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Traumatic Brain Injury Center of Excellence

TBI Hot Topics Bulletin

THIRD QUARTER 2021

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

The Natural History of Sport-Related Concussion in Collegiate Athletes: Findings from the NCAA-DoD CARE Consortium

Previous research has investigated clinical recovery from sports-related concussion (SRC). Most studies have small samples and vary widely in their characteristics (e.g., different sports; collegiate, amateur, or professional; men or women). Broglio et al. performed a prospective, longitudinal analysis of 1,751 concussed collegiate athletes participating in 22 different sports at 30 U.S. academic institutions. The study was part of the NCAA-DoD CARE Consortium, an effort to understand the natural history of sport-related concussion. Their analysis found that return to participation (RTP) was initiated, on average, 6.4 days post-injury. Full RTP status was achieved at a median of 12.8 days. Certain factors contributed to early symptom resolution (i.e., shorter RTP duration). These include early initiation of the RTP protocol, frequent post-injury assessments, concussions sustained during competition, use of ADHD medication, and being male. In contrast, greater symptom severity and longer RTP duration were associated with less frequent symptom assessments, concussions sustained during practice, three or more concussions, and participation in limited contact sports. Overall, most athletes were approved to begin RTP (92%) or participate in sports without restriction (85%) at 1-month post-injury.

Comment

The study found that intrinsic and extrinsic factors affect clinical recovery after SRC. A strength is its use of a large, diverse sample of collegiate athletes. Previous reports suggest that clinical recovery occurs within 10-14 days. This study indicates that it may take up to one month for full symptom resolution and RTP. The authors endorse a longer RTP duration as well as being mindful of the athlete's associated risk factors. This approach is more conservative compared to the protocols currently advocated by the NCAA and is consistent with the DoD's Progressive Return to Activity Clinical Practice Guidelines (health.mil/TBIProviders).

Broglio et al. (2021) *Sports Medicine*, Epub 8 Aug. PMID: 34427877

Complement Factor C1q Mediates Sleep Spindle Loss and Epileptic Spikes after Mild Brain Injury

Subcortical brain structures like the thalamus may be more vulnerable to secondary as opposed to primary brain injury. Holden et al. used a mouse model to examine the effects of chronic inflammation on corticothalamic function after mild traumatic brain injury (mTBI). Specifically, they investigated the initiating molecule for the complement pathway (C1q), as it is thought to play a role in post-TBI inflammation. The authors performed controlled cortical impact (CCI) and sham procedures on the right somatosensory cortex of mice. Immunohistochemical analysis was performed 3 weeks later to reflect the latent period following mTBI in humans. Compared to sham, CCI mice showed increased inflammatory markers (related to astrocytes and microglia) as well as C1q expression in the peri-injury site, the ventrobasal thalamus (VB), and the thalamic reticular nucleus (nRT). This resembles thalamic tissue samples taken from human TBI patients post-mortem. In addition, the increased expression of inflammatory markers in the CCI mice was associated with neuronal loss in the VB and nRT. Whole-cell patch clamp recordings revealed C1q expression was associated with changes in neuronal function, specifically a reduction in the frequency of inhibitory postsynaptic currents and the amplitude of excitatory postsynaptic currents. Single-nucleus RNA sequencing showed that microglial cells were the primary source of C1q expression in the thalamus. Finally, in vivo electrocorticographic recordings showed that elevations in C1q expression affected nRT-mediated electrical activity, specifically an increase in sleep spindles and a decrease in focal epileptic spikes.

Comment

The study showed that increased C1q expression is associated with inflammation, neuronal loss, and altered synaptic transmission in mice after mTBI. The authors also interrupted C1q activity using an antibody that binds to C1q, blocking its downstream activity. Administration of the antibody 24 hours post-injury (then twice a week for 3 weeks) reduced inflammation and neuronal loss in CCI mice. Future studies should examine the translation of these findings to humans, particularly whether C1q antibody treatment mitigates inflammation and post-concussive symptoms.

Holden et al. (2021) *Science*, Epub 10 Sep. PMID: 34516796

A Randomized Clinical Trial of Plasticity-Based Cognitive Training in Mild Traumatic Brain Injury

Cognitive rehabilitation may benefit mild traumatic brain injury (mTBI) patients. However, few rehabilitation studies have examined the efficacy of computerized, self-administered, cognitive training. Mahncke et al. addressed this gap in a multisite, randomized, double-blind clinical trial. The authors recruited mTBI patients with cognitive impairments from military and VA hospitals. They compared BrainHQ to other active control interventions (i.e., off-the-shelf computer games). BrainHQ is an adaptive, plasticity-based cognitive training program designed to improve the speed and accuracy of auditory and visual information processing. Under the supervision of a healthcare coach, the participants completed a self-administered training program consisting of 65 sessions, 5 days a week for 13 weeks. Neuropsychological tests were administered pre- and post-training. The BrainHQ group demonstrated more cognitive improvements compared to the active control group. This was true at both post-training and a 3-month follow-up.

Comment

The study found BrainHQ improves the speed and accuracy of information processing in mTBI patients. Computerized training can be self-administered under remote supervision and is a practical addition to a broader rehabilitation plan. Further research is necessary to explore the mechanisms of action and whether treatment effects are durable. For the latest clinical recommendations, please refer to the VA/DoD Clinical Practice Guideline for the Management and Rehabilitation of Post-Acute Mild Traumatic Brain Injury (www.healthquality.va.gov/guidelines/rehab/mtbi) and the DoD Clinical Recommendation: Cognitive Rehabilitation for Service Members and Veterans following Mild-to-Moderate Traumatic Brain Injury (www.health.mil/Reference-Center/Publications/2020/07/30/Cognitive-Rehabilitation-for-Following-Mild-to-Moderate-TBI-Clinical-Recommendation-Full).

