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Neuropathology of Explosive Blast Traumatic Brain Injury

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Abstract During the conflicts of the Global War on Terror, which are Operation Enduring Freedom (OEF) in Afghanistan and Operation Iraqi Freedom (OIF), there have been over a quarter of a million diagnosed cases of traumatic brain injury (TBI). The vast majority are due to explosive blast. Although explosive blast TBI (bTBI) shares many clinical features with closed head TBI (cTBI) and penetrating TBI (pTBI), it has unique features, such as early cerebral edema and prolonged cerebral vasospasm. Evolving work suggests that diffuse axonal injury (DAI) seen following explosive blast exposure is different than DAI from focal impact injury. These unique features support the notion that bTBI is a separate and distinct form of TBI. This review summarizes the current state of knowledge pertaining to bTBI. Areas of discussion are: the physics of explosive blast generation, blast wave interaction with the bony calvarium and brain tissue, gross tissue pathophysiology, regional brain injury, and cellular and molecular mechanisms of explosive blast neurotrauma.

Keywords Traumatic brain injury · Explosive blast · Cognitive function · Pathology · DTI · Histology

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Introduction

Explosive blast traumatic brain injury (bTBI) has likely existed since the introduction of gunpowder to warfare. Among the preferred weapons of the insurgency in Iraq and Afghanistan are improvised explosive devices (IEDs) and improvised rocket assisted mortars (IRAMs). Modern protective equipment, such as body armor and up-armored vehicles, as well as advanced medical care and evacuation, has saved many blast victims from the traditional lung injury caused by explosive blasts. Severe blast-victims who would have died in the past, now survive. An unfortunate consequence of surviving is the increased prevalence of bTBI. Data compiled by the Defense Medical Surveillance Center and Theater Medical Data Store and prepared by the Armed Forces Health Surveillance Center (AFHSC) indicates that during the period 2000–2011, 229,106 U.S. service members suffered TBI incurred during Operation Iraqi Freedom (OIF), Operation Enduring Freedom in Afghanistan (OEF) and Operation New Dawn [1, 2•, 3].

Evidence, mainly from clinical experience, suggests that traumatic brain injury (TBI) from explosive blast is distinct from either closed head (cTBI) or penetrating TBI (pTBI) [2•, 3]. Victims of explosive blast can experience injury ranging from mild to severe TBI. Mild bTBI is characterized by an initial aberration of awareness ranging from confusion to brief loss of consciousness, on the order of a few minutes or less. There may even be post-traumatic amnesia. Neuroimaging using CT or conventional T1/T2 weighted MRI is typically normal. Mild bTBI is commonly clinically indistinguishable from cTBI and is differentiated largely based on history.

Moderate to severe bTBI occurs when there is gross structural brain damage from the explosive blast. Patients

present with altered mental status, ranging from confusion to lethargy to coma. Neuroimaging is abnormal and can reveal intracranial hemorrhage, skull fracture, cerebral edema and parenchymal contusions. Diffusion tensor imaging (DTI) reveals dose-dependent diffuse axonal injury (DAI) that is different from concussive impact DAI [4••]. Brains receiving a bTBI can develop malignant cerebral edema very quickly, on the order of an hour or so, as opposed to several hours to a day following cTBI. Cerebral vasospasm occurred in almost 50 % of a cohort of severe bTBI patients and lasted as long as 30 days after injury [5]. This is much later than cerebral vasospasm reported following severe cTBI, which lasts for 14 days [6].

Another difference of bTBI from other TBIs is the common involvement of other body regions. The diffuse nature of the blast explosion puts other anatomic areas at risk, most notably the eyes, ears and vestibular system. To properly care for such patients, a complete physical exam should be done in addition to the complete neurological exam. Ear trauma is highly prevalent and generally occurs with eye injury. There is an 80 % likelihood of a bTBI patient with ear injury also having ocular damage [7••]. Compilation of the injuries noted at all physiologic levels is essential in order to understand which symptoms are related to TBI and which are not. It is also important to identify which are impacting TBI.

Physics of Explosive Blast

Modern explosives produce pressure waves and also acoustic, electromagnetic, light and thermal energies [2•]. Understanding blast wave dynamics, how they interact with the human body and how the body responds is an essential first step towards understanding and addressing bTBI.

