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Neuroimaging and traumatic brain injury: State of the field and voids in translational knowledge

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ABSTRACT

Traumatic brain injury (TBI) is a leading cause of death and disability in every developed country in the world and is believed to be a risk factor in the later development of depression, anxiety disorders and neurodegenerative diseases including chronic traumatic encephalopathy (CTE), Alzheimer's Disease (AD), Parkinson's Disease (PD), and amyotrophic lateral sclerosis (ALS). One challenge faced by those who conduct research into TBI is the lack of a verified and validated biomarker that can be used to diagnose TBI or for use as a prognostic variable which can identify those at risk for poor recovery following injury or at risk for neurodegeneration later in life. Neuroimaging continues to hold promise as a TBI biomarker but is limited by a lack of clear relationship between the neuropathology of injury/recovery and the quantitative and image based data that is obtained. Specifically lacking is the data on biochemical and biologic changes that lead to alterations in neuroimaging markers. There are multiple routes towards developing the knowledge required to more definitively link pathology to imaging but the most efficient approach is expanded leveraging of in vivo human blood, serum, and imaging biomarkers with both in vivo and ex vivo animal findings.

This review describes the current use and limitations of imaging in TBI including a discussion of currently used animal injury models and the available animal imaging data and extracted markers that hold the greatest promise for helping translate alterations in imaging back to injury pathology. Further, it reviews both the human and animal TBI literature supporting current standards, identifies the remaining voids in the literature, and briefly highlights recent advances in molecular imaging. This article is part of a Special Issue entitled 'Traumatic Brain Injury'.

Contents

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1. Introduction and scope of the problem

As reviewed in other articles in this special issue, TBI is a major public health problem and one that still lacks objective diagnostic tools, neurobiological predictors of outcomes, and allows the bounding criteria to identify those at greatest risk of poor long term outcomes including progression to neurodegenerative disease. What has clearly emerged from the recent literatures in military and sports medicine is that rapid and appropriate clinical management — ranging from rest to monitoring of intracranial pressure to neurosurgical intervention in more severe cases — can significantly alter the patient outcome particularly when started within 48 h of the injury. However, for such intervention and management to occur the injury must first be identified. For ensuring appropriate use of clinical resources, objective diagnostic studies and biomarkers of injury must be identified and validated. Neuroimaging, either alone or in combination with blood based biomarkers, is ideal in this role as it is still a clinical standard in cases with progression of behavioral or neurologic status to rule out contusion or hemorrhage. Beyond use to rule out emergent conditions that may require immediate neurosurgical intervention, the goal of neuroimaging should also include a role in identification of treatable injuries, to prevent secondary damage, and to provide useful prognostic information. Neuroimaging can provide important information for long-term treatment of TBI, identifying chronic sequelae, determining prognosis, and guiding rehabilitation for TBI patients.

Although TBI has long been known to be a major public health concern, the attention paid to TBI has increased recently in part due to the prevalence and incidence of injury among service members supporting the Global War on Terror and increased civilian awareness of the risk of sports concussions. The Armed Forces Health Surveillance Center (AFHSC) reported that during a 10-year period (January 1997–December 2006), 110,392 military members had at least one TBI-related medical encounter, and there were 15,732 hospitalizations with TBI-related diagnoses (Cameron et al., 2012; Cernak and Noble-Haeusslein; Lange et al., 2012). The prevalent use of improvised explosive devices (IEDs) increases the likelihood that American military personnel will be more frequently exposed to incidents that can cause TBI resulting in repeated TBIs in the same veteran increasing the risk for poorer long term outcomes.

In civilians, TBI is commonly caused by motor vehicle accidents, pedestrian versus motor vehicle accidents, sports, falls, and assaults. Within this list it seems prudent to separate out TBIs caused by athletic participation as the causes of injury are somewhat unique as is the risk for repeated concussions and repeated sub-concussive blows to the head. The question of the prevalence and risk caused by repeated concussions is still somewhat unknown as the bounding conditions for risk of later neurodegenerative disease have yet to be defined. However the risk of poor outcome and later neurodegeneration disease secondary to concussion is likely defined by some interaction between genetic factors, number of concussions, severity of injury, latency between concussions, age of injury and adherence to an appropriate clinical management protocol. Survivors of TBI are often left with significant cognitive, behavioral, and communicative disabilities, and some patients develop long-term medical complications, such as epilepsy and Alzheimer's disease (Centers for Disease Control and Prevention (CDC) et al., 2013; Gilbert et al., 2014; Pitkanen and Immonen, 2014; Prince et al., 2012; Sivanandam and Thakur, 2012; Yeh et al., 2013). Given the prevalence of sports concussions (300,000 sports-related concussions each year in the United States (Gessel et al., 2007)) and the high profile of those with exceptionally bad outcomes, public concern has become focused on the long term risk of repeated concussions and the associated long-term consequences. Similarly, those in occupations at high risk for repeated exposure (such as veterans) and repeated concussive injury have also driven not only public concern but also federal funding into the validation and development of diagnostic and prognostic markers as identification of a TBI is the first critical step towards risk reduction.

