Defense and Veterans Brain Injury Center
TBI Hot Topics Bulletin
FIRST QUARTER CY 2020

STAY INFORMED ABOUT TRAUMATIC BRAIN INJURY (TBI)

Are you a busy health care provider? Not enough time to keep up with research? Stay informed with the *TBI Hot Topics Bulletin*. We track the latest TBI scientific studies, advances, and discoveries most relevant to health care providers.

SCIENTIFIC STUDIES

Mental Health Outcomes Among Military Service Members After Severe Injury in Combat and TBI

Most studies on combat-related TBI and mental health outcomes have been limited to the first-year post-injury. In this retrospective cohort study, Chin et al. investigated associations between combat TBI and the incidence of mental health disorders over the course of several years. The authors accessed medical records from federal databases, including the DoD Trauma Registry (DoDTR), Armed Forces Medical Examiner System (AFMES), and other DHA sources. Their sample consisted of 4,980 service members from all branches who sustained critical injuries in Iraq and Afghanistan (between February 1, 2002 and January 31, 2011). They used the Injury Severity Score (ISS) to determine severity and the Barell Injury Matrix to identify TBIs (n = 1,574, 31.6%). Most injuries occurred among Army soldiers and Marines (71.7% and 24.7%, respectively). Blunt force trauma or penetration were the most common types of injury (78.4%). Follow-up records were reviewed for a median of 4.1 years. The authors used ICD-9-CM codes to count the incidence of mental health diagnoses including PTSD, anxiety and mood disorders, adjustment reactions, cognitive impairments, and psychotic disorders. Most of the sample showed at least one mental health disorder in the follow-up period (70.6%). PTSD (46.1%), adjustment disorder (40.9%), and anxiety (37.0%) were the most frequent diagnoses. Adjusted logit models showed TBI patients were more at risk than non-TBI patients for mental health disorders (incidence rate ratio, 1.52; 95% CI = 1.42 – 1.63). Cognitive disorders, in particular, were influenced by TBI status (odds ratio, 3.24; 95% CI = 2.78 – 3.77).

Comment

The results indicate that combat TBI is associated with a variety of mental health conditions for at least 4 years after injury. The sample, however, also included non-TBI combat injuries and lacked TBI severity and demographic information. The average follow-up period was 4.1 years post injury, allowing for the possibility that later comorbidities and life events influenced mental health outcomes. However, the results emphasize the importance of mental health screenings as part of routine medical follow-ups. Future work could focus specifically on brain injury data, establishing relationships between TBI severity, symptoms, and comorbidities.
Chin et al. (2019) *Mil Med*, Epub 31 Dec. PMID: 31889174

Brain and Blood Biomarkers of Tauopathy and Neuronal Injury in Humans and Rats with Neurobehavioral Syndromes following Blast Exposure

It is theorized that TBI may precipitate biomolecular processes that result in progressive neuropathologies like chronic traumatic encephalopathy (CTE). Finding biomarkers that diagnose and/or predict these conditions would be clinically beneficial. Dickstein et al. examined blood and neuroimaging biomarkers of neuronal injury in rats and humans exposed to blast. Their pre-clinical study involved 43 rats (22 experimental, 21 controls). The experimental animals were anesthetized, placed in a specially designed shock tube, and exposed to blast overpressure (74.5 kPa) once a day for three consecutive days. Controls went through a similar sham procedure without blast. Rats were then euthanized 6 weeks or 10 months after injury. A subset (n = 24) were dissected and stained for histological analysis. Brain extracts from the remaining group (n = 19) were analyzed by Western blot. The human participants (n = 17) consisted of 10 Veterans with a history of blast exposure (range: 1 to 50 incidents) and 7 neurologically healthy controls. All blast-exposed participants met VA/DoD/ American College of Rehabilitation Medicine requirements for mild TBI. Six of the ten were formally diagnosed with PTSD. All reported some combination of cognitive, somatic, and/ or affective symptoms (e.g., headache, memory deficits, depression, etc.) Participants provided blood samples which were analyzed for the biomarker neurofilament light (NFL) protein. They were also scanned by PET using [18F] AV1451 ligand (binds specifically to tau protein) and MRI. In the rats, the authors found phosphorylated tau (p-tau) and total tau were elevated at 6 weeks and 10 months after injury. Western blot analysis also revealed abnormal elevations and redistributions of tau throughout the blast exposed brains, especially in perivascular and astroglia processes. Half of the blast-exposed Veterans displayed cortical hyperintensities on MRI scans. PET analysis showed excess [18F]AV1451 ligand retention in 5 of the 10 TBI subjects, with tau deposition patterns similar to those seen in CTE. The highest serum levels of NFL were among Veterans with excess [18F]AV1451 retention. Veterans with high cortical diffusivity scores on MRI also demonstrated elevated NFL and [18F]AV1451 retention.

