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Traumatic Brain Injury Center of Excellence
TBI Hot Topics Bulletin
FIRST QUARTER CY 2021

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SCIENTIFIC STUDIES

Unique Diagnostic Signatures of Concussion in the Saliva of Male Athletes: The Study of Concussion in Rugby Union through MicroRNAs (SCRUM)

Recent advances in high-throughput screening indicate that multiple ribonucleic acid (RNA) species are diagnostic of mild TBI (mTBI)/concussion. Critically, RNA is detectable in saliva, which enhances its practicality as a concussion biomarker. In this prospective, observational study, Di Pietro et al. assessed small non-coding RNAs (sncRNA) in saliva. The authors' goals were to (1) determine whether sncRNA expression is associated with concussion, (2) evaluate the time course of expression post-injury, and (3) determine whether specific sncRNAs can predict clinical outcomes. The authors assessed professional rugby players from two UK clubs for two seasons. Testing in the first season identified biomarkers of interest. Testing during the second validated these biomarkers in predictive models. For all participants, head injury assessments (HIA) were performed at three time points: immediately after suspected concussions (HIA1); 3 hours later at post-game medical assessments (HIA2); and 36–48 hours later to monitor clinical progress (HIA3). Participants with head injuries were classified as HIA+(n = 106), and those without as HIA–(n = 50). Uninjured players and those with musculoskeletal injuries (MSK) were also evaluated. Season 1: Saliva samples were collected at each HIA. Next-generation sequencing identified RNAs of interest. The strongest candidates were validated with quantitative polymerase chain reaction (PCR). Initial screening found 38 known microRNAs (miRs), 233 putative miRs, and 168 other small-RNAs as being differentially expressed between the HIA+, MSK, and uninjured groups. Subsequent analyses revealed that 32 biomarkers were differentially expressed between HIA+ and HIA– at different time points. The sncRNA with the strongest discriminative ability was let-7f-5p at HIA3. Season 2: Receiver operating characteristic analysis (ROC) showed a panel of 14 sncRNAs differentiated between HIA+ and controls (i.e., HIA–, MSK, and uninjured) at the HIA2 and HIA3 time points. HIA2 had the largest area under the curve (AUC = 0.96).

Comment

The study demonstrates the ability of sncRNAs to distinguish between concussed and non-concussed rugby players. The expression of sncRNAs accurately discriminated between groups and changed with time since injury. The three-hour time frame (HIA2) may be most clinically relevant. Analysis of sncRNAs may facilitate the diagnosis of concussion. Moreover, their detection in saliva reduces the invasiveness of biomarker testing, which usually requires a blood sample. Further research should look for similar relationships in other brain injuries (e.g., falls, motor vehicle accidents, etc.).

Di Pietro et al. (2021) *Br J Sports Med*, Epub 23 Mar. PMID: 33757972

BBB Pathophysiology-Independent Delivery of siRNA in Traumatic Brain Injury

Small interfering ribonucleic acids (siRNA) can inhibit proteins involved in secondary brain injury. Nucleic acid-based therapeutics may prove effective in treating chronic TBI sequelae. However, siRNAs normally cannot cross the blood-brain barrier (BBB). In this study, Li et al. examined a nanoparticle platform for the delivery of siRNA-based therapies. They engineered siRNA nanoparticles (NPs) to have different surface chemistries (e.g., PEG, Tf, GSH, and 80 NPs) and tested their ability to cross the BBB and silence relevant genes. The authors first used a fluorescent probe to signal the uptake of NPs into cultured neural cells. They then examined the NPs' ability to silence luciferase expression. The GSH-NPs and 80-NPs showed significant gene silencing at all doses tested. These experiments were repeated in healthy mice. Mice were injected intravenously with different fluorescently tagged NPs. They were euthanized (4 and 24 hrs.) and their brains were examined with an in vivo imaging system. Mice injected with 80-NPs and GSH-NPs showed the highest fluorescent signals. Surface chemistry density also affected the results. High density (H) formulations, such as 80 (H)-NPs, showed better BBB transport, cellular uptake, and gene silencing. Finally, the authors evaluated 80 (H)-NPs in mice with experimentally induced TBI. They found 80 (H)-NPs cross the BBB of brain-injured mice at both early (2 hrs.) and late (2 wks.) time points. Moreover, 80 (H)-NPs were effective in silencing tau expression, a protein associated with neuroinflammation and neurodegeneration.