The challenge for diagnostics among those suffering a TBI is of greatest concern in the mildest form of injury. A traumatic brain injury (TBI) can be classified as mild if loss of consciousness and/or confusion and disorientation is shorter than 30 min (Hirtz et al., 2007; Vos et al., 2012). Mild TBI is not only the most prevalent severity of injury but it is often missed at the time of initial injury (McAllister et al., 2001; Mechtler et al., 2014; Vos et al., 2012). The challenge is exacerbated by usually normal MRI (magnetic resonance imaging) and CT (computerized tomography) scans. In the acute phase following injury, mild TBI is associated with a 10% risk for intracranial abnormalities like contusion, subdural or epidural hematoma, brain swelling, or subarachnoid hemorrhage (Vos et al., 2012). There is a very low risk (1%) of life-threatening intracranial hematoma and a very low mortality of 0.1% in adults and in children in mild TBI (although children have a lower risk) (Bigler and Maxwell, 2012; Eierud et al., 2014; McAllister et al., 2001; Mendez et al., 2005; Vos et al., 2012). Even in the absence of the severe consequences listed above and in the presence of normal neuroimaging, the concussed individual can experience cognitive problems such as headache, difficulty thinking, memory loss, attention deficits, mood swings and frustration and may be at an increased risk of poor outcomes if clinical management is ignored or a second injury occurs within some critical window. But, for the majority of those with a mild TBI, recovery and return to pre-injury baseline represents the gross majority (Bigler and Maxwell, 2012; Eierud et al., 2014). However, in 10 – 20% (approximately) of people with mild TBI, symptoms remain (Bazarian and Atabaki, 2001) and the factors that contribute to this minority are not well understood but likely include acute injury management, previous injury, genetic contributions and damage to the brain that is below the threshold for identification on standard clinical imaging.

2. Role of imaging in TBI

Neuroimaging can and should have a significant role in defining the bounding criteria and risk prediction model to identify those at increased risk of neurodegeneration in acute and chronic TBI. It is one of the few methods that allow in vivo and non-invasive assessments of neuropathology. The challenge with defining the role of imaging in TBI is that we do not have a single imaging modality that meets all of the following criteria: (1) accessible and safe for use in acute injury in those with altered consciousness; (2) equally sensitive to all injury severities, (3) equally sensitive to the acute through chronic time course, and (4) appropriate for identification of the earliest of pathological changes in the transition to neurodegenerative disease. Practically, this means that instead of assessment of the injury as a continuum (or continuous variable), we triage and segregate our imaging tools in large part by injury severity (to be treated as categorical). This is a challenge in terms of identifying factors that predict who will be at greater risk for neurodegeneration and the precipitating cause for increased concern as these factors likely can be found in all stages of injury (for example, less than full recovery in mild without acute imaging, delayed recovery in repeated TBI and MRI in the chronic stage only with less than full recovery). Further complicating this challenge is that there is an understandable disconnect between the clinical need and motivation for imaging and the lack of sensitivity of that imaging across our continuum.

Neuroimaging does provide some degree of diagnostic value in TBI (for example, identification by computed tomography (CT) scan of blood product or swelling following moderate to severe injury), characterization of acute reaction to injury (for example, PET ligands for inflammation), quantification of injury severity (for example, quantification of degree of white matter damage assessed via diffusion tensor imaging), assessment of degree of alteration of functional networks (for example, resting state functional magnetic resonance imaging), and chronic progressive alterations (for example, changes in cortical thickness, atrophy, alterations in biochemistry of high risk brain regions and the growing promise of imaging tau and amyloid pathology).