Comment

The study found that elevation in p-tau is a potential neural signature of blast TBI. Repeated blast exposure in rats produced abnormal p-tau accumulations in perivascular regions. Fifty percent of the Veterans showed heightened [18F]AV1451 ligand retention at the gray-white matter junctions. These patterns of p-tau accumulation are similar to those seen in CTE patients, a condition with no known in vivo biomarker. Limitations of the study include a small sample size and the use of a civilian control group. Future work should validate the connection between CTE and tauopathy through post-mortem neuropathological assessments.
Dickstein et al. (2020) *Mol Psychiatry*, Epub 25 Feb. PMID: 32094584

Associations of Time Since Injury to the First Clinic Visit with Recovery Following Concussion

Several factors may contribute to concussion recovery time, including pre-injury characteristics, comorbidities, age, and sex. The importance of a timely clinical evaluation after a concussion, however, has yet to be evaluated. In this retrospective, cross-sectional study, Kontos et al. investigated the timing of the initial clinical evaluation on recovery times in adolescents with sports-related concussion (SRC). The study examined data from 162 patients treated at a sports medicine clinic. The authors divided the sample into two groups: patients first seen within 7 days post-injury (n = 98) and those first seen 8 to 20 days post-injury (n = 64). Patients were interviewed and received a comprehensive clinical examination including the Post-Concussion Symptom Scale (PCSS), Immediate Post-Concussion Assessment and Cognitive Testing (IMPACT), and Vestibular/Ocular Motor Screening tool (VOMS). The groups did not differ significantly on demographic or medical characteristics, nor on cognitive, ocular, and vestibular outcomes. Recovery time ranged from 9 to 299 days with an average of 57 days. They found that patients seen between 8 to 20 days post-injury were 5.8 times more likely to have a recovery longer than 30 days (adjusted odds ratio, 5.8; 95% CI, 1.9 – 17.6). Patients evaluated within 7 days post-injury recovered approximately 20 days faster. The days before the evaluations seemed to account for the longer recovery, not the time patients spent under clinical care.

Comment

This study suggests that an early clinical evaluation may yield faster recoveries in SRC patients. This may be due to aspects of patient behavior. For example, without clinical guidance, athletes may engage in activities that are counterproductive to their recovery. Also, concussed individuals may simply put off treatment until they realize they are not getting better. More research is necessary to understand the cause(s). Future studies should also include military populations. Information on concussion management is available (https://dvbic.dcoe.mil/clinical-tools-providers-mild-tbi). Utilizing these tools may speed/enhance recovery, return patients to duty quicker, and improve mission readiness.

Kontos et al. (2020) *JAMA Neurol*, Epub 6 Jan. PMID: 31904763

Association of Blood Biomarkers with Acute Sport-related Concussion in Collegiate Athletes: Findings from the NCAA and Department of Defense CARE Consortium

Sports-related concussions (SRC) can be difficult to diagnose due to a reliance on self-reported symptoms. Certain blood biomarkers, however, have the potential to provide objective assessments of SRCs. In this study, McCrea et al. investigated blood biomarkers in patients with acute SRC as part of The National Collegiate Athletic Association (NCAA) and U.S. Department of Defense (DoD) Concussion Assessment, Research, and Education Consortium (CARE). The study included 264 NCAA college athletes with diagnosed concussion. Additionally, there were 138 contact sport and 102 non-contact sport controls. Clinical testing consisted of the Sport Concussion Tool Third Edition (SCAT-3), Standardized Assessment of Concussion (SAC), the Balance Error Scoring System (BESS) and Brief Symptom Inventory 18 (BSI-18). Participants completed testing and provided blood samples at five timepoints: 1) pre-season baseline, 2) acute post-injury period, 3) 24 – 48 hours post-injury, 4) when asymptomatic, and 5) 7 days after return to play (RTP). In addition, concussion participants were tested at the start of the RTP protocol and at 6 months post-injury. Molecular array technology (Quanterix Simoa) analyzed the blood samples for glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase-L1 (UCH-L1), neurofilament light (NF-L), and tau protein. Athletes with concussion had significantly higher blood levels of GFAP, UCH-L1, and tau at the acute post-injury period compared to pre-injury baseline levels. GFAP was a useful biomarker for discriminating between athletes with concussion and contact sport controls. Athletes with loss of consciousness (LOC) or posttraumatic amnesia (PTA) had significantly higher levels of GFAP in the acute post-injury period compared to concussed athletes without LOC or PTA.

