



Stewart, W., and Smith, D. H. (2016) Time to be blunt about blast traumatic brain injury. *Lancet Neurology*, 15(9), pp. 896-898.

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Deposited on: 8 August 2016

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Time To Be Blunt About Blast Traumatic Brain Injury

William Stewart^{1,2,3}, Douglas H. Smith¹

1. Penn Center for Brain Injury and Repair and Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA 19104, USA
2. Department of Neuropathology, Queen Elizabeth University Hospital, Glasgow G51 4TF, UK
3. Institute of Neuroscience and Psychology, University of Glasgow, Glasgow G12 8QQ, UK

Corresponding Author: Dr William Stewart, MBChB, Ph.D, FRCPath.
Department of Neuropathology
Queen Elizabeth University Hospital
1345 Govan Rd
Glasgow G51 4TF, UK.

Email: William.Stewart@glasgow.ac.uk
Tel: +44 (0)141 354 9535

In the last decade there has been growing realization that traumatic brain injury (TBI) can trigger a lifelong disease process¹. In particular, there is increasing alarm around recognition of a form of neurodegenerative disease, chronic traumatic encephalopathy (CTE), in former athletes from an ever-expanding list of contact sports². However, despite impressions from the popular media and certain sectors of the research community, TBI and its long-term consequences, including CTE, are far from exclusive to athletes.

Since 2001, over 2 million United States service members have been deployed to conflicts in Iraq and Afghanistan, with over 313,000 sustaining at least one TBI, the vast majority as concussion or mild TBI³. Of particular concern among these injuries are those arising from exposure to blast shockwave, such as from improvised explosive devices⁴. Indeed, blast associated TBI (bTBI) has often been referred to as a signature injury of modern military conflicts; with a combined US Veteran's Administration and Department of Defense research spending on TBI estimated at over 2 billion dollars in the past decade⁵. Nevertheless, despite this significant research investment, understanding of bTBI is paralyzed by a singular lack of human neuropathology studies in those exposed to blast. As a consequence, there have been no means to evaluate the relevance of preclinical models, resulting in substantial confusion over what constitutes bTBI. Furthermore, for service members with blast exposure and TBI, it remains unclear whether their symptoms are a result of blast alone or potential accompanying blunt forces from head impact.

In this edition Shively et al⁶ report their observations on the neuropathology of 8 former military personnel exposed to blast compared to small numbers of civilian controls with or without histories of TBI or opiate misuse. The authors report a distinctive astroglial pathology in all their chronic blast survival cases (greater than 6 months from injury) marked by dense astrogliosis at the boundary between cortical grey and underlying white matter, adjacent to the ventricles and

subpially. Furthermore, they report reactive gliosis in a similar distribution in more acute blast survival cases (4 to 60 day survival after injury). In contrast, no similar astroglial pathology was observed in their limited series of controls, including blunt/impact TBI cases. In addition to this glial pathology, the authors report axonal pathology in all three acute and 2 of 5 late blast cases, however, without formal characterization of pattern and distribution.

Remarkably, this short series almost doubles the number of cases in the modern era describing the human neuropathology of blast TBI. Prior to this study, only 10 contemporary cases of bTBI had been described in the literature, half reporting a pathology reminiscent of CTE^{7,8}, the remainder describing axonal pathology and no evidence of CTE⁹. Thus the picture of late pathology after bTBI remained unclear. However, while these previous reports fail to reach commonality in pathology described, they do share many unavoidable weaknesses in design, most notably in the considerable heterogeneity in survivals and in exposure to non-blast TBI among their limited number of cases.

Inevitably, this latest contribution also suffers from heterogeneity in survival from injury (4 days to 9 years) and in histories of exposure to non-blast TBI ('unknown' in 6 cases)⁶, and whether the observations on specificity of this glial pathology to bTBI stand up to scrutiny in more comprehensive studies remains to be seen. Intriguingly, tau pathology reminiscent of CTE was only observed in 2 of this current series. However, as with previous neuropathological studies in bTBI, it cannot be determined if this CTE pathology represents a consequence of blast exposure alone, or is confounded by coincidental or previous non-blast injury. In this regard, one bTBI case with CTE had a history of non-blast injury described as 'unknown', whilst the second had an extensive history including sports (wrestling, boxing) and non-sports (multiple motor vehicle accidents) TBI exposure. At issue is the inability to rule out a previous TBI for almost any service member, where years of potential TBI exposure through military training,

sports and accidents are more the rule than the exception.¹⁰

Unquestionably this current study is commendable in drawing attention to the need for careful study of human tissue to further understanding of TBI. However, far from an answer to the question, 'what is blast TBI', the work instead exposes the remarkable absence of robust and informed human neuropathology studies in this field. Unquestionably, progress in TBI research, both blast and non-blast, can only benefit from efforts directed specifically to facilitate acquisition of human tissue samples linked to detailed clinical information to support robust and informative neuropathology studies.

Meanwhile, we must remain cautious in interpreting the significance of any single pathology as unique to bTBI based on small and heterogeneous case series and with limited clinical information and control comparisons. The alternative is to risk repeating the errors of the past decade and the premature assumption that CTE is a unique disease of athletes, or even exclusively tau.

Supported by NIH grants, NS038104 (WS and DHS) and NS092389, NS056202 (DHS), and DOD grant, PT110785 (WS and DHS). WS is supported by an NHS Research Scotland Career Researched Fellowship

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