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Review

Updates on Improving Imaging Modalities for Traumatic Brain Injury

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Abstract

The Center for Disease Control and Prevention reports that traumatic brain injury (TBI) was related to over 64,000 deaths in the United States in 2020, equating to more than 611 TBI-related hospitalizations and 176 TBI-related deaths per day. There are both long- and short-term sequelae involved with the pathophysiology of TBI that can range from mild to severe. Recently, more effort has been devoted to understanding the long-term consequences of TBI and how early detection of these injuries can prevent late clinical manifestations. Obtaining proper, detailed imaging is key to guiding the direction of intervention, but there is a gap in the understanding of how TBI imaging can be used to predict and prevent the long-term morbidities seen with even mild forms of TBI. There have been significant strides in the advancement of TBI imaging that allows for quicker, more affordable, and more effective imaging of intracranial bleeds, axonal injury, tissue damage, and more. Despite this, there is still room for improved standardization and more data supporting the justification of using certain imaging modalities. This review aims to outline recent advancements in TBI imaging and areas that require further investigation to improve patient outcomes and minimize the acute and chronic comorbidities associated with TBI.

Keywords: multimodality imaging; diffused neuronal injury; ultra-high field magnetic resonance imaging susceptibility-weighted imaging; diffusion tensor imaging; traumatic microbleeds; convolutional neural networks; perfusion computed tomography; functional magnetic resonance imaging; near-infrared spectroscopy; transcranial doppler

1. Introduction

To prevent the high rates of mortality and long term morbidities associated with traumatic brain injury (TBI), when a patient is admitted to the neuro-critical care unit for TBI there are recommendations for which imaging modalities to proceed with, relevant thresholds, and ranges based on clinical evidence, facilitated primarily by the Brain Trauma Foundation (BTF) [1,2] and the Seattle International Severe Traumatic Brain Injury Consensus Conferences (SIBICC) [3]. Despite this, the heterogeneity of TBI and associated gaps in the understanding of its pathophysiology hinder reaching a consensus on standardized imaging protocols and classification. The standardization of TBI management protocols has been shown to be an important factor in contributing to lower risk-adjusted in-hospital mortality and further improving clinical outcomes of patients admitted to neuro-critical care units [4]. However, there are practices common in neuro-critical care units that are commonplace, but are not currently supported by the BTF and SIBICC due to a lack of evidence regarding efficacy, and inadequate understanding of how certain parameters affect patient outcomes and how multiple imaging modalities can be used in combination for optimized multimodal monitoring [5].

Multimodality imaging is critical to understanding the numerous, simultaneous physiochemical properties associated with TBI, and can be used to detect pathological changes more effectively and better deliver targeted therapies to specific neural regions. Currently, multimodality monitoring occurs primarily in neuro-critical care units and considers several metrics using both invasive and non-invasive imaging techniques. There are centers that have combined intracranial pressure (ICP), cerebral microdialysis (CMD), and tissue oxygenation for years, but the level of evidence that directs the accompanying thresholds and evidence of the prognostic capabilities of combining these modalities is lacking [6]. The Brain Trauma Foundation provides official guidelines for some of these metrics and thresholds as well, but there is still a lack of evidence to support the parameters associated with several of the techniques used in multimodality imaging [7].

Immediately upon injury, TBI is associated with prolonged inflammatory cytokine upregulation, decreased oligodendrocyte numbers, increased nitric oxide, and reduced cerebral blood flow. These mechanisms, while protective, exacerbate tissue damage by mobilizing immune and glial cells that cause edema, inflammation, and further diffuse damage [8]. The Glasgow Coma Scale (GCS) is the traditional way to diagnose and classify TBI based on neurological responsiveness and has a strong correlation with patient morbidity and mortality [9]. The GCS is based on three major scores that are categorically divided into eye-opening, verbal, and motor capabilities, scaled from 1–6 for a total score from 3–15. The score can then be related to the level of injury, with 3–8 corresponding with a severe injury, 9–12 with a moderate injury, and 13–15 with a mild injury. A multi-center investigation called the Transforming

Research and Clinical Knowledge in TBI (TRACK-TBI) assessed the usefulness in using the GCS to inform clinical decision making and found that considering the three categorical scores individually could improve the assessment and treatment of patients with TBI [10]. Furthermore, while the GCS has proven useful in triaging patients and directing treatment, it is unable to exclude long-term consequences, such as post-concussive syndrome, functional outcomes, and overall morbidity [11,12].