Comment

Crossing the blood-brain barrier is a significant obstacle to the delivery of pharmaceuticals. This article demonstrates proof-of-principle that siRNAs, engineered with specific nanoparticles, can cross the BBB and affect genes that influence secondary brain injury. However, findings in animals, mice in particular, often do not translate to human subjects. More research is necessary to replicate these findings in other species and pave the way for clinical trials.

Li et al. (2021) *Sci Adv*, Epub 1 Jan. PMID: 33523853

Differences in Sport-Related Concussion for Female and Male Athletes in Comparable Collegiate Sports: A Study from the NCAA-DOD Concussion Assessment, Research and Education (CARE) Consortium

Both male and female athletes risk sport-related concussion (SRC) when they compete. However, differences in anatomy, play style, and rules may yield different rates and/or types of concussion between the sexes. In this prospective, cohort study, Master et al. investigated differences in SRC (e.g., injury rates, characteristics, recovery, etc.) between male and female athletes in similar collegiate sports. The data were obtained from the Concussion Assessment, Research, and Education Consortium (CARE), a study run by the National Collegiate Athletic Association (NCAA) and the Department of Defense (DOD). The surveillance identified 1,071 individuals with SRCs that fit study requirements. Analyses showed females were more likely to sustain SRCs from impacts with sport-related objects, such as a ball or puck (29%). Males were more likely to sustain SRCs from direct collisions with opponents (35%). For both males and females, SRCs occurred more frequently in practice than in games. Initial assessments showed females had higher (worse) symptom severity scores on the Sport Concussion Assessment Tool-3 (SCAT3) and the Brief Symptom Inventory-18 (BSI-18). Cases of short-term amnesia were more common among males. Overall, males and females did not differ on loss of consciousness (LOC) or the number of days before return-to-play (RTP). However, subgrouping the data did reveal disparities for sport-type. Females had longer RTP times (i.e., median number days) for contact sports (e.g., basketball, soccer, lacrosse), whereas males had longer RTP times for limited contact sports (e.g., baseball, volleyball, gymnastics). Return-to-play was similar for Division I level sports, but females had longer RTP times for Division II/III.

Comment

In addition to biological factors, this research suggests there may be several extrinsic factors that contribute to SRC sex differences. The authors address numerous variables in their study. However, impact severity is absent, this being unattainable without accelerometers. Still, their findings could prove useful. Understanding how recovery varies between men and women and across extrinsic factors may inform clinical profiles, aid treatment, and improve return-to-play decision-making.

Master et al. (2020) *Br J Sports Med*, Epub 21 Dec. PMID: 33355211

Link Between Mild Traumatic Brain Injury, Poor Sleep, and MRI-Visible Perivascular Spaces in Veterans

Traumatic brain injury can hamper the ability to clear perivascular waste products via the brain's glymphatic system. Perivascular spaces (PVS), which are visible on MRI, are markers of this condition and associated with morbidity. In this study, Piantino et al. evaluated relationships between the presence of PVS, TBI status, post-concussive symptoms, balance measures, and sleep quality. Their initial sample consisted of 68 Iraq and Afghanistan veterans who were part of a larger cohort study. Of these, 12 had MRI motion artifacts that precluded further analysis. For the remaining 56, the authors used an automated program to determine the number and volume of PVS hypo-intensities on MRI scans. The authors evaluated the number and severity of mTBIs using a semi-structured interview. They assessed post-concussive symptoms and balance using the Neurobehavioral Symptom Inventory (NSI) and sleep quality with the Pittsburg Sleep Quality Inventory (PSQI). Multivariate linear regression demonstrated a relationship between mTBI and PVS. More mTBIs were associated with increases in PVS number and volume. There was also a significant interaction between mTBI number, poor sleep, and PVS volume. Finally, there were positive correlations between PVS burden, post-concussive severity, and balance problems.

Comment

Previous studies have quantified PVS in TBI patients. However, they have often relied on expert neuroradiological analysis with limited sensitivity. This study demonstrates the utility of an automated methodology to determine PVS number, volume, and morphology. PVS burden may be related to a disruption in glymphatic exchange, which normally occurs during sleep. Future work should leverage this technology in larger, more diverse samples. Laboratory sleep studies may also be informative.