Explosive blasts can result in primary, secondary, tertiary and quaternary injuries. Primary blast injury occurs from the blast wave pressure loading the body. Secondary blast injury occurs when fragments, shrapnel and debris impact and penetrate into the body. Tertiary blast injury occurs when the body is thrown through space into a structure such as a building, wall or the ground. Quaternary blast injury is due to burns, radiation, or anything not described in the first three injury mechanisms [2•]. Understanding the subtle differences in injury mechanisms aids in an understanding of the blast wave, and may help develop a predictive scale of bTBI relative to the explosive blast.

An explosive is defined as a material which is capable of producing an explosion by its own energy [8]. Different rates of burning can be used to distinguish explosives. Fast burning explosives release a large amount of energy in short duration. Slower burning charges release a relatively lower amount of energy over a longer period of time. The energy release rate is determined by the Detonation Velocity, which, for high performance explosives such as 1 kg of TNT, is 8000 m/s [8].

The inciting event in an explosion is detonation. Detonation results in rapid conversion of chemical energy into the shock front and blast wind. Kinetic energy associated with explosive fragments and shrapnel, thermal energy, and electromagnetic radiation if the weapon is metal cased and aerosolized chemical derivatives, are also products of detonation and may contribute to injury. An ideal blast wave is characterized by the Friedlander equation. A Friedlander plot results in an almost instantaneous rise in positive pressure followed by an exponential decay to below atmospheric pressure, ending with a return to atmospheric pressure; the negative pressure phase duration is roughly twice the positive pressure phase duration.

Blast Wave Generation

An individual blast waves is composed of a shock front followed by blast wind. An Eularian hydrocode cAst simulation of a 1 kg TNT spherical charge is representative of how a blast wave is generated from chemical changes occurring within the explosive [8]. In this simulation, a spherical above ground charge is detonated producing high pressure (20–30 GPa) and high temperature (7000 °C). The pressurized and heated air moves at a very high rate (8000 m/s) and is manifested as detonation waves [8]. As the energy from detonation is transferred to the surrounding air, a moving shock wave is formed. Due to the compressible nature of gases, the air molecules are forced together causing collisions. The colliding gas molecules raise the temperature even further (up to 10,000 °C), while the close proximity of the air molecules form a thin dense layer of gas. This region of high pressure, temperature and density is called the shock front and moves away from the detonation at supersonic speeds. The boom heard during an explosive detonation is due to gas generation during the detonation wave and the shock front moving faster than the speed of sound in the surrounding medium.

In the blast wave, the shock front precedes the blast wind. As the shock wave expands, the density, pressure, temperature and velocity of air molecules decrease and the shocked-air layer gives rise to rapidly moving air behind it, referred to as blast wind. The expansion of the shock front degrades into blast wind, which continues expanding until the pressure falls below atmospheric pressure. The low-pressure phase duration is roughly twice the positive pressure phase duration, and ends when the pressure equilibrates with the ambient pressure.

Blast Wave Reflection

What has been described thus far is generation of an ideal, above ground blast with no reflective waves. However, this is seldom the case in IED explosions, in which blast waves reflect off of surrounding structures, such as buildings, vehicles and the ground. Reflection occurs when a single blast wave impinges on a surface, much the way an acoustic wave reflects off canyon walls to make an echo. Unlike the linear amplification of sound pressure upon reflection, a blast wave can reflect from a surface such as the ground and result in a reflected pressure between two and eight times the incident pressure [8]. These reflection blast waves moving at different rates in different directions are collectively known as complex blast waves. Functionally, it means a victim can be hit repeatedly from different directions, from multiple blast waves emanating from a single explosion.

If explosion occurs in an enclosure such as a room or a vehicle, the explosive can exert more damage than an open field blast [8, 9••]. Reflective waves also differ from sound waves in that blast waves change the media in which they propagate, and the angle of incidence does not equal the angle of reflection [8]. Larger angles of incidence can result in the formation of a Mach stem.

Mach Stem

Blast waves interact with structures differently, based on the energy of the blast wave and the inherent properties of the encountered structure. Mach stem can occur when a blast wave impinges on a surface such as the ground at an angle of incidence greater than 40°. The blast wave is deflected and moves along the surface and intersects with the incident wave creating a pressure 2–8 times as great as the original blast wave. Reflective waves and the Mach stem are two possible explanations why victims in close proximity to each other and minor varying distances to an explosion can receive disproportionate severities of injury [8].

