One-hundred years (and counting) of blast-associated traumatic brain injury.

Abstract: Blast associated traumatic brain injury (TBI) is a major, signature issue in modern warfare, and now civilian population because of terrorist tactics. Despite being a recognised feature of combat since the introduction of high explosives in conventional warfare over a century ago, only recently has there been interest in understanding the biology and pathology of blast TBI and its potential long-term consequences. Still, progress has been slow and there remain remarkably few robust human neuropathology studies in this field. This article briefly considers the history of blast TBI and reviews the pathology described in the few scientific studies found in the literature.

The improvised explosive device (IED) has become synonymous with recent military conflicts and modern terrorism, with the preferential use of such devices responsible for the increasing incidence of traumatic brain injury (TBI) among military personnel. Since 2001, more than 2 million U.S warfighters have been deployed in-theatre, with just under 400,000 of these reporting at least one TBI,[1] the vast majority so-called mild TBI, with blast exposure the most common mechanism of injury in this population.[2,3] Indeed, such is the prevalence of blast-associated TBI in modern warfare it has been referred to as a signature injury of the conflicts in Iraq and Afghanistan. However, despite recent attention to the injury and recognition of the potential for long-term morbidity from blast-associated TBI, it is not a new phenomenon: blast TBI being a recognised feature of combat since the introduction of high explosives over one-hundred years ago. Nevertheless, only recently has there been interest in understanding the biology and pathology of blast TBI and its potential long-term consequences.

The Mechanics of Blast

An explosive blast results in the formation of a high-pressure wave caused by the almost instantaneous transformation of the explosive material from a solid or liquid to a gas.[4] This blast overpressure wave expands radially from the epicentre and then dissipates rapidly. This is followed by a more prolonged blast underpressure wave. Blast injuries occur through multiple mechanisms (Table 1) and whereas secondary and tertiary blast injuries are responsible for severe head trauma, it is the primary blast wave which is implicated in blast TBI.[5] Exactly how the primary blast wave affects the brain is, at present, incompletely understood.

A Brief History of Blast TBI

Primary blast TBI was widespread in World War I (WWI). Servicemen fighting on the frontlines of Europe were exposed to shell fire from heavy artillery barrages and mortar attacks. No sooner had conflict begun, than soldiers started to report symptoms such as tremor, poor concentration, dizziness, hypersensitivity to noise, amnesia, headache and tinnitus following exposure to blast and in the absence of signs of external head injury.[6] The term ‘shell shock’ – the signature injury of WWI – was used to describe such patients. However, its usage was short lived and in World War II (WWII) the British authorities banned the term, perhaps thinking that disavowing the existence of the disorder would prevent another epidemic.[7] Unsurprisingly, this did nothing to protect soldiers from blast exposure or prevent them from reporting associated symptoms. By 1941, the term post-concussion neurosis had become ersatz shell shock, with victims describing familiar symptoms of headache, dizziness, fatigue, tinnitus, memory impairment, poor concentration and nervousness.[8] Several decades later, this same complex of symptoms is recognised as the syndrome of blast TBI in modern

conflicts. Nevertheless, despite in excess of US$2 billion research spending on military TBI over the past decade by the US Veteran's Administration and US Department of Defense,[9] our understanding of the biology and pathology of blast-associated TBI has not progressed significantly since WWI.

Limited Insight into Acute Blast Neuropathology

Despite a century of recognition of blast TBI, remarkably few cases have been examined at autopsy. In the first reported series dating to WWI of three soldiers who had been exposed to blast, but showed no external evidence of injury to the head, Major Frederick Mott described punctate, petechial haemorrhages in the white matter of the centrum semiovale, corpus callosum, and internal capsule, with extravasation of blood into the subarachnoid space.[10-12] Following WWII a further 9 cases were added to the literature, again describing prominent haemorrhagic features, with diffuse leptomeningeal bleeding, intracerebral clots and multifocal white matter haemorrhages.[13] More recently, Shively and colleagues[14] report pathology in three further cases regarded by the authors as acute blast TBI (survival 4 days or 2 months). In these examples, the authors describe reactive gliosis at the boundary between cortical grey and underlying white matter, in periventricular areas and subpially. Furthermore, they describe focal axonal pathology in cortical white matter and corpus callosum, without further comment on the pattern and distribution of this pathology, although they do report an absence of amyloid β plaques or tau pathology in all cases. These 15 cases remain the only published experience of acute blast TBI neuropathology to date (Table 2).