Piantino et al. (2021) *J Neurotrauma*, Epub 18 Feb. PMID: 33599176

Head Injury and 25-Year Risk of Dementia

Research suggests that a history of head injury is associated with a higher rate of dementia in later life. Prior studies have focused on specific populations such as those represented in military and medical claims databases. In this study, Schneider et al. used data from the Atherosclerosis Risk in Communities (ARIC) Study to evaluate relationships between head injury and later dementia in a diverse population. The ARIC is a community-based, longitudinal cohort study (n = 14,376) with varied racial (Black and White) and sex (female and male) representation (Mean age 45 years at baseline; 56% female; 27% Black). Self-report and examination of clinical records determined 3,440 participants had sustained a head injury during or before the study. The sample also had 2,350 cases of dementia (730 in the head injury group) identified through self-evaluations, ICD, and death certificate codes. The authors used covariate-adjusted models to calculate the cumulative incidence of dementia over a 25-year time frame. For the whole sample, they found head injury increased the hazard ratio for dementia (HR = 1.44; 95% CI = 1.32 – 1.57). They observed a dose-dependent relationship, where participants with two or more head injuries had higher HRs (HR = 2.14) than those with only one (HR = 1.25). They also found head injury and dementia were more strongly associated among females (HR = 1.69) compared to males (HR = 1.15) and among White individuals (HR = 1.55) compared to Black individuals (HR = 1.22).

Comment

While prior research has linked head injury and dementia, the specifics are not well understood. This study sought to further elucidate these relationships and observed some potential sex and racial differences. While the sample size is impressive, the authors lacked detailed information on the participants' head injuries and relied on self-report data. Further research is necessary to validate these differences and uncover contributing factors.

Schneider et al. (2021) *Alzheimers Dement*, Epub 9 Mar. PMID: 33687142

Poor Sleep Correlates with Biomarkers of Neurodegeneration in Mild Traumatic Brain Injury Patients: A CENC Study

Mild traumatic brain injury (mTBI) is associated with chronic disorders like sleep impairment. Few longitudinal studies have examined relationships between TBI neuropathology and sleep. Blood-based biomarkers such as neurofilament light (NFL), tau, and amyloid-beta (Aβ42) are reliable indicators of TBI severity, as well as correlates of neurodegenerative disease. In this study, Werner et al. examined sleep quality, cognitive performance, and levels of blood biomarkers (i.e., NFL, tau, and Aβ42) in mTBI patients (n = 138) and controls (n = 44). The data were collected as part of the ongoing Chronic Effects of Neurotrauma Consortium (CENC) longitudinal study. The mTBI patients were all in the chronic phase of injury (mean time since injury = 8.3 yrs.). Participants were assessed for sleep quality with the Pittsburgh Sleep Quality Index (PSQI) and for cognitive performance (i.e., cognitive flexibility, inhibitory control, and working memory) with a neuropsychological battery. Overall, the authors found no differences in tau, NFL, and Aβ42 between mTBI patients and controls. However, subdividing the sample into good and bad sleepers showed that the mTBI group had elevated NFL and lower scores on executive function and "stop-go" tasks. This relationship was not observed in controls. The PSQI was correlated with NFL and tau, but not Aβ42.

Comment

This study found that sleep quality and executive function scores in mTBI patients were moderately correlated with blood NFL, suggesting a link between sleep, executive functioning, and neurodegeneration. Further investigations should examine these relationships using laboratory sleep quality measures. Such research would contribute to an understanding of the relationship between sleep and mTBI as well as assess the utility of NFL as an objective biomarker.

Werner et al. (2020) *Sleep*, Epub 6 Dec. PMID: 33280032

ABOUT

The *Bulletin* is a product of the Traumatic Brain Injury Center of Excellence (TBICoE) Research Branch and provides a quarterly summary of TBI research and information relevant to health care providers. This issue covers research published from January to March 2021.

DISCLAIMER: The *Bulletin* is not intended as a comprehensive report on all TBI-related scientific literature published during the quarter. Scientific articles included are selected from Google News and PubMed searches as well as FDA and industry alerts on TBI or concussion. News stories are selected based partly on the quantity of news coverage and partly 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 us at 800-870-9244 | dha.TBICoEinfo@mail.mil.