Blast Wave and Body Interactions

Blast waves impinging on the human body can be reflected, transmitted or a combination of both. Early experiments by Clemedson demonstrated that as the shock wave penetrates adjacent tissues, the loading pressure rise-time is increased while the pressure decays as an inverse function of distance from the impingement [10, 11, 12••]. The importance of these two points becomes evident due to cellular injury being more related to increased stress-rate than total applied stress [12••, 13]. Intuitively this makes sense; two pressure waves of the same peak pressure but different rise times will result in the pressure wave with a greater rise time, having a larger impulse.

Internal response to blast wave can vary, due to the wave moving at variable speeds relative to tissues of different density. This can lead to relative motion between the tissue, resulting in shearing and tearing at the tissue interface [8].

Transmission of blast waves from distal body regions to the brain has had varying results. Comparison of abdominal and brain pressure transients when either the abdomen or head is individually exposed to a blast wave indicates the blast pressure decreases rapidly from the point of exposure to the point of measurement downstream [14]. Similarly, comparison of pressure transients in the heads of live swine to those in the heart and inferior vena cava during exposure to explosive blast indicate injury is not exclusively due to an intravascular pressure pulse [9••].

However, experiments conducted by Suneson, et al., where pressure transients were measured in the abdomen and left-frontoparietal brain parenchyma while a swine was shot in the left thigh with a rifle, resulted in 270 kPa and 125 kPa pressure in the abdomen and brain, respectively. High-energy missile impact, as described by Suneson, can generate short lasting oscillating pressure waves of high frequency and amplitude. The pressure waves transmit through the body at the speed of sound in the tissue, and can result in peripheral and central nervous tissue damage [15].

Variability in experimental results may be due to variable tissue density in air-filled organs such as the lungs. The physical density of the lung depends on the lung tissue, blood, and air volume which continuously change during respiration [16]. Lung tissue density gradient has been found to be significant at 10 % vital capacity, but decreases progressively as lung volume increases with the density gradient becoming increasingly smaller at 90 % vital capacity [16].

Transmittance of blast waves throughout the body requires further research. Blast wave pressure loading and velocity in tissue, variable tissue density, pressure rise-time and pressure decay are all variables which affect tissue response to explosive blasts.

Blast Wave and Head Interactions

Explosive blast waves transfer energy to surrounding structures, causing the structures to deform and accelerate [12••]. The extent of structural deformation is dependent on blast wave shape, impulse and peak pressure interacting with the structure's natural frequencies [8]. Blast wave pressure loading of the human head has two components, the first being the incident shock front or reflective shock front, depending on the aforementioned reflective waves. The second pressure is due to the slower moving blast wind [8]. Blast wave impingement on a spherical surface wraps itself around the sphere, resulting in an elevated point of pressure where the

circumnavigating waves meet opposite the blast source [8]. Pressure loading of the skull has been noted to cause skull flexure [17], and increases in intracranial pressure [9••, 14, 18].

Head rotational-translational acceleration may also occur in response to blast waves with a long duration positive pressure phase, causing contusions and tissue shearing. Results from studying a Hybrid III manikin head (HIII) responding to a 92.4 kPa blast wave shows the shock front pressure-loading the head and continuing past before acceleration of the head occurs [12••]. Developed by investigators studying automobile injury, the Head Injury Criteria (HIC) relates head acceleration to cTBI. This is a useful metric, but unfortunately has not been validated for bTBI. The HIC was validated for vehicle impacts of durations exceeding 20 ms. A typical 10 kg IEDs generally has acceleration durations below 20 ms. [12••]. An HIII covered with Explosive and Ordnance Disposal (EOD) ensemble exposed to an explosive blast was compared to an unprotected HIII. The results showed an increased HIC but were still below the validation level of 20 ms [12••].

Due to the dynamic nature of explosive blasts and wave mechanics, it is not surprising that there is variability in the results. In order to understand the pathology of bTBI, there must be a full understanding of brain tissue structure in response to stress and strain.