No Clear Understanding of Late Blast Neuropathology

Studies examining the chronic pathology of blast TBI are equally few in number and observations only started to appear in the literature in 2011, with the case report of a former marine in which the authors describe neurofibrillary tangles and tau pathology[15] similar to that seen in chronic traumatic encephalopathy (CTE).[16] This pathology was also implicated in a subsequent study from a second group of authors reporting on the neuropathology of four military veterans exposed to blast.[17] However, despite these early accounts of CTE pathology in blast-exposed military personnel, this has been an inconsistent finding in later studies. Thus, in their case series of six former military veterans Ryu and colleagues[18] reported no evidence of CTE pathology, instead describing axonal pathology in five cases, four of which had a survival time greater than 2 months following blast exposure. Adding further to the constellation of pathologies described in late survivors of blast TBI, Shively and colleagues[14] report pathology in five cases of chronic blast TBI (survival greater than 6 months). In all five the authors describe a distinctive astroglial pathology, marked by a prominent interface astrogliosis mirroring the reactive gliosis reported in each of their three

acute blast TBI cases reported in the same study. Interestingly, the authors also describe tau pathology, similar to CTE, in two out of five of these late survival cases (Table 2). McKee AC et al[19] describe CTE-like pathology in 21 military veterans (most of whom were also athletes) with a history of mild repetitive TBI, this being the principle inclusion criteria of the study. Incidentally, in three cases there is a concomitant history of exposure to blast, although the survival time in each case is not commented on.

It is worth acknowledging that in addition to limited human studies, looking into both the acute and chronic neuropathological sequelae on the brain, there exist an abundance of animal models, of varying clinical relevance. The most valuable animal models, certainly in translational research, recognise the need to accurately replicate not only pathophysiological mechanisms and neuropathological features of blast TBI observed in humans, but also clinically relevant endpoints. In this regard, the careful study of human tissue perhaps offers the greatest promise in furthering our understanding of blast TBI.

Moving Forward

As we approach the centenary of the end of the WWI, and despite almost a century of recognition of the neurological complications of exposure to explosive blast injury, remarkably little progress has been made in our understanding of the biology and pathology of blast TBI and its long-term consequences. Moreover, what was formerly an injury confined to military personnel, recent terrorist activities across the UK and elsewhere have resulted in IEDs being deployed among civilian populations.

Among the recurring problems in studies thus far reporting on the neuropathology of individuals exposed to blast are inconsistencies in definitions of blast exposure and survival time and consideration of confounding factors, not least of which being exposure to non-blast TBI, including sports-associated TBI, which is common in this population. Given this, it is perhaps not surprising that in the few cases thus far described there is lack of consensus in descriptions of both acute and late blast TBI pathology. There is, therefore, a pressing need to gain a better understanding of the injury to inform research into strategies for its identification and monitoring in life and, ultimately, the development of effective therapeutic options for blast TBI. A first step to achieving this might be coordinated efforts to obtain human tissue samples to support robust neuropathology studies, together with detailed longitudinal cognitive and imaging studies in cases of chronic blast TBI.

References:

1. US Department of Defense Worldwide Numbers for TBI. Defense and Veterans Brain Injury Center. http://dvbic.dcoe.mil/dod-worldwide-numbers-tbi (last accessed September 17, 2017)

2. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild Traumatic Brain Injury in U.S. Soldiers Returning from Iraq. *N Engl J Med* Massachusetts Medical Society; 2008 Jan 31;358(5):453–63.

3. Masel BE, DeWitt DS. Traumatic brain injury: a disease process, not an event. *Journal of Neurotrauma.* Mary Ann Liebert, Inc. 140 Huguenot Street, 3rd Floor New Rochelle, NY 10801 USA; 2010 Aug;27(8):1529–40.

4. DePalma RG, Burris DG, Champion HR, Hodgson MJ. Blast injuries. *N Engl J Med*. 2005 Mar 31;352(13):1335–42.

5. Taber KH, Warden DL, Hurley RA. Blast-related traumatic brain injury: what is known? *J Neuropsychiatry Clin Neurosci*. American Psychiatric Publishing, Inc; 2006;18(2):141–5.

6. Turner WA. Remarks on cases of nervous and mental shock: observed in the base hospitals in France. *BMJ*. 1915 May 15;1(2837):833–5.

7. Shepard B. “Pitiless psychology”: the role of prevention in British military psychiatry in the Second World War. *Hist Psychiatry*. 1999 Dec;10(40 Pt 4):491–524.

8. Wittenbrook JM. The post concussion syndrome: a clinical entity. *The Journal of Nervous and Mental Disease*. 1941 Aug;94(2):170–6.

9. US Army Medical Research and Materiel Command. Congressionally Directed Medical Research Programs. Annual Report. September 30, 2015.
http://cdmrp.army.mil/pubs/annreports/2016annrep/2016annreport.pdf
(last accessed September 17, 2017).

