Defense and Veterans Brain Injury Center
TBI Hot Topics Bulletin
THIRD QUARTER CY 2019

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

Olfactory, Cognitive and Affective Dysfunction Assessed 24 Hours and One Year After a Mild Traumatic Brain Injury (mTBI)

Olfactory dysfunction is often reported after TBI. However, its relation to mild TBI (mTBI) is not well understood, in part because of the time-variability of post-injury reporting. Giguère et al. evaluated the integrity of olfaction in 20 mTBI patients within 24 hours of injury using the Sniffin' Sticks Inventory Test (SSIT).[1] Patients were compared to 22 neurologically healthy controls with orthopedic injuries. The mTBI group had lower olfactory function composite scores compared to the controls. Hyposmia (diminished olfaction) was present in 55% of the mTBI patients but only 4.5% controls. After one year there were no significant differences between the groups on olfactory function. Because others have reported an association between deficits in cognition and olfaction, the study also evaluated cognitive (RBANS; within 24 hours post-injury), executive function (Delis-Kaplan Executive Function System, Trail Making Test, Digit Span task from the WAIS-IV; within 24 hours post-injury), and affective profiles (Hospital Anxiety and Depression Scale; within 24 hours and one year post-injury). There was no significant correlation between olfaction and cognitive, executive function, or anxiety/depression scores in the mTBI patients.

Comment

While this article contributes to the scarce literature on mTBI and olfaction, the findings are preliminary. The sample size (20 mTBI, 22 orthopedic control) was small with significant attrition at follow-up: only 12 mTBI and 7 orthopedic control patients were available. In addition, the use of different olfaction measures across time points (SSIT within 24 hours of injury; self-administered University of Pennsylvania Smell Identification Test at 1 year follow-up) and the assessment of symptoms (Rivermead Post-concussion Symptoms Questionnaire) exclusively at follow-up complicates causal interpretation. Further studies with larger sample sizes and better controls are warranted.

[1] Giguère et al. (2019) *Brain Inj*, Epub 21 June. PMID: 31223039

In vivo Detection of Cerebral Tau Pathology in Long-Term Survivors of Traumatic Brain Injury

It is possible that a single TBI may precipitate a series of biomolecular changes that result in neurodegenerative disease (e.g., dementia, Alzheimer's disease, CTE). These conditions are often characterized by the aggregation of hyperphosphorylated tau, a misfolded protein which accumulates in the neocortex. Positron emission tomography (PET) using the flortaucipir ([18F]AV-1451 and [18F]T807) radioligand has recently been used to quantify tau pathology in vivo. In this study Gorgoraptis et al. used PET flortaucipir to examine the spatial distribution and relationships of tau pathology in individuals with a history of a single TBI.[1] They compared 21 participants who sustained a moderate-to-severe TBI at least 18 years prior and 11 neurologically healthy controls. All participants were administered flortaucipir intravenously and scanned by PET. In addition, they underwent MRI, blood and CSF sampling, and neuropsychological testing. The authors quantified tau using voxel-wise, *z*-score maps that compared flortaucipir binding between the TBI and control groups. The extent of flortaucipir binding varied among the TBI participants, but there were significant decreases in focal lesions compared to non-lesioned areas. The authors also observed a mean increase in flortaucipir binding in the right lateral occipital cortex for TBI participants compared to the controls. Binding in TBI participants was significantly correlated with total tau in cerebrospinal fluid (CSF), ubiquitin C-terminal hydrolase L1 (UCH-L1) in the cerebral gray matter, and phosphorylated tau in the white matter. In contrast, control participants showed no correlations between flortaucipir binding and biomarkers. Finally, there was a negative correlation between the extent of binding and white matter integrity in TBI participants: Flortaucipir binding was increased in white matter showing lower fractional anisotropy (FA) and reduced tissue density.