Stress and Strain

Normally, the brain remains buoyant in cerebral spinal fluid (CSF) because the densities of both brain and CSF are equivalent [19]. The CSF behaves like a homogenous viscous liquid, allowing the brain to move within the skull under low levels of translational and rotational acceleration. At low impact speed the brain slows rigid body displacement, while at higher impact speeds brain motion is due to deformation [20]. Due to the thin, CSF filled, dural-space between the skull and brain, application of excess external forces can cause the skull to collide with the brain or the brain to collide with the skull. Relative motion such as this can result in subdural hematomas through tearing of bridging veins. Intracerebral hematomas may also occur due to parenchymal blood vessel rupture during brain and skull collision.

Shear resistance of tissue samples from the corona radiata depends on structural orientation of fiber tracts. Pre-compression is also shown to stiffen samples [21]. Variability in tissue shear-strain, combined with variable orientation to explosive blast, provides an explanation for the differences in blast injuries between subjects. Stress relaxation tests performed on porcine brain samples indicate that cerebellar grey and white matter, brainstem and the corpus callosum are the softest areas measured. The stiffest areas of the brain included the cortex and the hippocampal CA1/CA3 regions [22]. Another study measured the linear viscoelastic properties of the cerebellum in human volunteers using magnetic resonance elastography (MRE), which showed that the cerebellum is less stiff than the cerebrum [23].

Explosive Blast TBI: Clinical Signs and Symptoms

Mild explosive blast TBI can cause headache, confusion, amnesia, difficulty concentrating, short-term memory loss, mood alteration, sleep disturbance, vertigo and anxiety. Generally, these symptoms occur immediately after injury and resolve after a few hours or days [2•]. Clinicians have developed criteria based on patient's signs and symptoms to better characterize TBI severity.

The Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine (1993) defines TBI as a cause of loss of consciousness, loss of memory preceding or following the injury, alteration in mental status at the time of injury, and/or focal neurological deficit. Mild bTBI is defined as loss of consciousness <30 min, post-traumatic amnesia <24 h and GCS 13–15 after exposure to an explosive blast. Moderate bTBI is defined as loss of consciousness for >30 min but <24 h, amnesia lasting >30 min but <1 d, GCS 9–12 and possible skull fracture. Severe bTBI is defined as loss of consciousness >24 h, amnesia >1 d, GCS 3–8 and possible cerebral contusion, laceration or intracranial hemorrhage. This scale relies heavily on a patients' level of consciousness; however, historical pTBI data indicates patients may not suffer any loss of consciousness even with severe head trauma [24].

The Vietnam Head Injury Study (VHIS) of pTBI patients reveals that the areas most associated with traumatic loss of consciousness included the posterior limb of the internal capsule, left basal forebrain, midbrain and hypothalamus [25]. Only 15 % of the original 342 people in the VHIS who survived pTBI experienced prolonged traumatic loss of consciousness. Also, when first given medical care, 40 % of the veterans were alert and could remember the event [25]. Variations in presentation between pTBI and bTBI may indicate the need for revision of the bTBI rating criteria to better encompass pTBI or a separate pTBI rating criteria.

Victims may not be aware of their brain injury after blast exposure. Two or more blast exposures may occur before the individual realizes their brain has been injured. The first symptoms of bTBI may be persistent post-concussive symptoms such as headaches, vertigo, short-term memory loss, and concentration or multi-tasking difficulties. Personnel that experience a second bTBI before fully recovering from the previous insult may experience second-impact syndrome

(SIS) [2•]. Second-impact syndrome is characterized by rapid loss of consciousness, development of malignant cerebral edema, intracranial hypertension and coma. Second-impact syndrome is associated with up to 50 % mortality.

Vision

Eye trauma can occur by any of the four mechanisms of blast injury. Secondary blast injuries are the most common cause of ocular trauma. Significant eye damage may be present without alteration in vision or significant symptoms and may be hidden by concomitant injuries [26].

Ocular injuries may not be detected initially, due to maxillofacial trauma or more serious systemic injuries. Serious nonpenetrating injuries to the eye include choroid rupture, hyphema, optic nerve injuries, retinal detachment, traumatic cataract and vitreous hemorrhage [26]. From August 2004 to October 2006, the Defense and Veterans Brain Injury Center (DVBIC) found that 66 % of TBI diagnosed at Walter Reed Army Medical Center (WRAMC) also suffered ocular trauma. Closed-globe injuries are more common with TBI than open-globe [27]. Retinal detachment and vitreous hemorrhage have also been noted in a dog exposed to primary explosive blast only [28].