10. Mott FW. The microscopic examination of the brains of two men dead of commotio cerebri (shell shock) without visible external injury. *BMJ*. British Medical Journal Publishing Group; 1917 Nov 10;2(2967):612–5.

11. Mott FW. The effects of high explosives upon the central nervous system, lecture I. *The Lancet.* 1916 Feb;187(4824):331–8.

12. Mott FW. The effects of high explosives upon the central nervous system, lecture II. *The Lancet.* 1916 Feb;187(4826):441–9.

13. Cohen H, Biskind GR. Pathologic aspects of atmospheric blast injuries in man. *Arch Pathol (Chic)*. 1946 Jul;42:12–34.

14. Shively SB, Horkayne-Szakaly I, Jones RV, Kelly JP, Armstrong RC, Perl DP. Characterisation of interface astroglial scarring in the human brain

after blast exposure: a post-mortem case series. *Lancet Neurol.* 2016 Aug;15(9):944–53.

15. Omalu B, Hammers JL, Bailes J, Hamilton RL, Kamboh MI, Webster G, et al. Chronic traumatic encephalopathy in an Iraqi war veteran with posttraumatic stress disorder who committed suicide. *Neurosurgical Focus.* American Association of Neurological Surgeons; 2011 Nov;31(5):E3.

16. Hay, J, Johnson, VE, Smith, DH, Stewart, W. Chronic traumatic encephalopathy: the neuropathological legacy of traumatic brain injury. *Ann Rev Pathol*. 2016; 11, 21-45 DOI: 10.1146/annurev-pathol-012615-044116

17. Goldstein LE, Fisher AM, Tagge CA, Zhang X-L, Velisek L, Sullivan JA, et al. Chronic traumatic encephalopathy in blast-exposed military veterans and a blast neurotrauma mouse model. *Science Translational Medicine*. American Association for the Advancement of Science; 2012 May 16;4(134):134ra60–0.

18. Ryu J, Horkayne-Szakaly I, Xu L, Pletnikova O, Leri F, Eberhart C, et al. The problem of axonal injury in the brains of veterans with histories of blast exposure. *Acta Neuropathologica Communications*. BioMed Central; 2014 Nov 25;2(1):331.

19. McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*. 2013 Jan;136(Pt 1):43–64.

Table Legends

Table 1. Classification of blast injury. Theoretically, blast may result in four types of independent mechanisms of injury: primary, secondary, tertiary, and quaternary. One or all of these mechanisms of blast injuries can occur simultaneously, resulting in casualties with significant polytrauma. Whereas many of the injuries listed result in physical wounds, blast TBI is sometimes known as the invisible wound, but nonetheless results in debilitating symptoms.

Table 2. Summary of all studies in the literature examining the neuropathology of acute and chronic blast TBI. There is little commonality in pathology between studies and a reliable consensus on what precisely characterises blast TBI pathology is lacking. Just under half of all studies into chronic blast TBI show pathology resembling CTE. Survival time corresponds to time between most recent blast exposure and death. McKee AC et al[19] is excluded due to significant confounding factors and absence of survival time data.

Table 1

BLAST INJURY	MECHANISM OF INJURY	EFFECT
PRIMARY	Blast overpressure wave	Blast induced TBI, soft tissue deformation, blast lung injury, acoustic barotrauma and gastrointestinal injury
SECONDARY	High energy projectile fragments and shrapnel	Penetrating wounds
TERTIARY	Thrown through air and striking solid object	Injuries associated with acceleration/deceleration forces, blunt force trauma to brain
QUARTENARY	Injuries not directly attributable blast, but which result from the effects of the blast	Burns, radiation injury, inhalation injury, crush injuries following building collapse

Table 2

Year	Author [reference]	Number of cases	Survival	Pathology
Acute Blast TBI				
1917	Mott [10-12]	3	2 days	Petechial haemorrhages in white matter.
1946	Cohen and Biskand [13]	9	5 days	Petechial haemorrhages in subcortical grey and white matter; diffuse leptomeningeal and intracerebral haemorrhages.
2016	Shively et al [14]	3	4 days or 2 months	Subpial, grey–white matter junctions and periventricular astrogliosis; cortical white matter and corpus callosum axonal pathology
Chronic Blast TBI				
2011	Omalu et al [15]	1	3 years	Neuronal and glial tau pathology consistent with CTE
2012	Goldstein et al [17]	4	1 - 6 years	Neuronal and glial tau pathology consistent with CTE
2014	Ryu et al [18]	6	19 days - 4 years	Cortical white matter and corpus callosum axonal pathology
2016	Shively et al [14]	5	6 months - 9 years	Astroglial scarring involving subpial glial plate, penetrating cortical blood vessels, grey–white matter junctions and periventricular areas; cortical white matter and corpus callosum axonal pathology (2 cases)