A major goal in the advancement of TBI imaging is to develop techniques that can prognosticate potentially debilitating, chronic consequences of even mild TBI so that early treatment can be implemented to prevent this. The standard initial imaging protocol for TBI involves computed tomography (CT) followed by 1.5 T and 3.0 T magnetic resonance imaging (MRI), often paired with CT angiography to detect any possibility of cerebrovascular injury. CT are relatively quick and affordable and thus are beneficial for triage, time-sensitive decision making, follow-up imaging, and detecting fractures associated with epidural hematomas, vascular injuries, and cerebrospinal fluid leaks [12]. MRI are more expensive and require specialized equipment that may not be accessible in every clinical environment, but are more specific for detecting axonal injuries and pathological blood byproducts following the initial injury. In addition to accessibility and affordability, MRI speed and sensitivity to disruptive motion are also limitations associated with its use [13].

2. Detecting Microbleeds and Diffused Axonal Injury

Minutes to days following TBI, secondary injury can result from excitatory neurotransmitter release, leading to elevated intracellular calcium which activates caspases and free radicals that contribute to tissue degradation and cellular apoptosis [14]. Ultra-high field MRI susceptibility-weighted imaging (SWI) is being investigated as a superior method compared with the traditional evaluation using 1.5 T and 3.0 T MRI, and has been shown to better detect diffuse axonal injury (DAI), which can allow for better prognostication and treatment. SWI MRI combines filtered-phase data and magnitude data gathered from three-dimensional (3D) gradient-echo sequence evaluations to compare the magnetic susceptibility of adjacent tissues and detect early microhemorrhages that may be associated with DAI [5]. Axonal degeneration can be found in as many as 72% of patients with moderate or severe TBI and is related to both the acute clinical manifestation of TBI and progressive, chronic neurodegenerative issues following the initial injury [15–17]. Traumatic microbleeds result from damage to cerebral vessels and can be used as an indirect marker of DAI [18]. Some studies suggest that this relationship between microbleeds and DAI is questionable and should be further investigated to reliably detect DAI following TBI [19–22]. Nonetheless, one study shows that the number of microbleeds has a substantial association with the acute clinical state of patients and chronic neurobehavioral parameters following head injury; therefore, obtaining imaging that can reliably detect microbleeds is an important consideration for both the short and long-term benefit of patients [23,24].

Diffusion tensor imaging (DTI) is another modality that may help advance the classification system for TBI through heightened sensitivity for detecting axonal injuries with more accuracy. DTI uses the spatial diffusion weight of water to determine multiple different TBI parameters, including fractional anisotropy and mean diffusivity [25]. There is a lack of conclusive data on the usefulness of DTI due to the variable pathophysiology and severity of TBI [26]. In general, increases in mean diffusivity and decreases in fractional anisotropy are associated with the decreased structural integrity of neural white matter. These changes can also be seen with other comorbidities and vary between demographics, so useful quantitative assessment via DTI requires a comparison with control readings [27]. In mild TBI, DTI has been shown to detect increases in fractional anisotropy and decreases in diffusivity, which may be associated with acute cytotoxic edema [28]. Some studies suggest that mild TBI patients with severely reduced fractional anisotropy are associated with worse outcomes, as measured by the Glasgow Outcome Scale [29]. Conversely, other studies show that patients with severe TBI and high fractional anisotropy are associated with more favorable outcomes, possibly due to late axonal regrowth [30]. For moderate to severe TBI, fractional anisotropy and diffusivity, as measured by DTI, has been shown to change up to 18 months after the initial injury and may be correlated with long-term functional outcomes [31]. Further work is required to understand the normal range of DTI metrics within different demographics and how these changes correspond with the severity of injury and symptom resolution, and to further standardize DTI interpretation [5,32]. To better understand the baseline range of normal DTI measurements, acquisition of pre-injury data needs to be improved. This is difficult to do based on the unpredictability of sustaining a TBI; however, one study that was able to image a TBI patient 12 and 23 months prior to the injury and then 2 weeks and 8 months post-injury found that using 7 Tesla MRI was beneficial in collecting this longitudinal data [33].