Comment

The study results suggest GFAP and UCH-L1 are discriminative of sport-related concussion. These findings are significant, as they may contribute to the development of clinically useful biomarkers for mild TBI. A specific combination of biomarkers could provide health care providers with an early diagnosis and a way to monitor recovery. Once diagnosed, initiation of PRA protocols may enhance recovery of mild TBI patients.

McCrea et al. (2020) *JAMA Netw Open*, Epub 3 Jan. PMID: 31977061

Impact of Pre-Existing Migraine and Other Co-Morbid or Co-Occurring Conditions on Presentation and Clinical Course Following Deployment-Related Concussion

Blast exposure in combat often results in mild TBI or concussion. Previous studies have shown associations between concussion and various cognitive, somatic, and behavioral complications. Migrainous headache is a common comorbidity. In this retrospective chart review Scott et al. examined the clinical presentation and course of injury in concussed U.S. service members deployed to Iraq and Afghanistan. They reviewed the medical charts of 40 service members and assessed acute clinical symptoms and chronic comorbidities. The most frequent cause of injury was blast to a motor vehicle (42.5%). Headache was the most frequent symptom and occurred in 38/40 (98%) patients, followed by insomnia (82.5%), tinnitus (63%), impaired concentration (62.5%), nausea (45%), dizziness (50%), anxiety (42.5%), impaired balance (35%), depression (30%), and hearing loss (18%). Reported chronic co-morbidities included headache, insomnia, anxiety/depression, and post-traumatic stress disorder (PTSD). A majority of service members (25/40, 63%) reported having headaches before deployment. Daily headaches with migraine features were common after injury (68%). Of those treated with triptans (42%), 75% responded positively.

Comment

The study shows service members with concussion often experience comorbid conditions, with headache being the most common. The results should be interpreted with caution as questionnaires are limited by recall bias and misunderstanding of responses. The study still emphasizes the importance of taking a comprehensive patient history of all symptoms and comorbidities for better clinical management. Understanding which symptoms are new and which existed pre-injury may influence the treatment plans.

Scott et al. (2020) *Headache*, Epub 3 Jan. PMID: 31898813

TECHNOLOGY UPDATES

A Randomized, Double-Blind, Placebo-Controlled Trial of Blue Wavelength Light Exposure on Sleep and Recovery of Brain Structure, Function, and Cognition Following Mild Traumatic Brain Injury

Traumatic brain injury can result in sleep disorders which contribute to long-term cognitive and affective problems. Killgore et al. examined the effect of blue-wavelength phototherapy on sleep patterns and neurocognitive abilities in TBI patients. The study was a randomized, double-blind, placebo-controlled trial of 32 adults who had sustained a mild TBI in the past 18 months and demonstrated significant sleep-related problems after injury. The experimental group (n = 16) was exposed to 30 minutes of blue light (λ = 469 nm) from a LED (light emitting diode) lightbox each morning for six weeks. Controls (n = 16) were exposed to an amber placebo light (λ = 578 nm) at the same schedule. Over the course of the intervention, sleep quality and circadian rhythms were assessed by wrist actigraphy. The researchers also acquired behavioral (personality, neuropsychological, and multiple sleep latency tests) and neuroimaging (functional MRI, DTI) data before and after the intervention. Relative to amber light, blue light was more effective in shifting sleep-wake periods, reducing sleepiness, and improving the cognitive performance of participants. Neuroimaging analysis showed increased gray matter volume in the posterior thalamus, greater thalamo-cortical connectivity, and increased axonal integrity for the blue-light group. These neuroimaging measures were correlated with reduced daytime sleepiness and improved cognitive performance.

Comment

Previous research demonstrates blue-light phototherapy is useful in treating sleep problems and seasonal affective disorder. The current study explored blue-light exposure in relation to neurocognitive changes in mild TBI patients. The results indicate blue-light phototherapy may enhance neural connectivity and cognitive recovery after brain injury. While the results are intriguing, limitations include the small sample size, the fact that the light therapy was self-administered, and the use of actigraphy rather than the gold standard of polysomnography. The study is an important addition to literature on sleep disorders, light therapy, and their relation to TBI.

Killgore et al. (2020) *Neurobiol Dis*, Epub 18 Nov. PMID: 31751607

ABOUT

The *Bulletin* is a product of the Defense and Veterans Brain Injury Center (DVBIC) Research Branch and provides a quarterly summary of TBI research relevant to health care providers. This issue covers research published January to March 2020

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For more information, contact DVBIC: 800-870-9244 | dha.DVBICinfo@mail.mil