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Research report

Combat blast related traumatic brain injury (TBI): Decade of recognition; promise of progress

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HIGHLIGHTS

- Between 2007–2015, out of the one million combat veterans screened for traumatic brain injury (TBI), 8.4% of these Veterans received a diagnosis of TBI after comprehensive evaluation, the majority are characterized as mTBI/Concussion (mTBI) and, in great proportion, related to blast exposures.
- Mild traumatic brain injury called 'a signature injury' also known as 'the invisible injury' of war received increased attention during current conflicts.
- Specific clinical and research challenges in mTBI include identification and assessment of neuropathological, cellular and resulting cognitive, emotional, behavioral and neurological consequences.
- Enhanced research support for understanding TBI promises opportunities for advances in its diagnosis, management as well as for understanding pathogenesis of degenerative brain disease and other brain related disorders.

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ABSTRACT

Between April 2007 and December 2015, the Veterans Health Administration (VHA) screened one million combat veterans for traumatic brain injury (TBI), among 2.6 million deployed during operations Enduring Freedom, Iraqi Freedom and New Dawn (OEF/OIF/OND). Since 2007, among those reporting, screened and referred for definitive evaluation, approximately 8.4% of these Veterans received a diagnosis of TBI, the majority characterized as mTBI/Concussion (mTBI) and, in great proportion, related to blast exposures. Mild Traumatic brain injury called "a signature injury" is also known as 'the invisible injury' of these conflicts. Identifying and assessing neuropathological, cellular and resulting cognitive, emotional, behavioral and neurological consequences of mTBI comprise vast clinical and research challenges. We provide a brief overview of current history, injury mechanisms related to blast exposure, coordinated research support, and the need to understand specific cellular and neurological changes occurring with blast injury, particularly mTBI.

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1. Recognition of blast injury and neurotrauma

> The success of...any physical investigations...of primary importance, combined with an abstractions of the mind, attractive as these may appear, we are not as yet advanced enough to investigate with profit. James Clerk Maxwell, Physicist: 1831–1879

Concern about blast injuries in returning Veterans sustained during OEF/OIF/OND prompted initiation of screening of all Veterans who served in theater and presented to VHA for health care beginning in April 2007. A task force reviewed existing literature on TBI, examined efforts of individual military medical treatment facilities and VHA Medical Centers that had implemented TBI local screening, consulted with the Defense and Veterans Brain Injury Center (DVBIC), and reviewed data on the natural history of TBI. The screening tool consisted of four key questions: events increasing the risk of TBI, immediate symptoms following the event, new or worsening symptoms following the event, and current symptoms. If any one or more of these queries are answered positively, further detailed evaluation by specialized teams is offered to these Veterans. The detailed evaluation, Comprehensive TBI Evaluation (CTBIE), includes a history of the origin or etiology of the patient's injury, assessment for neurobehavioral symptoms (using a 22-question Neurobehavioral Symptom Inventory), a targeted physical

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examination, and provision of a comprehensive follow up treatment plan.

These processes began in April 2007; by December 2015 one million Veterans had been screened; 20% of these screens were positive. These Veterans were then offered CTBIE; among these 137,810 completed CTBIE and 82, 468 (8.4%) screened positive, mainly for mTBI/concussion. An additional 45,000 Veterans presented to VHA with an established diagnosis of mTBI/concussion from DOD and other sources brought the total to 137,841 diagnosed with combat TBI, mainly mTBI and in great proportion blast related [1]. This injury is defined by loss or alteration of consciousness for up to 30 min after injury, a confused or disoriented state lasting less than 24 h, normal structural brain imaging on computerized tomographic (CT) scanning and a Glasgow Coma Scale [2] of 13–15. This particular 'invisible' mTBI/concussion injury attracted considerable attention and concern about its potential long term effects.

The initial screen, with a sensitivity of 84–94%, casts a wide net. Its specificity is lower and ranges 13–59%. TBI, particularly mTBI/concussion, often blast related, remains a significant clinical problem for service members and Veterans. The Department of Defense (DOD), VHA and DVBIK, early recognized the unique aspects of blast TBI during current conflicts [3–6]. Attention to combat blast injury energized a variety of clinical approaches for its diagnosis, management and late rehabilitation. A rich portfolio of preclinical research sought to model the neuropathology and behavioral mechanisms following brain injury. PubMed lists 460 of about 573 articles appearing after hostilities began in 2003. Coordinated clinical and basic research support evolved to include coordinated efforts between the VA, the DOD, National Institutes of Health, the National Institute on Disability and Rehabilitation Research, and other nongovernmental agencies. A robust variety of shock tube experimental models, recently summarized, resulted from enhanced interest in blast injury specifically [7,8]. The results have shown the importance of interwoven systemic and cerebral responses to measured blast trauma [7] as well as suggesting protective measures [8].