Comment

This study situates the use of flortaucipir PET among other, more established, measures of TBI pathology. However, the small sample size does limit generalizability. More importantly, it remains an open question whether biomarkers, such as tau, may be diagnostic of specific neurodegenerative diseases. To this end, location is likely just as important as sensitivity. The 2019 NIH CTE Diagnosis Conference concluded that "the tau lesion considered pathognomonic [for CTE] was an abnormal perivascular accumulation of tau in neurons, astrocytes, and cell processes in an irregular pattern at the depths of the cortical sulci."[2] Gorgoraptis et al.'s study lacks this spatial precision, as do many neuroimaging investigations. Accordingly, more research is necessary to study the spatial distribution of this ligand in both TBI and neurodegenerative disease.

[1] Gorgoraptis et al. (2019) *Sci Transl Med*, Epub 4 Sept. PMID: 31484787
[2] National Institutes of Health. (8 Aug. 2019) www.ninds.nih.gov/Current-Research/Focus-Research/Traumatic-Brain-Injury/NIH-Chronic-Traumatic-Encephalopathy. Accessed 15 Nov. 2019.

Association of Concussion Symptoms With Testosterone Levels and Erectile Dysfunction in Former Professional US-Style Football Players

Trauma-induced pituitary damage from TBI may lead to posttraumatic hypopituitarism, which could result in low testosterone and/or erectile dysfunction (ED). In this study, Grashow et al. explored the relationships between time-of-injury, football-related concussive symptoms, and medication recommendations/use for low testosterone and/or ED in a large cohort of former National Football League (NFL) players.[1] Participants (n = 3,409) completed questionnaires with items on concussive events, symptom history, recommendations/use of medication for low testosterone and/or ED, and the following variables: race/ethnicity, football position, number of seasons, body mass index (BMI) during professional play, current BMI, use of performance enhancing drugs, prescription medications for select conditions, diagnosed medical conditions, anxiety/depressive symptoms, and alcohol intake. Overall, 18.3% and 22.7% of participants reported indicators of low testosterone and ED, respectively. Of those reporting indicators, approximately 40-50% were taking medications for the indicated condition. A robust, positive relationship was observed between self-reported history of concussive events/symptoms at the time of injury and self-reported history of low testosterone and/or ED indicators. When current health conditions were included in the model, prescription pain medication use and sleep apnea were the largest statistical mediators of the relationship between concussive symptoms and outcome.

Comment

The study addresses an important research gap regarding concussion and male sexual dysfunction. While the population was large, the reliance on self-report data over the course of an entire career may have resulted in recall bias. The changing perceptions on concussive sports injuries and the stigma of sexual dysfunction warrant more tightly controlled studies.

[1] Grashow et al. (2019) *JAMA Neurol*, Epub 26 Aug. PMID: 31449296

A Common Neural Signature of Brain Injury in Concussion and Subconcussion

The midbrain is susceptible to the biomechanical forces exerted by TBI. However, it may also be damaged by repetitive, subconcussive head impacts (RSHI). Quantifying the effect of these injuries is important as they may factor into the development of neurodegenerative diseases. Hirad et al.'s study explored midbrain integrity in two cohorts of collegiate football players: RSHI and mTBI.[1] For the RSHI cohort, they monitored players (n = 42) over the course of a season (practice and games) using helmet-based accelerometers, which recorded the number and intensity of impacts. RSHI participants were scanned with diffusion tensor imaging (DTI) before and after the season. For the mTBI cohort, the authors conducted a retrospective analysis of concussed football players (n = 29) and neurologically healthy controls (n = 58) with no history of concussion. The mTBI cohort underwent plasma sampling and DTI scans within 72 hours of injury. Subsequent analyses focused on the midbrain. For all groups (RSHI, mTBI, and controls), they defined regions of interest situated on the left and right corticospinal tract (CST). For the RSHI cohort, there was reduced fractional anisotropy (FA) in the CST for post-season compared to pre-seasons scans. FA scores were also negatively correlated with the number of head impacts, particularly for cases involving rotational acceleration. The mTBI participants had lower FA compared to the controls. In addition, CST FA was negatively correlated with levels of peripheral tau in 13 participants.

