Traumatic Brain Injury

Its Outcomes and High Altitude

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Traumatic brain injury (TBI) has been frequently called a hallmark of military conflicts in Iraq and Afghanistan. In addition, the Armed Forces Health Surveillance Center reports an increasing rate of TBI in US Armed Forces that is greatest in the US Army. The Congressional Research Service reports a total of 253,300 TBI cases between 1 January 2000 and 20 August 2012, with the Army averaging about 20,000 TBIs per year from 2007 to 2011.1

Posttraumatic headache (PTH) remains the most frequent symptom after TBI and will continue to be a problem in the military healthcare system. One study showed that 19% of Soldiers returning from combat duty in 2005 had symptoms consistent with migraine and that, for migraine-like PTH, individuals who had the most severe headache pain had the highest headache frequencies.2 However, TBI can also lead to a number of other negative outcomes, such as stroke, depression, various cognitive dysfunctions, posttraumatic stress disorder (PTSD), anxiety disorder, sleep disorders, epilepsy, visual disturbance, hearing loss, tinnitus, and memory loss.3,4 For example, injured active-duty Operation Iraqi Freedom personnel presented with a substantially higher prevalence of PTSD than did uninjured personnel (32% versus 14%).5 Population-based research evidence suggests that TBI may increase risk of stroke by 10-fold, even after adjusting for the most important confounders.6

Among other sequelae, TBI triggers neuroinflammation and activates microglia. While inflammation is reparative acutely, chronic persistence may lead to secondary injuries, causing neurological symptoms such as headache.7 Further, mechanical trauma from TBI and resulting neuroinflammation can alter blood–brain barrier (BBB) function, allowing entry of substances from circulating blood into the brain’s interstitial space, both protective and harmful. TBI induces a myriad other responses, including involvement of the peripheral immune system and influx of potentially cytotoxic bloodborne proteins and pathogens. This causes neuronal damage and glial activation that can further contribute to BBB permeability. Leukocytes, cytokines, and other inflammatory mediators cross the BBB after TBI, contributing to chronic pathology. Many of these sequelae persist for days, months, or years.

Severity and duration of postconcussion syndrome (including PTH) are not related to the severity of TBI. There must be other factors at play. Wartime theaters of operation have occurred in various parts of the world and very often much above the sea level. Altitude was a factor in recent military operations in Iraq (Operation Iraqi Freedom and Operation New Dawn) and Afghanistan (Operation Enduring Freedom). Iraq has an upper elevation of approximately 12,000 ft (3,600m), and Afghanistan has an upper elevation of approximately 24,000 ft (7,200m). High altitude (4,900–11,500 ft) brings the onset of physiological effects of diminished oxygen pressure. At very high altitude (11,500–18,000 ft), maximum arterial oxygen saturation falls below 90%.8

On one hand, cellular hypoxia is caused by decreased barometric pressure, predisposing to various negative post-TBI outcomes. Hypoxic injuries are closely associated with disturbed BBB function,9 allowing substances to cross the BBB. In addition, high elevation results in lowered partial pressure of oxygen and the human brain responds to it by changing the responsiveness of cerebral circulation.10 Exposure to hypoxia has been also shown to result in multiple changes to the central nervous system, such as verbal working and short-term memory impairment, hippocampal atrophy, and neurodegeneration, as well as a significant difference in the middle, posterior cerebral, and basilar artery flow velocity.10

On the other hand, hypoxia can also trigger some potentially beneficial physiological reactions to protect the human body from damage. One potentially beneficial reaction is the higher production of erythropoietin (EPO) by human kidneys. Previous research evidence suggests that subtle hypoxia can result in moderate production of...
EPO, whereas presence at 3,000m above sea level may result in a sharp, almost twofold renal EPO production.11 EPO has been shown to possess multiple neuroprotective properties.12 EPO was also shown to protect the astrogial space by reducing the concentration of extracellular glutamate.12 In addition, EPO was shown to be an effective agent protecting and repairing many important processes in the nervous system. Furthermore, synthesis of EPO in astrocytes could protect them against apoptogenic chemicals or even low oxygen pressure.12 Overall, EPO is currently viewed as a substance that can sustain antiapoptotic responses in many tissues where it can be regarded as a general tissue-protective cytokine.

TBI is a complex process with several stages, the initial stage being the impact itself (i.e., blunt object or blast) followed by several complex physiologic and biochemical reactions, such as accumulation of free radicals, direct trauma to cell membranes by free radicals, and a cascade of inflammatory reactions following cell apoptosis.13–15 Cumulatively, these reactions are likely to cause neurodegeneration and subsequent PTH7 and potentially other adverse outcomes such as depression, PTSD, or sleeping disorders. An alteration or elimination of one or more of these posttrauma reactions is likely to result in fewer adverse outcomes as well as a better prognosis for TBI. If head trauma has occurred at high altitude, both profound cellular hypoxia and higher EPO production by the kidneys are likely to affect many complex physiologic and biochemical reactions following injury and, therefore, all post-TBI outcomes. Thus, it is unclear whether high altitude is an additional risk factor for all negative outcomes associated with TBI such as PTH, depression, or PTSD acutely or chronically post-TBI, and there is a need to conduct further research in the area. It is likely that high altitude can trigger many negative post-TBI outcomes; however, some of them could be more affected than others due to the protective role of EPO.

Knowledge that high altitude may trigger various post-TBI outcomes may help justify additional screening, diagnostic, preventive, and treatment procedures among Warfighters returning from military duties at high altitude. This is particularly important because, for example, untreated headaches are known to cause various mental issues, ranging from mental anguish and substance abuse to suicide. Moreover, PTSD and depression are the leading causes of medical visits and missed workdays among Soldiers with TBI. Thus, proper diagnosis of post-TBI outcomes among Soldiers returning from military duties at high altitude would be essential and could include not only additional diagnostic procedures but also detailed evaluation for conditions such as PTSD, depression, epilepsy, visual disturbance, cognitive functions, hearing loss, tinnitus, memory loss, anxiety, and insomnia. This could improve return-to-duty times and bolster performance. In addition, it will help establish new research directions in this area, such as those focusing on a better classification or a new treatment for PTH, PTSD, or depression.

Disclosures

The authors have nothing to disclose.

References


Dr Ismailov is a medical doctor who earned his PhD in injury and cardiovascular epidemiology from the University of Pittsburgh. Together with his collaborators from Pacific Institute for Research and Evaluation and University of Pittsburgh, he conducted the first population-based studies that examined the
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Dr Lytle earned her PhD in interdisciplinary neuroscience from Georgetown University Medical Center in Washington DC. In 2007, she was awarded a National Defense and Global Security Fellowship with the American Association for the Advancement of Science and served at the Office of Naval Research, managing biomedical research and development programs. She has also served as a programmatic reviewer for the US Department of Defense Congressionally Directed Medical Research Program. In 2009, Dr Lytle joined AVIAN LLC as their Science and Technology Division Director and went on to become a director of Business Development and chair of AVIAN’s Science and Technology Center of Excellence. In 2009, she was awarded the Chief of Naval Research Gold Coin for her contributions to the US Naval Science and Technology Strategic Plan. In 2012, Dr Lytle was awarded the Commander Naval Air Forces Force Surgeon Gold Coin for her efforts associated with their hypoxia mitigation program. She is currently a Director at the Pacific Northwest Research Institute (www.pnri.org), Seattle, Washington.

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