2. Blast injury and other mechanisms of neurotrauma

During OEF/OIF/OND military actions, improvised explosive devices, IEDs, had become enemy weapons of choice. Terrorists also used and continue to employ conventional high explosive devices to injure civilian populations. With increasing use of explosive weapons, blast related brain injury, in the absence of direct skull trauma or penetration, was noted to occur with increasing frequency. Depending upon blast exposure intensity, immediate symptoms and signs of concussion ensue, followed by a variable intermediate period of evolving neuropathological effects. After mTBI/concussion, particularly with repeated exposures, subtle chronic disabilities, estimated to range about 15%, reportedly follow [9]. These include cognitive, emotional, behavioral and neurologic disorders. In sharp contrast to the significantly delayed post war recognition of Agent Orange and Gulf War Syndrome effects, the unique aspects of TBI blast injury were recognized relatively early during OEF/OIF [3,5,6]. A decade of clinical observational studies and experimental investigations followed. Also, in contrast to the suppression of the diagnosis of blast injury then called 'shell shock' during World War I, the existence and epidemiology of blast TBI were recognized by VA leadership in research and clinical services, by the DOD and by the NATO alliance [10]. Joint VA and DOD Clinical Practice Guidelines for diagnosis, symptom management and rehabilitation strategies appeared in 2009; these were updated in 2016 [11]. Preclinical research efforts to delineate pathogenesis, pathophysiology and potential treatments expanded. A parabolic increase in the number of research papers on blast TBI appeared after March 2003. Mild TB/concussion, however, remains a clinical diagnosis, self-reported, often without immediate physical signs or findings on conventional imaging and with scanty information about direct relationships between explosive force exposures and outcomes of these exposures.

We early noted that tympanic membrane perforation appeared as a specific but not a sensitive physical sign of blast injury [5]. Rupture of the tympanic membrane can occur with as little as 5 psi (34.5 kPa) over baseline atmospheric pressure of 14.7 psi (101.3 kPa). By contrast, higher overpressures of 56–76 psi (3.8–5.6 atm or 385 kPa to 567 kPa) depending upon blast impulse, seriously damage other organs, particularly the lungs and hollow viscera [12]. One dimension for assessing blast wave effect, [13]"incident" or "side on" pressure, is measured as loading to the body or body part on the side facing the blast. A blast wave travelling at supersonic speeds, greater than 340m/s in air, can exert acceleration effects as it encounters the skull. At maximum peak survival pressures of 60–80 psi or 414–552 kPa, simulations show that the head could be accelerated by large forces up to 300G [12,13]. Such forces, at a clearly lethal threshold, are of sufficient magnitude to produce rotational effects and brain injury due to stress at the interface between grey and white matter or alternatively by rotation of the cerebrum about the brain stem. By contrast, blast charges with less energy or those taking place at greater distances may not produce notable impact or accelerating effects. Slow motion videography of the effects of a C4 charge size simulating a non-lethal blast shows minimal head motion in helmeted manikins exposed to such lower level blast effects [14]. Of interest in these field explosions was the observation that maximum blast forces impacted the skull at about 30° of frontal rotation, while the helmet was protective for side on or posterior exposures.

A recent comprehensive review described the physics of a variety of brain injuring modalities [15]. However, disconnects remain between the physical mechanisms, cellular pathophysiology and clinical outcomes of blasts causing mTBI/concussion and its later effects. A novel model for a potential cause of mTBI, published in the *Journal of Applied Physics* [16], predicts that brain tissue damage occurs within extremely minute intervals, at intervals of ~200 nm with breakage of cellular components in the range of 4 5 nm—about the dimensions of cell membranes. The damage takes place within microseconds after the blast shock wave passes through brain tissue; its initial cellular effects are much smaller than the resolution offered by conventional CT imagining. Neurotraumatic effects are predicted to occur 1000 times more rapidly than the milliseconds characterizing classic impact and acceleration injuries.

This hypothesis, based on phonon behavior in water at time scales of E^{-12} to E^{-6} seconds, is supported by a recent proof that this mechanism explains brittle fracture of materials. With blast exposure, body tissue water itself becomes brittle; an effect, even at low energy levels particularly injurious in brain tissue as compared to bodily tissues such as muscle. This physical analysis correlates with experimental findings of low intensity blast pressures ranging from 68 to 108 kPa that induce mTBI in murine experimental models [17–19].

During the OEF/OIF era, the medical and scientific community coincidentally became aware of a chronic brain disease, chronic traumatic encephalopathy (CTE). This condition related to repeated injuries intrinsic to contact sports: football, boxing and hockey. Whether or not combat or blast trauma also causes CTE became controversial. Clinically, CTE relates to repeated impact and acceleration forces sustained during contact sports which cause concussive or even subconcussive injuries. Combat soldiers often participate in contact sports and also may suffer similar head injuries, apart from blasts, during training and combat. Omalu first described CTE as a neurodegenerative disease affecting National

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