is based on experience accrued from civilian patients, even though the conditions under which war-related injuries occur differ vastly from those of civilian injuries. TBIs of civilian patients typically result from falls or motor-vehicle or sports-related incidents, whereas war-related TBIs are more often sustained under emotionally traumatic circumstances. Furthermore, since a major portion of current war-related injuries result from blast exposure, inherently different mechanical processes are involved.

Although the definition of mTBI varies, it typically refers to injuries that are associated with loss or alteration of consciousness for <30 minutes, posttraumatic amnesia for <24 hours, and an acute Glasgow Coma Score of 13–15 [6]. The most frequent complaints include headaches, fatigue, irritability, and attention and memory problems. Based on civilian experience, the belief is that the majority of otherwise healthy young individuals fully recover from a single uncomplicated mTBI within anywhere from several days to, at most, several months. However, a minority of patients with mTBI experience persistent problems. Diagnosing TBI may be difficult when patients arrive months after the initial injury and present with symptoms that are concordant with traumatic exposure.

Postconcussive syndrome (PCS) is diagnosed when patients with mTBI present with ongoing symptomatic complaints. Those who experience multiple TBIs are more likely to have long-lasting symptoms [7]. PCS can occur with any level of head injury severity. According to recent reports, U.S. soldiers returning from Iraq have a high rate of coexistence of mTBI-related complaints and posttraumatic stress disorder (PTSD) [8]. PTSD is an anxiety disorder that may develop after exposure to a traumatic event in which grave harm occurred or was threatened [9]. PCS and PTSD have many symptoms in common, but a hallmark of PTSD is reexperiencing the traumatic event. As expected, PTSD is more prevalent than TBI in combat veterans.

An important issue that complicates differentiating traumatic stress and TBI is the retrospective diagnosis of war-related mTBI. The diagnosis is

difficult because it requires documenting the history of an injury that would typically have involved alteration of consciousness or amnesia for events before, during, or after injury in the midst of a battle. Despite their overlapping symptoms, PTSD and mTBI may be two distinct disease entities with differential responses to various treatment approaches.

Patients who survive severe TBI commonly suffer cognitive impairments (e.g., memory, executive functions, and processing speed), language difficulties, emotional problems, sensory-motor losses, posttraumatic epilepsy, and a variety of other impairments and disabilities. Unlike the symptoms of a majority of patients with mTBI, these problems, in spite of some initial improvement, may persist and become chronic. These chronic cognitive, physical, and emotional impairments often interfere with individuals' abilities to function independently and resume their prior family, workplace, and social roles and responsibilities.

Currently, no well-validated therapies exist to treat war-related TBI other than existing TBI rehabilitation programs and careful supportive care. To target and develop appropriate therapies, one must understand the underlying biological mechanisms. Recent research has suggested that dysfunction of the medial prefrontal cortex, hippocampus, or amygdala may be associated with PTSD [10–11]. The question of whether TBI induces subtle structural lesions in the emotional-regulatory pathway that may manifest themselves as PTSD remains to be answered. Equally important to advances in basic science has been the gradual change in the medical culture toward greater awareness of the psychosocial aspects of war-related injuries such as TBI. Rather than simply focusing on physical impairment, the medical community and the public are now more aware of the psychosocial consequences of the injuries for the individuals, their families, and community.

