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Defense and Veterans Brain Injury Center
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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

Mapping Brain Recovery after Concussion: From Acute Injury to 1 Year after Medical Clearance

The abatement of symptoms after concussion often determines when an athlete can return-to-play (RTP). However, secondary physiological changes can continue well beyond clinical recovery. The natural course of sport-related concussion (SRC) is largely unknown. In this study Churchill et al. conducted the first longitudinal neuroimaging evaluation of sport concussion patients after they were cleared for RTP.[1] The goal was to examine the persistence of structural and functional brain alterations. A total of 146 university athletes participated. Twenty-four were diagnosed with concussion via the Sports Concussion Assessment Tool 3 (SCAT3). The other 122 were neurologically healthy controls. The concussed participants were scanned by MRI within a week of injury, at RTP, and again approximately one year later. They also retook the SCAT3 at RTP and at one month after injury. The controls were scanned at the beginning of their season. They took the SCAT3 at the beginning and end as well. Between-group comparisons on global functional connectivity (Gconn), cerebral blood flow (CBF), and white matter integrity (FA and MD) were conducted at the following time points: early symptomatic injury (SYM), return to play (RTP), and one year post-RTP. The authors found some physiological differences (e.g., Gconn, FA, and MD) persisted from SYM to the RTP. However, no significant effects were observed for Gconn or FA at one year post-RTP. Changes in cerebral blood flow were insignificant at RTP. There were significant reductions in the middle frontal and temporal regions at one year post-RTP. There were significant increases in MD in the posterior and superior corona radiata at all time points. In addition, the spatial extent of MD seemed to increase at later time points. These effects were also modulated by variables like acute symptom severity and the time to RTP, which varied across the concussed sample.

Comment

While the effects of Gconn and FA were insignificant after a year post-RTP, CBF and MD effects persisted. These findings indicate chronic physiological alterations for some variables but not others. There are some weaknesses. Three time points are a coarse evaluation of changing pathophysiology. There were also no pre-injury scans of the concussed participants. While the authors used a large control group, the effects of demographic factors and concussion history are unknown. Despite these limitations, the study is a credible evaluation of the natural history of sport-related concussion.

[1] Churchill et al. (2019) *Neurology*, Epub 16 Oct. PMID: 31619480

Post-traumatic Stress Disorder Increases Odds of REM Sleep Behavior Disorder and other Parasomnias in Veterans with and without Comorbid Traumatic Brain Injury

An estimated 60-70% of patients with rapid eye movement (REM) sleep behavior disorder (RBD) will develop synucleinopathy (i.e., Parkinson's disease and related disorders). Traumatic brain injury (TBI) and/or post-traumatic stress disorder (PTSD) are risk factors for RBD, but the association with idiopathic-RBD and synucleinopathy is unknown. Veteran populations are at particular risk for TBI and PTSD. For these reasons Elliott et al. sought to describe the prevalence rates of RBD and other parasomnias in veterans with TBI and/or PTSD.[1] This prospective cross-sectional study was conducted at the VA Portland Health Care System in a sample of 394 veterans (94% male, mean age = 54.4 ± 15 years). Participants completed questionnaires and a sleep-study using in-lab video-polysomnography. They were stratified into 4 groups based on REM sleep activity and dream enactment: 1) normal REM, no dream enactment (Normal; n = 333); 2) normal REM, dream enactment (Other Parasomnias; n = 211); 3) Abnormal REM, no dream enactment (REM sleep without Atonia [RSWA]; n = 27), and 4) Abnormal REM, dream enactment (RBD; n = 34). Participants were assessed for TBI and PTSD by diagnostic screening (Post-Traumatic Stress Disorder Checklist) and medical record review. In the sample, 37 had TBI, 74 had PTSD, 39 had comorbid TBI and PTSD, and 244 had neither TBI nor PTSD. The authors found 34 out of 394 participants had RBD, a crude prevalence rate of 9%. The prevalence rates for Other Parasomnias and RSWA were 31% and 7% respectively. These rates are significantly higher than those for the general population. In addition, the prevalence rates increased for veterans with PTSD and TBI+PTSD to 15% and 21%, respectively.

Comment

The study presents further evidence that neuropsychiatric trauma is associated with RBD and other parasomnias, important information for the care of veterans with TBI and PTSD. The data indicate that PTSD, rather than TBI, is the main driver of the association. However, the authors stress this is not conclusive. They note the sample is small and TBI was determined by medical record review, not diagnostic interview. Future longitudinal studies are needed to better understand the relationship between PTSD, TBI and sleep disorders.