Comment

This study indicates that injury to the midbrain CST is a salient indicator of head injury, both for concussive and subconcussive exposures. While the authors argue the data show a connection between subconcussive impacts and neurotrauma, the observational design limits causal inferences. In addition, focusing solely on CST overlooks potential connections between RSHI and other white matter tracts.

[1] Hirad et al. (2019) *Sci Adv*, Epub 7 Aug. PMID: 31457074

Copenhagen Head Injury Ciclosporin (CHIC) Study: A Phase IIa Safety, Pharmacokinetics, and Biomarker Study of Ciclosporin in Severe Traumatic Brain Injury Patients

Ciclosporin is believed to limit the secondary effects of TBI through inhibition of cyclophilin D-dependent activation. To date, ciclosporin's neuroprotective effects have been demonstrated in more than 20 experimental studies. Its safety has been addressed in three phase IIa clinical trials. The CHIC study was conducted as an uncontrolled, phase II study to investigate the pharmacokinetics (PK) and safety profiles of two different doses of NeuroSTAT (a novel lipid emulsion of ciclosporin) in severe TBI patients.[1,2] Patients (n = 16) with non-penetrating, severe TBI (Glasgow Coma Scale 4-8) received a 2.5 mg/kg bolus dose infusion of NeuroSTAT followed by either a 5 mg/kg/day (first 10 patients) or 10 mg/kg/day (last 6 patients) schedule. PK parameters indicated that all patients had detectable and dose-proportional levels of ciclosporin in the blood and cerebrospinal fluid (CSF). The authors found that blood levels of biomarkers of brain injury such as glial fibrillary acidic protein (GFAP), ubiquitin C-terminal hydrolase L1 (UCH-L1), neurofilament light (NF-L), and tau decreased during the days of NeuroSTAT infusion followed by increasing concentrations after cessation of the treatment. There were no significant adverse effects associated with treatment.

Comment

Current pharmacologic options for severe TBI treatment are limited. Overall, administration of ciclosporin at higher doses over a 5-day infusion were found to be safe and well-tolerated with preliminary signs of efficacy. Given that safety was the primary endpoint for this study, administration of NeuroSTAT was permitted at a more delayed time (Mean = 36 hours post-injury). Future studies of the neuroprotective efficacy of ciclosporin should focus on an earlier therapeutic window.

[1] Kelsen et al. (2019) *J Neurotrauma*, Epub 1 Aug. PMID: 31210099
[2] EudraCT number: 2012-000756-34. ClinicalTrials.gov number: NCT01825044

Association Between Plasma GFAP Concentrations and MRI Abnormalities in Patients with CT-negative Traumatic Brain Injury in the TRACK-TBI Cohort: A Prospective Multicentre Study

Previous research has found that levels of glial fibrillary acidic protein (GFAP) are correlated with intracranial injuries visible on CT scans. However, in some CT-negative patients subsequent MRIs detect intracranial injury. Yue et al. investigated relationships between GFAP and MRI findings using TRACK-TBI data.[1] Their cohort consisted of TBI patients seen at level 1 trauma centers across the United States. All had a Glasgow Coma Scale (GSC) score between 13 and 15 (*n* = 1,234). The authors also recruited neurologically healthy controls with and without orthopedic injury. Blood samples were collected within 24 hours of injury. MRIs were obtained within 7-18 days of injury. For the CT-negative patients, a receiver operating characteristic analysis assessed the ability of GFAP to discriminate between MRI-positive and MRI-negative cases. The area under the curve (AUC) was 0.78 (95% CI 0.726 - 0.829). GFAP levels in the CT negative patients were as follows: MRI-positive cases (414.4 pg/mL); MRI-negative cases (74.0 pg/mL); orthopedic controls (13.1 pg/mL); and healthy controls (8.0 pg/mL).