CONSENSUS PROCESS

Given this background, the Office of Research and Development of the U.S. Department of Veterans Affairs (VA) convened a conference entitled "Research to Improve the Lives of Veterans: Approaches to Traumatic Brain Injury; Screening, Treatment, Management, and Rehabilitation" in Arlington, Virginia, from April 30 to May 2, 2008. This conference determined relevant research questions that would generate the knowledge needed to advance the understanding and treatment of TBI. First, a planning committee comprising 17 subject matter experts outlined the content of the conference. An interdisciplinary group of 100 researchers, clinicians, and administrators from the VA, Department of Defense (DOD), National Institutes of Health (NIH), Defense and Veterans Brain Injury Center (DVBIC), and academia participated in the conference. Extensive literature reviews were also prepared and disseminated to conference participants before the meeting and are published in this issue. Participants self-selected one of six work groups. Content topics were basic science, neuroimaging, sensory deficits, comorbidities, rehabilitation and community reintegration, and care management. For most of the first day, each work group spent time developing consensus recommendations for their assigned topic based on the literature reviews provided and the input of the members of the group. Each work group had a facilitator and recorder. At the end of the day, presentations were prepared for the plenary session. On the second day, each work-group chair presented the recommendations of the work group with input and discussion by the panel and all conference participants. After the presentations, work-group recommendations were modified based on the input provided.

The recommendations of the work groups were grouped into three main categories: (1) diagnosing TBI, (2) understanding the short- and long-term TBI effects, and (3) understanding existing and developing new treatment approaches. The remainder of this editorial describes key issues that conference participants raised and the research questions that resulted from the conference (**Figure**).

Diagnosing TBI

Brain trauma results in both primary and secondary injury. The primary injury may include contusion, intracerebral hematoma, and diffuse axonal injury (DAI). The secondary injuries result from hemodynamic and metabolic disturbances. In the

1. Diagnosing TBI.

a. Screening.

- What are the best approaches and tools for documentation of acute injury characteristics, including biomechanical parameters of the injury-causing event, loss of consciousness, and posttrauma amnesia?
- What are the most effective approaches and tools for use of predeployment baseline testing to determine acute and postacute TBI impairment?
- What are the most effective screening instruments for identification of postacute TBI?
- What are the most appropriate acute and postacute assessment tools for visual, auditory, and vestibular issues?

b. Imaging.

- How do imaging findings relate to animal models of TBI/PTSD?
- What are the differences between concussive and blast-related TBI?
- What are the neurobehavioral factors that correlate with imaging markers?
- What imaging markers distinguish TBI from PTSD?

2. Understanding Short- and Long-Term Effects of TBI.

a. Neuropathology/Animal Models.

- What is the neuropathology of combat blast-related/concussive TBI? What are the subtypes of blast and concussive injuries?
- How does repetitive TBI effect neuropathology and outcome?
- What are the acute and postacute outcomes in animal models?

  –Functional (i.e., behavioral).

  –Imaging.

  –Molecular markers.

- What factors most influence TBI course and progression in animal models (e.g., genetics, context of injury [stress, psychological factors], other trauma)?

b. Clinical Follow-Up Studies.

- What are the postacute neurological, psychological, and other outcomes in veterans exposed to blast and concussive TBI?
- What are the long-term outcomes of combat TBI? What is the relationship between TBI, aging, and neurodegenerative diseases?
- What are the factors that predict readiness for return to active military duty?
- What are the factors that predict poor versus successful outcome in combat veterans in terms of cognitive and social functioning?
- What are the genetic, physiological, neurologic, and other factors that are predictive of TBI outcome, including PTSD and PCS?

c. Sensory Deficits.

- What are the acute and postacute auditory, vestibular, and/or vision injuries related to combat-related blast and concussive TBI? How do these injuries affect outcome?
- What are the best methods and tools for visual and audiology assessment after TBI?

d. Consequences and Comorbid Conditions.

- What is the prevalence and burden of consequences and comorbid conditions in individuals with TBI (e.g., seizures, PTSD, depression, pain, cognitive impairments)?
- What are the biomarkers and other risk factors associated with the consequences and comorbidities of TBI?

- What are the psychometrically sound measures that best evaluate (across time) the various consequences and comorbidities of patients with TBI?
- What are the methods and tools available to reliably measure pain associated with TBI?
- How do these consequences and comorbidities influence outcome for TBI patients?

–How does lack of insight influence outcome?

–Does pain increase risk?