[1] Elliott et al. (2019) *Sleep*, Epub 7 Oct. PMID: 31587047

Dynamic Blood-Brain Barrier Regulation in Mild Traumatic Brain Injury

Repetitive subconcussive injuries may affect long term brain function. These injuries frequently occur in contact sports such as football, prize-fighting, and rugby. In this study, O'Keeffe et al. examined the effect of impact exposure on blood-brain barrier (BBB) integrity in rugby and mixed martial arts (MMA) athletes.[1] They examined two groups: five adult MMA fighters and 22 adolescent rugby players. The MMA fighters were scanned by MRI pre- and post-fight. They wore instrumented mouthguards (MiG2.0) during the fights to record the number and magnitude of head hits. The rugby players were scanned pre- and post-season. All 22 received a pre-season scan. However, only 11 returned for the post-season scan. A subset (n = 8) of players were also scanned two hours after a rugby match. The authors created BBB permeability maps from the MRIs. These were compared to pre-analyzed controls (n = 27) to produce BBB permeability metrics. The authors also collected blood samples from the rugby players, which were screened for 14 common TBI biomarkers (e.g., BDNF, MCP/CCL2, S100B, etc.). For the MMA fighters, the authors found that the number of impacts and the maximum head acceleration were correlated with the BBB permeability metrics. For the rugby players, the post-season scans revealed more BBB-disrupted voxels than pre-season scans, particularly for periventricular regions. Levels of the BDNF biomarker were also significantly elevated post-season. Analyses of the subset showed increased BBB permeability post-match compared to pre-season. Levels of MCP/CCL2 and S100B were also elevated post-match.

Comment

The study indicates head hits from fighting and rugby can contribute to BBB permeability. The authors show BBB metrics are measurable via MRI and are related to kinematic data and molecular biomarkers, though the clinical implications (e.g., symptoms/drug treatment for the symptoms) of these findings are unclear. Their sample size limits generalizability. The design would have benefited from collecting kinematic, biomarker, and MRI data on the same sample. Still, the study presents important pilot data which may inform larger, longitudinal efforts to understand the effects of SRC on the BBB.

[1] O'Keeffe et al. (2019) *J Neurotrauma*, Epub 8 Nov. PMID: 31702476

Suicide and Traumatic Brain Injury Among Individuals Seeking Veterans Health Administration Services Between Fiscal Years 2006 and 2015

The scientific literature evidences a link between TBI and suicide. The Veterans Health Administration (VHA) also recognizes veterans have a disproportionate risk of suicide compared to the general population. Hostetter et al. examined the association between TBI and suicide in veterans who accessed VHA services between fiscal years 2006 and 2015.[1] In their sample, a total of 215,610 individuals were previously diagnosed with TBI and another 1,187,639 had no history of TBI. Data regarding age, disease severity, psychiatric diagnosis, commission of suicide, and the method of suicide were extracted. The authors found the rate of suicide for those with TBI was 86 per 100,000; for those without, 37 per 100,000. Overall, veterans with a history of TBI had a suicide hazard ratio (HR) of 2.19, meaning their risk of suicide was approximately 2.19 times greater than their counterparts without TBI. Among the TBI cases, 90.1% were mild in severity (mTBI); 9.7% were moderate/severe. After controlling for covariates, both groups showed a greater risk of suicide compare to those without TBI (HR = 1.62 for mild; HR = 2.25 for moderate/severe). Psychiatric conditions and substance abuse also affected suicide rates. Diagnosed depression resulted in the highest hazard ratio (HR = 2.22). Finally, veterans with moderate/severe TBI were 2.39 times more likely to commit suicide by firearm than those without TBI. Those with mild TBI, however, did not demonstrate a greater risk of suicide by firearm.

Comment

The study contributes to understanding the link between TBI and suicide. While the cohort was large, some details were not accessible, such as the number of TBIs or whether psychiatric diagnoses and substance abuse predated TBI. Still, the study provides compelling evidence of an increased risk of suicide in TBI patients. Health care providers should consider suicide screening as part of their assessment. More detailed research on TBI and psychiatric variables may improve suicide prevention (See CUBIST Podcast Episode 301 which discusses this study: https://dvbic.dcoe.mil/training/podcasts/cubist-clinical-updates-brain-injury-science-today).

[1] Hostetter et al. (2019) *J Head Trauma Rehabil*, PMID: 31369450

Pupillary Changes after Clinically Asymptomatic High-Acceleration Head Impacts in High School Football Athletes

Diagnosis of a sports-related concussion (SRC) often depends on the self-report of symptoms by the injured athlete. Fifty-percent of SRCs go unreported, perhaps due to insufficient concussion education and the athlete's desire to return to play. A rapid, objective, non-invasive method for detecting SRCs is needed. Previous research shows quantitative pupillometry (QP) detects abnormal pupillary response (e.g., decreased dilation velocity, decreased average constriction velocity, and increased constriction latency) in patients with blast-induced TBI. The current study by Joseph et al. used QP to determine if high-acceleration head impacts (HHI) result in measurable changes in pupillary light reflex in the absence of neurocognitive findings.[1] A total of 13 (18 initially, 5 excluded) high school football athletes were monitored for the frequency and magnitude of head impacts throughout the sports season (July-October 2017). Their football helmets were fitted with an encoder for the Head Impact Telemetry System. An HHI was defined as an impact with a linear acceleration of > 95g and a rotational acceleration of > 3760 rad/sec2. Those diagnosed with a concussion were removed from the study. Participants were evaluated with QP (NPi-200 Pupillometer System) and the Sport Concussion Assessment Tool, 5th Edition (SCAT5) at baseline (during a period of rest), midseason (2-2.5 months after baseline and within 1 hour post-game), and 1 week after the final game (during a period of rest). An additional SCAT5 evaluation and QP were performed immediately if an HHI was detected. Seven athletes sustained an HHI without a concussion diagnosis. QP examinations at impact were compared to those from midseason. There was a significant decrease in pupil dilation velocity, percent change of pupil diameter, and maximum constriction velocity after an HHI. There were no significant differences in maximum and minimum size metrics, latency to constriction, or constriction velocity. In addition, SCAT5 evaluations performed after an HHI showed no significant differences from midseason scores.