Advances in ballistic protective eyewear for military personnel has reduced the incidence of eye injury among military personnel [29]. CT of the orbits is the most important diagnostic procedure in evaluation of globe and orbit injuries. Admission/treatment time is the most important factor in determining postoperative vision [30]. Retrospective chart review of veterans screened for TBI has indicated the strongest predictor of visual impairment is auditory impairment and vice versa [7••].

Hearing

The ear is a complex organ allowing for sensation of pressure waves, motion and the body's response to gravity. Noise induced hearing injuries have been the most common during OIF/OEF [29]. Retrospective analysis of 10,431 medical records from OIF/OEF veterans who suffered a bTBI indicates that 68.5 % have hearing impairment [7••]. The most common otologic complaints immediately post-blast are aural fullness, distorted hearing, dizziness, hearing impairment, loudness sensitivity, otalgia and tinnitus [31]. Injury to the tympanic membrane, boney ossicles and/or cochlear hearing apparatus is common following explosive blast. Blast injury to the inner-ear nerves, tracts and nuclei are less common.

Blockage of sound transduction or damage to the structures of the outer and middle ear results in conductive hearing loss (CHL). Damage to the cochlea, nerves, nuclei or auditory cortex can result in sensorineural hearing loss (SNHL). Literature comparisons of hearing loss indicate SNHL and mixed (CHL and SNHL hearing) losses are more common in blast-exposed individuals, while CHL is seen more in non-blast groups [32]. Retrospective analysis of blast-induced hearing loss indicates 50 % of the hearing loss is SNHL [33]. A small cohort study of bTBI patients showed that 62 % had hearing loss, of which pure SNHL comprised over half of the individuals with a hearing deficit [34]. A common symptom of SNHL is tinnitus.

Tinnitus is a symptom characterized by the perception of sound without an external source [35]. According to the 2011 International State-of-the-Science Meeting on Blast-Related Tinnitus, tinnitus is the number one service-connected disability for veterans from all periods of service, with 744,000 veterans receiving disability compensation totaling $1.1 billion for 2010 and expected to increase to $2.3 billion by 2014. Tinnitus is one of the most common post-blast complaints and can occur even when hearing thresholds are in the clinically normal range [33, 36]. The neuropathology resulting in tinnitus remains incompletely characterized.

Tinnitus has been shown to occur in conjunction with cochlear dead regions and after auditory nerve sectioning [36, 37]. Damage to the cochlea or cochlear nerve results in enhanced spontaneous firing rate (SFR) of the dorsal cochlear nucleus (DCN) [36]. Fusiform cells are the main neural output of the DCN. Excitatory and inhibitory fibers synapse on the fusiform cell modulating the fusiform cell output; increased excitation or decreased inhibition of the DCN can result in tinnitus [38]. Imaging studies may be useful in detecting changes to auditory brainstem and central auditory structures.

Positron emission tomography (PET) reveals elevated blood flow in auditory structures in individuals with tinnitus compared to controls [39]. Structures with increased blood-flow include the auditory brainstem, medial geniculate nucleus (MGN), auditory cortex and temporal-parietal association areas [40]. Decreased grey matter in the right inferior colliculus (IC) and left hippocampus was noted on functional MRI (fMRI) in 28 tinnitus patients [41]. Diffusion tensor imaging (DTI) has indicated changes in the IC and LL in patients with SNHL. Air-blast tube studies on rats evaluated with DTI show major changes in axonal integrity of the IC and MGN. [35].

Vestibular System

Little is known about the effect of explosive blasts on the peripheral and central vestibular systems. It is likely more common than documented, as vestibular pathology can be overlooked or masked due to concomitant physical and psychological injuries [42].