3. Understanding Existing Treatment Approaches and Developing New Treatments.

- How do genetic and molecular markers and other factors improve our understanding of selection of the most appropriate TBI therapy?
- How do current treatment approaches, including pharmacological, visual, audiological, or other treatments, influence speed of recovery or outcome?
- What is the best timing and intensity of therapeutic interventions (pharmaceutical and rehabilitation interventions)?
- Which neurotrophic factors, nerve growth factors, or other factors influence synaptogenesis and enhance arborization, neuroplasticity, and cell survival after TBI? [bullet] Which hold the most promise for patients?
- What is the role of imaging for predicting or monitoring therapeutic response?
- How do we target therapies to particular neuropathologies? How does neuropathology impact the effectiveness of therapeutic interventions?
- What are the long-term outcomes for surgical management of eye injury after TBI?
- What are the best approaches for seizure management after TBI?

a. Case Management.

- What are the best approaches for risk stratification for care management? What are optimal models of care management for each level of injury severity?
- Which interventions improve veterans' and family members' ability to navigate the healthcare system?
- What are the factors that facilitate successful transition from each level of care throughout the health care system (including to home)?
- How can technology improve care coordination and access to care?
- How important is family experience in patient outcome?

b. Rehabilitation and Community Integration.

- What are the best approaches for peer and family support and involvement?
- What are the most important factors influencing short- and long-term veteran vocational outcomes?
- Which factors influence the maintenance of social relationships, family dynamics, and vocational outcomes?
- What is the most appropriate treatment milieu (e.g., group/individual; clinic/community)?
- What is the effectiveness of community-integration treatment models (e.g., neuropsychological rehabilitation, supported employment, community-based treatment)?

Figure.
Research questions that resulted from workgroup deliberations. PCS = postconcussive syndrome, PTSD = posttraumatic stress disorder, TBI = traumatic brain injury.

acute phase of TBI treatment, computed tomography (CT) scanning is often performed for identifying surgically treatable damage, such as intracranial hemorrhage. A minority of patients with mTBI (7%–20%) will have positive CT findings in the acute phase [12]. Magnetic resonance imaging (MRI) is more sensitive than CT scanning of DAI and nonhemorrhagic contusions. A key unresolved question concerns the unique

aspects and damage caused by primary blast injury, which may or may not be accompanied with acceleration/deceleration injury. A need also exists for a consensus definition of mTBI, because some definitions identify that mTBI cases must have normal structural neuroimaging findings.

Imaging techniques such as functional MRI and diffusion tensor imaging (DTI) are highly relevant to TBI. Functional MRI is a promising imaging method used to visualize cognitive functioning. DTI allows detection of white matter tracts in the brain and can be used to visualize DAI. A recent study determined that fluid-attenuated inversion recovery, gradient echo, and diffusion-weighted imaging were superior to conventional spin-echo MRI in detecting DAI, but unlike DTI, these do not image the damaged axon tracts directly [13]. Given time, the brain may eventually recover, at least partially, from a single injury. However, work in animal models suggests that repetitive mTBI (commonly experienced by soldiers) causes additional cognitive deficits and cellular injury if recovery time between injury episodes is insufficient [14]. The brain has the capacity to recover function after injury by using alternate neural pathways [15]. Image analysis may also be important in understanding postacute TBI changes, particularly regional brain volume loss [16]. The major challenge now facing the field of war-related TBI is understanding the underlying structural and functional pathology in the types of blast injuries suffered by the warrior. Further unresolved questions include—

1. What are the best imaging approaches to detect the underlying pathology in TBI?
2. What is the best approach to screen for TBI?
3. What are the most effective clinical evaluation protocols? A potential key to TBI screening may be identifying deficits in the visual, auditory, and vestibular systems.