3. Detecting Tissue Perfusion and Brain Activity

When a mechanical force causes a head injury that results in brain swelling, the increased intracranial mass results in a decrease in intracranial cerebrospinal fluid and blood flow to compensate for the increase in pressure, as described in the Monro-Kellie hypothesis [34]. Initially upon injury, the expansion of the brain is offset by the elastic

nature of the brain tissue, but as intracranial pressure increases the compliance of the tissue decreases, creating a pressure gradient that affects cerebral perfusion. Based on these physiological principles, the Lund concept was developed as the first holistic guideline for treating TBI based on brain volume maintenance and optimizing brain perfusion. The Lund concept was followed by alternative guidelines suggested by the BTF based on meta-analyses and systematic reviews. When comparing the Lund concept and BTF guidelines, they differ substantially [35]. The Lund concept suggests a range of 50–70 mmHg while the 2017 BTF and SIBICC guidelines recommend 60–70 mmHg [28,35]. The lack of consensus between standard practices can lead to differing health outcomes and it is necessary to stay up to date with the evolution of TBI imaging care.

Historically, global cerebral hypoperfusion is associated with worse outcomes and cannot be detected by traditional non-contrast head CT [36]. Tissue perfusion is not only a major concern during the acute phase of TBI, but is linked to chronic clinical deterioration and worsened outcomes following treatment of the primary injury [37]. Tissue perfusion is commonly evaluated with perfusion computed tomography (CTP), dynamic susceptibility-weighted contrast-enhanced perfusion magnetic resonance imaging (DSC-MRI), and MRI arterial spin labeling (ASL) [5,38]. CTP has been shown to detect cerebral contusions 7 days earlier than non-contrast CT and predict 6-month outcomes through the evaluation of frontal lobe perfusion [39,40]. CTP has also been shown to be useful in tracking changes in cerebral perfusion pressure and targeting cerebral loci at risk of hypoxia [41]. Despite this, clinical trials that clearly suggest CTP should be part of the standard of care for TBI imaging are lacking [5].

TBI imaging modalities can be categorized as invasive or non-invasive. Non-invasive monitoring modalities are gaining traction in the detection and treatment of TBI-related injuries, but there is still work to be done regarding the standardization and understanding of their benefits, as much of the research originates from single-center retrospective reviews [7]. Invasive approaches are used in iatrogenic hemorrhages in around 10% of cases and are not typically associated with severe, long-term negative effects [42]. Intracranial pressure (ICP) monitoring and cerebral microdialysis (CMD) are two of the primary invasive methods of brain monitoring used following TBI.

ICP monitoring can be used to derive cerebral perfusion pressure and pressure reactivity indices that can provide information about brain tissue oxygenation. The standard practice of ICP involves implementing a closed external ventricular drain, which is affordable and can simultaneously alleviate cerebrospinal fluid (CSF) build-up contributing to elevated ICP, although this carries a higher procedural risk [43]. Due to the risk of inserting closed external ventricular drains, intraparenchymal monitoring devices are becoming more commonplace because they are easier to insert and can be delivered at the patient's bedside, although they are unable to provide the same inherent CSF drainage utility [42]. A recent advancement in the utilization of intraparenchymal monitoring devices involves their combination with CSF pumps to match the benefit of closed external ventricular drains [44].

CMD can directly measure biomarkers in cerebral extracellular fluid, such as glucose, lactate, and pyruvate, by inserting a catheter into the brain parenchyma [44,45]. Some studies show that high lactate to pyruvate ratios, low extracellular glucose, low tissue oxygenation, and impaired pressure reactivity indices measured by CMD are associated with worse outcomes [46,47]. While there is a consensus of appropriate thresholds and management strategies for these modalities based on international consortiums, high-level, evidence-based studies to support these recommendations are lacking [7].

Functional magnetic resonance imaging (fMRI) is useful for measuring the activity of specific areas of neural tissue based on oxygenation [48,49]. Severe TBI can be associated with less brain tissue functionality which can lead to comatose states and disorders of consciousness [50]. There is a lack of imaging modalities that can directly track and predict the return of consciousness, though fMRI has shown changes in cortical function in unresponsive patients and may represent a promising tool for predicting the prognosis of TBI-associated loss of consciousness and coma [51]. Proton magnetic resonance spectroscopy (1H-MRS) is another imaging modality that can be useful in prognosticating the functional outcomes of TBI patients. 1H-MRS detects the interaction of protons to quantify the cellular changes in neural tissue based on the chemical alterations associated with neuronal death and demyelination [52]. Reduced levels of *N*-acetylaspartate may be associated with early brain injury and long-term outcomes in patients with TBI [53]. In mild TBI, 1H-MRS readings have been shown to vary even after concussion symptoms are no longer noticeable [54,55]. Magnetic resonance elastography (MRE) is non-invasive way to measure mechanical function in the brain using MRI pulses to create acoustic wave propagation from which to measure tissue displacement [56]. This measurement of brain "stiffness" has been used to study several other clinical concerns, such as multiple sclerosis and aging, and may be useful in the prognosis of TBI [5].