Effects of otologic blast injuries include benign paroxysmal positional vertigo (BPPV), centrally or peripherally mediated disequilibrium, vertigo, or post-traumatic Meniere's disease [43]. Scherer and Schubert compiled a broad review containing signs and symptoms of bTBI-vestibular pathology [42]. Explosive blast can cause vestibular injury resulting in imbalance and dizziness [31]. The most common balance disorder associated with bTBI is BPPV [31]. Of the 17 survivors of a bus explosion, seven suffered from BPPV [44]. A cohort of 3,973 soldiers returning from OIF had 797 cases of bTBI. Although headache was the main symptom of the bTBI group, half also suffered from dizziness and one-fourth had imbalance [45].

Evaluation of 24 bTBI patients indicated a greater incidence of peripheral vestibular hypofunction in patients complaining of dizziness. Central vestibular injury that manifested as nystagmus and/or oculomotor deficits were present in 42 % of these OIF veterans [46]. Vestibular symptoms can last for months [47].

Seizures

The extent of bTBI induced seizures/epilepsy in military personnel from OIF/OEF is unknown at this time. Variability of seizure onset, compounding medical conditions and detection techniques are issues of posttraumatic epilepsy (PTE), which need further investigation. Posttraumatic epilepsy is considered when two or more unprovoked seizures occur after a head injury. Unprovoked seizures are those seizures that occur more than seven days after a head injury. Seizures occurring within seven days after TBI are defined as provoked seizures [48]. Seizures in PTE usually occur within five years of TBI[48].

Vietnam PTE provides a meaningful reference in predicting which TBI patients are at risk for PTE. In the VHIS, pTBI veterans had a 53 % risk of developing PTE [24]. From 2000 to fourth quarter 2011, there have been 3,786 pTBI in military personnel according to the AFHSC [1]. If cerebral injury is present, then the risk of PTE is 10–25 % [48]. By fourth quarter 2011, the AFHSC recorded diagnosis of 38,943 cases of moderate cTBI. Conservative estimates of those injured indicate about 4000 service personnel will suffer PTE [48].

Gross pathologic findings are used as indicators of impending PTE. Severe TBI is associated with a higher incidence of PTE. Structural lesions common after severe TBI include skull fractures, intracranial hematoma and parenchymal contusion. Often, such patients have severely depressed level of consciousness at time of initial treatment [49•]. The likelihood of developing PTE is associated with the presence of lesion consistent with cerebral injury that can be seen on cerebral CT/MRI scans[48].

The risk of developing PTE following mild bTBI is unknown. DTI imaging of mild bTBI patients can give false negatives and miss the diffuse injury to the white matter tract [4••]. Most of the data pertaining to PTE concerns generalized or complex partial seizure activity. However, simple seizures can be encountered in this patient population. Simple partial seizures may manifest with only behavioral or sensory alterations. These subtle seizures are difficult to detect and may require video electroencephalography (EEG) to diagnose [48]. Because of this, the prevalence of PTE may not be fully realized for years to come.

Explosive Blast Neuropathology

Intracranial Hypertension

Edema, intracranial hemorrhage and vasospasm are the most prominent pathophysiologic characteristics of bTBI [9••]. Intracranial hypertension is common in severe bTBI with hyperemia and severe edema occurring in the acute period. This pathological sequence of events has been noted more often when there is a traumatic subarachnoid hemorrhage indicated by CT imaging [2•]. Blood in the basilar cisterns is ominous and may indicate an impending increase in ICP, which may be delayed as long as 2–3 weeks after the bTBI occurred [2•].

Vascular Effects

Traumatic cerebral vasospasm (TCV) is a prominent feature of blast wave exposure [9]. Swine exposed to explosive blast and evaluated by angiography have shown narrowing of the primary arteries supplying blood to the brain [9••]. In non-human primates (NHP) exposed to explosive blast, collapsed capillaries surrounded by hypertrophic end-feet of astrocytes and vacuolated endothelial-cell cytoplasm [50] indicate the entire vascular tree is subject to bTBI TCV.