Understanding Short- and Long-Term TBI Effects

A fundamental issue in understanding the effects of war-related TBI is an understanding of the effects of blast injury to the brain. Blasts produce rapid shifts in air pressure (blast wave), which cause primary blast injury. The lungs, colon, and ears are the most susceptible to primary blast injury, but animal models have demonstrated DAI in the brain as well [17]. In previous conflicts, blast injuries severe enough to cause brain damage also produced such profound hemorrhagic damage to the lungs and intestine that victims did not survive. But in the current conflicts in Iraq and Afghanistan, improved body armor and Kevlar helmets (DuPont; Wilmington, Delaware) have led to survival of blast victims who previously would have died. This improved technology and the increased use of improvised explosive devices have also resulted in a marked increase in blast TBIs. Brain injury has come to be called a “signature injury” of the current conflicts. Researchers have postulated that primary blast brain injury results from elevations in cerebrospinal fluid or venous pressure [18–19]. In addition, objects propelled from the explosion can cause penetrating or blunt-force injury. Individuals can also be thrown and fall or collide with stationary objects. These subsequent blast effects are likely similar to other acceleration/deceleration injuries. Rapid brain edema onset and large cerebral artery vasospasm are some of the unusual features reported in those with severe brain injury from the wars in Iraq and Afghanistan [20]. However, the effects of primary blast injury to the brain are not well understood. This type of injury may cause a unique pattern of pathology and long-term sequelae. Therefore, understanding the neuropathology of the primary blast injury is an important research goal.

In addition, identifying predisposing factors to poor outcomes is important. Biomarkers for TBI may play a significant role in this regard. Although potential protein biomarkers have been identified, they lack the characteristics needed for clinical use. For example, serum S100B, a calcium-binding protein, is associated with central nervous system injury [21]. However, it has a short half-life and lacks specificity. S100B is also elevated by other traumatic events. Other potentially useful biomarkers include neuron-specific enolase, myelin basic protein, and glial fibrillary acid protein [22]. Further research is needed to evaluate the strengths and limitations of these and other biomarkers, as well as the most appropriate clinical use.

Long-term cohort studies are needed for understanding the long-term cognitive, sensory-motor, emotional, functional, vocational, and quality-of-life consequences of war-related TBI. Determination of the factors associated with outcome and the relationship of these injuries to the risk of epilepsy and future neurodegenerative conditions, such as Parkinson disease and potential for early-onset dementia need to be evaluated. A recent study that followed audiological data from a group of patients with moderate to severe TBI (from Operation Iraqi Freedom/Operation Enduring Freedom) exposed to blast injury and screened at Walter Reed Army Medical Center found that 60 percent had hearing loss, 49 percent experienced tinnitus, and 32 percent reported a history of tympanic membrane perforation [23]. Another sensory deficit commonly associated with TBI is visual dysfunction, which was reported in approximately 40 percent of individuals with all severities of TBI [24]. Determination of the best approaches to understanding the full extent of associated auditory, vestibular, and/or vision injuries associated with war-related TBI is also a priority.

The consequences of TBI may include sensory-motor symptoms, posttraumatic seizures, cognitive deficits (e.g., problems with memory, executive functions), emotional difficulties (e.g., depression or irritability), and numerous other conditions, including headaches, sleep disturbances, and pain. A recent review of noncombat head injury studies identified chronic headache after TBI as a significant problem, with a 58 percent prevalence [25]. A review of TBI and substance abuse noted that 37 to 66 percent of civilian patients have a history of alcohol abuse and 37 to 51 percent were intoxicated at the time of injury [26]. In a recent study of 452 patients with mild to severe TBI, insomnia was reported in 52 percent of cases and 29 percent of the patients had the diagnosis of insomnia syndrome [27]. Determination of risk factors associated with consequences and comorbidities of TBI and the most effective preventive strategies and intervention are important research areas. Additionally, understanding how to manage and coordinate treatment of comorbid conditions such as PTSD is important.

UNDERSTANDING EXISTING TREATMENT APPROACHES AND DEVELOPING NEW TREATMENTS

The development of new therapeutic approaches for TBI and identification of the most effective existing therapies is an urgent priority. Key information regarding existing rehabilitative therapies is lacking. For example, to which specific patient population should a particular intervention be applied, at which intensity, and at which stage of recovery?