Comment

The study indicates GFAP may reveal some brain injuries not apparent on conventional CT. A limitation of this study is the lack of any DTI investigation of microstructural integrity. While further research is needed, the study may inform the development of objective technologies to rapidly identify TBI, which would be particularly useful for military operations in theatre.

[1] Yue et al. (2019) Lancet Neurol, Epub 23 Aug. PMID: 31451409

TECHNOLOGY UPDATES

TBI Diagnostic Kit Developer Medicortex Receives DoD Funding

The DoD Combat Casualty Care Research Program recently funded the biotechnology company Medicortex Finland to further advance their TBI diagnostic kit, ProbTBI.[1] When completed, it is anticipated ProbTBI will consist of a paper strip (similar to the current pregnancy test kits) that reveals a "+" or "-" when dipped in saliva or urine to signify whether a person has sustained a TBI. Although the company has not specified the test's biomarker, a 2016 review paper by the Medicortex identifies 12 potential candidates.[2] According to the Medicortex website, they observed significant elevations in certain body fluid biomarkers for TBI patients versus healthy controls in a preclinical study and a clinical trial (*n* = 24). Currently, a second clinical trial (*n* = 160) is underway which aims to determine the sensitivity/specificity and time-related fluctuations of these biomarkers for application in the ProbTBI kit.[3] The study will collect neurological status assessments, and blood, urine, and saliva samples, five times a year and compare these findings between healthy, orthopedically injured, and TBI groups.

Comment

At present, ProbTBI has not published any preclinical/clinical data or specified the biomarkers they plan to investigate. This limits independent evaluation of their technology.

[1] Science Business. (5 July. 2019) www.sciencebusiness.technewslit.com/?p=36987. Accessed 31 Sept. 2019.
[2] Adrian et al. (2016) *eNeuro*, Epub 21 Dec. PMID: 28032118
[3] ClinicalTrials.gov number: NCT03306563

Machine Learning May Optimize Head Trauma Decision Rules Used for Children

A new study aims to build a computer program to identify children who may forgo computed tomography (CT) scans after head injury. CT scans are used to rule out the need for immediate surgical intervention after TBI. However, CT scans expose children to ionizing radiation so it would be helpful to have guidance on when scans can be safely avoided. The Pediatric Emergency Care Applied Research Network (PECARN) developed head trauma rules in 2009 to triage child TBI cases. One group is defined as individuals with low risk of clinically important TBI and not in need of a CT. Recently, researchers at Brown University and the Massachusetts Institute of Technology collaborated to improve the original PECARN head trauma rules using an optimal classification tree (OCT), a method of machine learning.[1] OCT maps possible outcomes from initial conditions by creating decision nodes from which multiple outcomes branch out, akin to branches on a tree. The study developed the OCT-based rules by leveraging the same data (*n* = 42,412 children across 25 hospital emergency departments) used to develop the original PECARN rules. The OCT-based rules showed statistically significant improvements in specificity compared to the PECARN (69.3% vs 52.8% in children < 2 years; 65.6% vs 57.6% children ≥ 2 years) but no statistical difference in sensitivity.

Comment

The study demonstrates the efficacy of OCT-based rules and presents a promising starting point toward building an effective tool for triage of child TBI cases. However, their implementation requires a computer whereas PECARN involves only a pen and paper questionnaire. There may then be technological and/or cultural resistance to OCT's adoption. Moreover, factors affecting the feasibility of this tool in real-world emergency situations have not been assessed. So at present, this methodology is not practical for implementation by most clinicians.

[1] Bertsimas et al. (2019) *JAMA Pediatr*, Epub 1 Jul. PMID: 31081856

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 July to September 2019.

DISCLAIMER: The *Bulletin* is not intended as a comprehensive report on all TBI-related scientific literature published during the quarter. Scientific articles and technology updates included are selected from Google News searches on TBI or concussion based on the number of news sources covering the article. News stories are selected based in part on the quantity of news coverage and in part on a subjective evaluation of relevance and importance. Inclusion in the TBI Hot Topics Bulletin does not represent an endorsement of the research or findings.

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