Comment

Although the SCAT5 did not indicate a concussion, QP demonstrated significant changes in pupillary response. The authors suggest that the forces experienced by the seven athletes were enough to alter brain reflex pathways. The study is limited by its sample size and the use of within-subject controls. However, it shows pupillary changes have clear clinical implications for TBI. Further research in pupillometry and TBI is needed to develop diagnostic technologies and validated measures for clinicians.

[1] Joseph et al. (2019) *J Neurosurg*, PMID: 31770721

TECHNOLOGY UPDATES

MRI Volumetric Quantification in Persons with a History of Traumatic Brain Injury and Cognitive Impairment

Traumatic brain injury may precipitate later brain atrophy. Global and regional volume loss are associated cognitive impairments and later dementia. Accordingly, brain quantification via MRI volumetrics may be useful in assessing TBI patients and predicting clinical outcomes. Meysami et al. evaluated the utility of the FDA-cleared volumetric program Neuroreader.[1] The authors selected 40 adult subjects via a retrospective review of medical records from UCLA hospitals. All had a history of TBI and cognitive impairments as demonstrated by Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), or other tests (e.g., CNS Vital Signs, Web Neuro). The mechanism of TBI, time since injury, and the presence of vascular disease were also documented. For each subject, Neuroreader analyzed the MRI, quantifying 45 brain regions and comparing them to a normative database. Metrics included region volumes (ml), their ratio to total intracranial volume (TIV), and their difference in relation to normative data (i.e., Z-scores). On average, the analysis showed volume loss in the ventral diencephalon, putamen, pallidum, temporal lobe, and brain stem of the TBI subjects. Regression analysis showed TBI status, age, and gender interact to affect volume loss. However, vascular disease showed no interaction effect. The volumes of several regions were also correlated with MMSE and MoCA scores.

Comment

The study demonstrates the utility of Neuroreader software in detecting brain atrophy. These results may inform ways to diagnose and monitor the effects of TBI using MRI volumetric data. However, the study does not establish causal connections between brain atrophy and cognitive impairment. Future studies should increase the sample size and correlate regional brain atrophy with measures from neuropsychological tests.

[1] Meysami et al. (2019) *J Alzheimers* Dis, PMID: 31561375

Machine Learning-Based Dynamic Mortality Prediction after Traumatic Brain Injury

Moderate-to-severe TBI patients often require immediate treatment in intensive care units (ICUs). The purpose of the ICU is to stabilize the patient and mitigate the risk of secondary injury. This typically involves monitoring several physiological variables, included intracranial pressure (ICP), cerebral perfusion pressure (CPP), mean arterial pressure (MAP), among others. In this study, Raj et al. used automated machine learning algorithms to predict patient mortality based on ICU data.[1] They retrospectively identified adult TBI patients (n = 472) treated at three university hospitals. All were monitored in ICUs for more than 24 hours. The authors sampled ICP, CPP, MAP, and GCS (Glasgow Coma Scale) data at 5 minute intervals. The GCS component involved a neurological "wake-up" test administered by ICU nurses. The authors analyzed these data, identifying feature variables and applying them to two dynamic algorithms: ICP-MAP-CPP and ICP-MAP-CPP-GCS. Performance of the algorithms in predicting 30-day, all-cause mortality was assessed by the receiver operating characteristic. The AUC of ICP-MAP-CPP algorithm was 0.67 at day one and 0.81 at day five. For the ICP-MAP-CPP-GCS algorithm, AUC was 0.72 at day one and 0.84 at day five. Performance of both algorithms was better than the widely-used IMPACT–TBI prognostic model. The study demonstrates the clinical utility of just four ICU variables in identifying TBI patients at risk of death.

Comment

The study provides evidence that machine learning can identify TBI patients at risk of death. While the algorithm is reliable, it could be improved by examining the mortality rate beyond 30 days, as well as accounting for the clinical manipulation of feature variables. More sophisticated neural network approaches may produce even better results. While further research is needed, the ability to identify vulnerable patients would allow more intensive monitoring and treatment by hospital staff.

[1] Raj et al. (2019) *Sci Rep*, PMID: 31776366

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 October to December 2019.

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For more information, contact DVBIC: 800-870-9244 | usarmy.ncr.medcom-usamrmc-dcoe.mbx.dvbic-pao-requests@mail.mil