Current pharmacological treatments for TBI include neurostimulants, antidepressants, antipsychotics, cholinesterase inhibitors, and antiepileptic agents. Nerve growth factors are also under investigation and can affect brain repair and mediate cell survival and differentiation. They may also be important in neural stem cell proliferation and differentiation after TBI. Compounds such as progesterone citicoline, cyclosporin A, and erythropoietin are being evaluated as neuroprotective agents. For instance, in animal models, progesterone reduced the incidence of cerebral edema and lesion volume [28]. Also in animal models, citicoline administration decreased cortical contusion, reduced cognitive impairment, and improved neurological recovery [29].

Neural stem cells and precursor cells can be isolated, maintained, and grown in vitro for an extended period. Thus, they could provide a source of neurons and glia for treatment of neurological disorders. Stem cells can also inhibit inflammation, protect host neurons, and enhance other endogenous neural responses for repair [30]. Transplantation of neural stem cells shows promise in animal models of stroke, spinal cord injury, Parkinson disease, and amyotrophic lateral sclerosis [31].

TBI may lead to changes in expression of some genes [32]. The targets and functional impact of these genetic changes are not fully understood, and this must be corrected before we can exploit these changes to develop treatments. Identification of neurotrophic factors and nerve growth factors that influence synaptogenesis and enhance dendritic arborization, drive axonal sprouting, promote physiological neuroplasticity, and improve cell survival will be an important area for future TBI treatment. Most likely, a combination of treatment

approaches will likely be needed to obtain maximal anatomical repair and functional recovery [33].

CARE MANAGEMENT, REHABILITATION, AND COMMUNITY REINTEGRATION

Patients with TBI are treated with a full spectrum of acute and postacute rehabilitative approaches involving physical therapy, occupational therapy, speech and language therapy, psychotherapy, and other modalities. Interaction with the family and the community is important in recovery. Cognitive rehabilitation and other approaches may also assist in the recovery. However, important questions relating to the optimal therapies, intensity, and timing of rehabilitation interventions need to be evaluated for all rehabilitative approaches. Care support activities are critical for the patient and family to navigate the healthcare and community reintegration system successfully. Determining factors that facilitate effective transition and identifying information technology are important research topics that assist patient access and successful functioning.

A common problem for patients with TBI is lack of insight regarding cognitive or emotional difficulties. At the same time, many patients with TBI need support and long-term care. Families are important not only in providing this support but also in helping to communicate issues to health care providers and to the patient. Transitioning into the community—in particular, returning to work and social relationships—can be a challenge for patients with TBI. Identifying the most effective vocational and family support approaches is critical to successful community integration, which is the desired outcome of successful rehabilitation.

The ultimate goal of TBI research is to improve the lives of injured individuals, allowing them to reintegrate into society as productive participants at home, workplace, and in the community. This conference is an example of the collaboration between Federal and non-Federal researchers and health care providers to achieve this goal. The wide spectrum of TBI and mental health issues calls for an integrated research endeavor. Important efforts have begun in the VA, NIH, and DVBIC, the primary operational TBI component of the Defense Centers of Excellence. Collaborations are increasing between the VA, DOD, Federal agencies, and multiple academic institutions. A key issue from the consensus conference is the need for common and collaborative approaches related to long-term evaluation of patients with TBI. Underlying this need is identifying common measures for assessing patients with TBI. To this effect, NIH, DOD, and the VA have initiated an Interagency Brain Injury Work Group to establish and implement common data elements. Another important issue is the need for understanding the neuropathology of the blast mechanism. Additional opportunities for collaboration are encouraged through a DOD Congressionally Directed Medical Research Program, as well as through the planned establishment of a Center for Neuroscience and Regenerative Medicine, Uniformed Services University. NIH also supports a robust research portfolio in all TBI research areas, including basic understanding of neuroscience to clinical intervention and outcome.

We hope that research focused on these priorities will help clinicians better understand mild to severe TBI and significantly improve life for military personnel, veterans, and others affected by these conditions.

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