VIEWPOINT

Traumatic Brain Injury
An International Knowledge-Based Approach

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Traumatic brain injury (TBI) is a multifaceted condition, not an event. Traumatic brain injury is broadly defined as an alteration in brain function or other evidence of brain pathology caused by an external force that can occur in traffic, at home, at work, during sports activities, and on the battlefield. Traumatic brain injury is an important cause of death and disability for children and an exponentially increasing source of morbidity and mortality in older adults.[1] Each year in the United States, at least 1.7 million people seek medical attention for TBI; it is a contributing factor in a third of all injury-related deaths.[2] Many more persons, particularly those with mild TBI, are never seen by a clinician. These injuries (at times considered to be "concussions") are often dismissed by the medical community as mild with few or no consequences. Although no single definition of concussion is widely accepted, it typically affects orientation, memory, and may involve loss of consciousness.[3] Often, patients are not carefully followed up over time, despite the increasing appreciation that TBI can affect long-term physical, cognitive, emotional, and social domains of function. The Centers for Disease Control and Prevention estimates that 2% of the US population lives with disabilities directly attributable to TBI,[2] with annual direct and indirect costs estimated at more than $76.5 billion.[1]

Although the current media attention on TBI in the military and sports has raised awareness, it also has highlighted just how little is known. Many basic questions remain unanswered, such as whether a brain injury has actually occurred, when an athlete can safely return to play, or which individuals with TBI will develop postconcussive syndrome or posttraumatic stress.

Understanding of the molecular and cellular mechanisms of TBI has improved; however, these advances have failed to translate into a single successful clinical trial or treatment. These failures are largely attributable to the broad classification of TBI as mild, moderate, or severe that does not incorporate newer insights and findings from diagnostic tools, such as imaging and proteomic biomarkers. This classification scheme is derived from the Glasgow Coma Scale (GCS); outcomes are measured using the Glasgow Outcome Scale-Extended (GOSE), which is global and relatively insensitive. This symptom-based approach does not permit mechanistic targeting for clinical trials. A nuanced, more advanced approach requires the transition to a more precise disease classification model that is based on pathoanatomical and molecular features. Clinical research has further been limited by lack of standards for data collection and limited multidisciplinary collaboration. However, the increasing recognition of the complexity of TBI and of the limitations of previous research are beginning to foster collaborative changes in research and clinical approaches for TBI.

The US National Institute of Neurological Disorders and Stroke, US Department of Defense, and the National Institute on Disability and Rehabilitation Research have identified and supported the need for improved TBI classification using diagnostic and outcome tools beyond the GCS and GOSE as well as the need for a standardized approach to data collection. In response, multidisciplinary, international expert panels were convened that comprised clinician-scientists from 49 institutes and agencies across the TBI care spectrum from emergency services to rehabilitation. By consensus, these panels developed the TBI Common Data Elements for clinical data, imaging, biospecimens, and outcomes.[4] Work by various groups has further refined the TBI Common Data Elements and validated the feasibility of collecting these data across sites and across the injury spectrum, ranging from mild to severe.[5] Integrated databases, imaging repositories, biosample repositories, and multicenter expertise have also been developed. This dataset is the first to populate the Federal Interagency Traumatic Brain Injury Research (FITBIR) repository, an informatics system that provides a collaborative platform for imaging, assessment, and genomics research.

The future success of TBI research and clinical care requires interdisciplinary and international collaboration that concentrates concurrently on the following: establishing a new TBI classification and taxonomy, improving outcome assessments, identifying the economic effects, and creating a scalable and sophisticated infrastructure for clinical care and research.

Recent work in each of these areas holds promise. In the Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study,[6] magnetic resonance imaging uncovered structural abnormalities in approximately 30% of 135 patients with mild TBI and a normal computed tomographic (CT) scan.[6] The presence of these abnormalities predicted unfavorable outcome at 3 months. This represents an important step toward improved stratification of heterogeneous patient subgroups within the population traditionally classified as having mild TBI or concussion. Additionally, newly validated blood-based glial proteomic biomarkers have been shown to detect reliably the presence and severity of brain injury seen on CT scan.[7] Ongoing work is using the TBI Common Data Elements outcome measures to examine patient-oriented domains, including cognitive, psychosocial, physical function, and quality of life. Combining these more refined outcome data in a multidimensional scale is expected to improve the detection of treatment effects. Large between-center and between-country dif-

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ferences in outcome[8] may facilitate comparative effectiveness of clinical decisions. As with other diseases, patient-, clinician-, and system-level factors may influence outcome and costs.

The European Commission and the Canadian Institutes of Health Research have each announced the first recipients of funds from the International Initiative for Traumatic Brain Injury Research. This initiative was established in 2011 as a collaborative effort of the European Commission, Canadian Institutes of Health Research, and the US National Institutes of Health, with the goals of advancing global clinical TBI research, treatment, and care. The US National Institute of Neurological Disorders and Stroke will soon announce the US recipient of a multicenter award to participate in the International Traumatic Brain Injury Research Initiative. This represents the beginning of an innovative research model, developed collaboratively through public-private partnerships. The large, international TBI patient database should have sufficient power to identify new diagnostic and prognostic markers of disease, refine outcome assessments, and identify best practices.

The complexity of TBI is such that no single investigator, institution, funding organization, or private company can make progress on its own. Traumatic brain injury needs a broad-based, sustainable, multidisciplinary approach aimed at elucidating mechanisms of TBI biology, identifying risk factors, and developing treatments. First steps should include the design of longitudinal studies to follow the natural history of TBI, which should help prioritize promising avenues for research.

President Obama recently unveiled The BRAIN Initiative—Brain Research Through Advancing Innovative Neurotechnologies.[9] This "big data and team science" approach has been successfully operationalized in the National Institutes of Health's Alzheimer's Disease Neuroimaging Initiative and is uniquely applicable to TBI. Traumatic brain injury research and clinical care are decades behind other diseases, such as cancer and cardiovascular disease, and there is an important need to close existing knowledge gaps. Political will and resources are needed to create meaningful change for the global disease that is traumatic brain injury.

ARTICLE INFORMATION

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