Human studies also demonstrate TCV. In a study of severe bTBI patients who underwent cerebral angiography, there was 47 % and 35 % incidence of TCV and pseudoaneurysm, respectively [5]. Average TCV lasted 14 days after ictus but could last up to 30 days. This is much longer than cerebral vasospasm following subarachnoid hemorrhage in cTBI which typically lasts only up to 14 days. Another finding indicated that TCV can present 10 or more days after the initial injury and there is a positive correlation to acute blast traumatic subarachnoid hemorrhage (SAH). The strongest predictors of TCV were the number of lobes injured and the presence of a pseudoaneurysm [5]. Two explanations for the presence of a pseudoaneurysm with TCV include: 1) arterial damage at the time of injury resulting in SAH that dissipated due to tamponade and pseudoaneurysm

formation, or 2) penetrating fragment moving in the lumen of the blood vessel injuring the endothelia lining [5]. Early detection with transcranial Doppler (TCD) ultrasound may allow for early intervention [5].

Hemorrhage

Brain hemorrhage is a common feature in animals exposed to explosive blast. Common sites of injury noted by Saljo and Knudsen are the brainstem, cerebellum and midbrain [51, 52]. However, pigs wearing chest protection while exposed to blast waves of 131–366 kPa showed no signs of brain hemorrhage or vascular abnormalities [53]. This led to speculation that pressure waves impacting the thorax lead to transmission of pressure waves through the thoracic blood vessels up into the cerebral vasculature. Evidence supporting or refuting this hypothesis remains lacking.

Explosive Blast Regional Neuropathology

Explosive blast TBI can result in diffuse injury to the brain due to increase in ICP from pressure loading, and coup-contrecoup impact with the skull caused by primary or tertiary injury mechanisms. Diffuse axonal injury due to sheer strain can occur as a result of transmitted waves or rotational-translational acceleration. Local regions of injury can occur due to the brain colliding against the skull.

Cortex

Symptoms of exclusively cortical bTBI are difficult to identify due to the complexity, proximity and connectivity to other structures. Explosive blast TBI has been shown to cause shrinkage of pyramidal cells in layer V, as well as distortion of the apical dendrites [50]. Various white matter tracts arising from the cortex show diffuse axonal injury in bTBI patients [4••].

White Matter Tracts

A common type of brain damage in TBI is DAI, particularly fronto-striatal, fronto-parietal and fronto-temporal pathways [54]. Fiber degeneration due to bTBI has been shown in fiber tracts of the ipsilateral superior corona radiata and white matter of the ipsilateral cerebellum of swine exposed to moderate-high blast pressures [9••]. Exposing swine to 131–538 kPa explosive blast where the chest is protected results in periventricular axonal injury, but not cerebral vascular injury [53]. Exposure of non-human primates (NHP) to relatively lower pressure blast wave, 80 kPa and 200 kPa, resulted in subcortical white matter oligodendrocyte and astrocyte apoptosis combined with disorganized myelin sheaths suggesting conduction defects [50]. In a study of bTBI patients, DTI abnormalities were identified in the orbitofrontal white matter and cingulum bundles [55•].

Lesions in white matter tracts due to bTBI can be difficult to identify on standard MRI and CT scans [4••]. Diffusion tensor imaging can resolve lesions in white matter tracts by the degree of water diffusion in the area. In the absence of resistance in the brain, water diffuses randomly and is characterized as having a high average diffusion coefficient (ADC) with low fractional anisotropy (FA). In the tight confines of the white matter tract, diffusion is limited and directional; this is characterized as low ADC and high FA. In the acute stage of white matter injury, cells swell, increasing FA and decreasing ADC. In the chronic stage of injury, cells lyse or die, resulting in high ADC and low FA [56].

Various DTI analysis methods have been used to evaluate bTBI. Evaluation of veterans with bTBI using volume averaging DTI did not reveal abnormalities [55•]. Due to the diffuse nature of bTBI compared to cTBI, traditional techniques that average measures of white matter integrity or regions of interest (ROI) may miss the diffuse nature of bTBI. During analysis of DTI in mTBI patients, the magnitude and number of areas affected should be evaluated [4••, 57]. Diffusion tensor imaging of mild bTBI patients indicates a greater number of low FA voxels (decreased white matter integrity) in ROI and in total white matter, while traditional averaging techniques fail to detect either type of injury. This non-averaging technique also shows greater FA in patients exposed to multiple explosive blasts [4••]. Combining this DTI analysis method with EEG has allowed for greater sensitivity in detecting TBI.

Application of time-frequency based method for measuring EEG phase synchronization, combined with FA measures in DTI, has shown that mild bTBI patients have diminished EEG phase synchrony. Results indicated diminished interhemispheric coordination of brain activity in frontal lobes, thalamic radiations, and forceps minor due to blast [58].