Mahncke et al. (2021) *Brain*, Epub 7 Jul. PMID: 34312662

Functional Outcomes Over the First Year after Moderate to Severe Traumatic Brain Injury in the Prospective, Longitudinal TRACK-TBI Study

Moderate-to-severe traumatic brain injury (msTBI) is associated with poor health outcomes and the need for long-term care. Studies show msTBI patients often have residual symptoms and disabilities. However, few have tracked outcomes from the acute through chronic phases of recovery. McCrea et al. conducted a large, longitudinal study examining the extent of recovery in moderate-to-severe TBI patients. They accessed data from 18 level 1 trauma centers in the U.S. using the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study. There was a total of 484 patients, 17 years of age or older, with msTBI. All were admitted to participating trauma centers within 24 hours of injury. The authors used the Glasgow Coma Scale (GSC) to evaluate initial severity, then the Glasgow Outcome Scale-Extended (GOSE) to assess functional difficulties in six major life domains: independence at home, independence outside the home, work functioning, social/leisure functioning, relationship problems, and other problems that affect daily life. On admission, patients had low mean GCS scores (moderate: 10.4; severe: 4.3) and most required assistance in basic functioning (GOSE scores: 1-3). However, by 12-months post-injury, 75% of the moderate group and 50% of the severe showed functional independence at home (GOSE scores: ≥ 4). Functional improvement began earlier than 3 months post-injury for 70% of the moderates and 45% of the severe. In addition, severe acute impairment (i.e., a vegetative state) did not necessarily signify poor long-term functional outcomes.

Comment

The study's findings have implications for the clinical management of msTBI. Findings suggest the degree of impairment within the first 2 weeks is not necessarily indicative of unfavorable long-term outcomes. Many patients regained functional independence a year post-injury. A limitation of the study is the initial determination of severity. The GCS was obtained upon emergency department arrival. Because many patients were sedated, pharmacologically paralyzed, and/or intubated, the GCS may not accurately reflect the real severity of brain injury.

McCrea et al. (2021) *JAMA Neurology*, Epub 1 Aug. PMID: 34228047

Head Impact Modeling to Support a Rotational Combat Helmet Drop Test

Head injury is a major concern for the U.S. military. Warfighters are at risk of blunt trauma and blast exposure. The primary method for head protection is the helmet. However, some aspects of helmet technology are outmoded. The Advanced Combat Helmet (ACH) military specification (mil-spec) provides blunt impact acceleration criteria based on translational (150 G) acceleration. These criteria are applicable for skull fractures and hematomas, but not diffuse axonal injury (DAI) which is caused by rotational head movement. The ACH mil-spec needs an update with rotational standards. Terpsma et al. provided this information using an impact simulation model specialized for recording rotational metrics. They first obtained an experimental baseline using an ACH-fitted magnesium (Mg) Department of Transportation (DOT) headform. Further simulation tests included both a linear constrained configuration and a modified rotational configuration. The linear configuration included a hemispherical target with a constrained drop arm. The modified configuration included an anvil with a flat surface inclined 45° and a cradle to allow the helmeted headform to have a freefall impact with the anvil. The rotational configuration also replaced the DOT headform of the ACH mil-spec with a Hybrid III headform. All other variables were constant across the two tests, including an impact speed of 3.1 m/s (10 ft/s). The results showed that the rotational configuration produced brain strains 4.3 times greater than those of the linear configuration.

Comment

The study's findings support the use of a rotational impact component in ACH mil-spec test requirements. These data may be useful for determining whether helmets provide adequate protection, as the rotational component more closely resembles the real-world mechanisms of TBI. This study and subsequent research may aid in the development of more effective personal protective equipment for the warfighter.

Terpsma et al. (2021) *Military Medicine*, Epub 11 Sep. PMID: 34508268

Pathological Computed Tomography Features Associated with Adverse Outcomes after Mild Traumatic Brain Injury: A TRACK-TBI Study with External Validation in CENTER-TBI

Computed tomography (CT) can identify a wide spectrum of intracranial lesions. Analysis of these features may enhance TBI assessment and prognosis beyond a simple positive test. Yuh et al. identified different lesions in CT scans and determined their association with recovery status and outcomes after mild traumatic brain injury (mTBI). The study included 1,935 participants from the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study. Participants were recruited from level 1 trauma centers in the U.S. within 24 hours of injury. They were at least 17 years of age at the time of enrollment with a GCS score of 13-15. The Glasgow Outcome Scale-Extended (GOSE) was used to assess incomplete recovery (GOSE scores < 8 vs. 8) and unfavorable outcomes (GOSE scores < 5 vs. ≥ 5), measured at 2 weeks and 3-, 6- and 12-months post-injury. The findings indicate that subtypes of intracranial hemorrhage differ in their prognostic implications up to 1-year post-injury (i.e., some lesions lead to worse outcomes compared to others). The results were comparable to those from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study.

Comment

Evaluating CT results at a granular level (i.e., beyond the simple presence or absence of abnormal findings) may improve providers' prognosis of mTBI. For example, patients presenting with contusions, subarachnoid hemorrhage, and/or subdural hematoma may have worse outcomes at 12 months post-injury than those with an epidural hematoma. Information such as this could assist in TBI treatment and management, especially in military hospitals where triage is critical.

Yuh et al. (2021) *JAMA Neurology*, Epub 1 Sep. PMID: 34279565

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 July to September 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.

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