Hippocampal Formation

Explosive blasts of 80 kPa and 200 kPa resulted in apical dendrites of pyramidal neurons being distorted, with shrunken and condensed soma in the CA3 region while the CA1 region showed a significant reduction in pyramidal neurons [50]. This loss may be due to pyramidal neurons being susceptible to hypoxic and ischemic conditions [50, 59]. Identified by DTI, bTBI patients have DAI in the uncinate fasciculus and various white matter tracts [4••].

These studies indicate TCV combined with DAI may be the basis of memory dysfunction symptoms in bTBI patients.

Cerebellum

Patients with bTBI show marked abnormalities in the middle CP on DTI [55•]. Non-human primates exposed to explosive blast showed changes in cerebellar Purkinje neurons, combined with behavioral changes in motor coordination. The Purkinje neurons showed irregular nuclear outline containing condensed and homogenous chromatin, while the dendrites from the Purkinje neurons showed degeneration [50].

Cerebral Ventricles

The ventricle system has shown changes in swine exposed to explosive blast. There are increased numbers of injured axons appearing in the periventricular area [53].

Explosive Blast TBI Cellular Neuropathology

Astrocytes

Astrocytosis has been confirmed in NHP cortical regions that are ipsilateral to explosive blast. Ipsilateral hippocampal formation (HF) also showed astrocyte activation in the dentate and hippocampal regions [50]. A pig study indicated an increase in the number of astrocytes in an even distribution throughout the brain [53].

Neurons

The cytoskeletal components of the neuron are susceptible to damage and rearrangement in bTBI. Axonal microtubules reassembly after post blast can result in the axon-transport system being partially or completely disrupted. Axons take on an undulating appearance and presence may indicate diffuse axonal injury.

Amyloid precursor protein (β-APP) is produced in neurons. The β-APP is transported from the soma along the axon by fast axonal transport. If axonal injury occurs the β-APP accumulates at the site of axonal injury, accumulation may occur within 2 h following injury [60, 61] and results in "axonal varicosities". De Lanerolle et al. report accumulation of β-APP in periventricular axons in all swine with bTBI [53].

Oligodendrocytes

Following blast exposure of NHP, there appeared to be apoptosis of oligodendrocytes in subcortical white matter. This reduction in myelin producing cells suggest neural conduction would be reduced ,[50].

Molecular and Biochemical Changes

Molecular changes are of specific importance not only for understanding bTBI, but also in detection of bTBI. A possible biomarker for bTBI is neurofilament heavy chain (NfH) and Pavlov's enterokinase (PE). Swine exposed to explosive blast show a time dependent increase in NfH following injury. Serum NfH levels peak at six-hours post severe blast and correlates with poor outcomes [62]. PE cleaves the neurofilament heavy chain (NfH) at positions 476 and 986. The two NfH cleavage products can be measured quantitatively in vivo by cortical microdialysis. There appears to be a positive correlation between NfH and brain temperature, systemic blood pressure and anaerobic brain metabolism; all of which rise following TBI [63]. Higher extracellular fluid NfH levels are also found in the presence of traumatic subarachnoid hemorrhage [63].

The phagocytic Mato cells of the blood brain barrier have been shown to increase after bTBI [50]. Along with migration of phagocytic cells, brain metabolism has been noted to change due to bTBI.

A study of mild bTBI patients indicates cerebral glucose hypometabolism compared to controls. Decreased rates of glucose metabolism occurs in the pons, cerebellum, vermis and medial temporal lobe on fluorodeoxyglucose PET scans [64]. Decreased glucose metabolism is noted in Alzheimer disease and may indicate functional disorder of a region.

Conclusion

Explosive blast TBI is an old condition that has gained renewed notoriety. It may be a different form of TBI, distinct from cTBI and pTBI. Although it shares clinical features of both, there are distinguishing signs and symptoms. The understanding of the neuropathology of bTBI remains incomplete. Investigations at the subcellular, cellular, regional anatomic and physiologic levels are all needed. It is only through proper and thorough scientific analysis that meaningful treatment strategies will be developed. The insights gained will hopefully translate into better clinical care of patients suffering from this and other forms of TBI.

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