Though it is not currently supported by the Brain Trauma Foundation guidelines, near-infrared spectroscopy (NIRS) is a promising non-invasive method for prehospital screening of intracranial bleeding. NIRS uses chromophore absorption to detect fluid and hemoglobin oxygenation near the brain, which can help to detect executive dysfunction in post-TBI patients with neurocognitive disorders. One study compared handheld NIRS Infrascanner scan time, ease-of-use, and change in treatment compared with CT in the prehospital screening of TBI. The Infrascanner had a sensitivity of 93.3% and a specificity of 78.6%, took from 1.5–10

minutes to perform, and had a median ease-of-use of 7 out of 10. On the downside, the Infrascanner detected three false positive and one false negative, is difficult to obtain scans of the dorsal occipital site when the patient is supine, did not significantly change the ultimate course of treatment of any patients, and emits an audio signal when scanning is complete, which can be difficult to hear in noisy environments [57].

The Brain Trauma Foundation also does not endorse the use of transcranial doppler (TCD) ultrasonography due to lack of evidence of its usefulness. Despite this, TCD is commonly used in the management of TBI; one study found it to be the second most used form of ICP monitoring at the patient's bedside and that 40% of neuro-intensive care units use TCD in the management of TBI [58]. The use of TCD may be questioned due to the dependency on user-experience, but robotic TCDs are being investigated as an alternative that could eliminate this tendency for user error and allow TCD to become more reliable in monitoring TBI [5].

4. Automated Reading and Processing of Data

The sheer volume of imaging data requires clinical settings to adopt a system that can systematically and thoroughly analyze and predict the status of TBI patients. In addition to this, manual analyzation of imaging data can be time consuming and prone to human error, potentially leading to delayed intervention and misdiagnosis of cerebral injury. Convolutional neural networks (CNNs) utilize biological neural machine learning to interpret brain imaging by hierarchically breaking down and comparing complex images through pattern recognition. In the future, CNNs could be used to specify protocols to best treat brain injuries based on the specific neural networks interrupted [59]. One study showed that CNNs can detect microbleeds with a similar accuracy to experienced radiologists, though there are many false positives associated with automatic algorithms for detecting cerebral microbleeds. This study suggested a two-stage detection framework based on 3D fast radial symmetry transform of images from SWI and false positive reduction by CNN analysis of high-pass filtered phase images through CNN to improve the utility of automatic TBI imaging. The suggested two-stage cerebral microbleed detection algorithm had an optimal sensitivity of 95.8%, precision of 70.9%, and 1.6 false positives per case. This performance is comparable with experienced human raters and demonstrates the applicability of deep learning techniques to imaging analysis [60]. Another advancement in the processing of TBI imaging data is the use of automated methods of MRI segmentation to increase the speed and accuracy of MRI readings. Like the detection of cerebral microbleeds, the use of region segmentation is critical in the processing of MRI data and is often performed manually, which is time consuming and can result in user-error variability. There may be benefit in investigating how deep learning algorithms can be applied to automated MRI segmentation frameworks to improve the ease and quality of imaging analysis [61].

Nanoparticles are a recent advancement in TBI treatment that could increase the site-specific delivery of TBI therapy by promoting the accumulation and retention of these treatments to specific injured regions of the brain. Currently, nanoparticle delivery systems are either limited by single imaging modalities or have multimodal imaging capabilities, but are limited by complicated synthesis methods. One study suggested that mixed lanthanide oxide magnetic nanoparticles with a ultrasmall 2 nanometer core and hydrodynamic size of 13.5 nanometers can be detected by multimodality imaging using high spatial fluorescence imaging and temporal MRI frequencies and can quickly accumulate and be retained by brain parenchyma [62].

In addition to the advancements in automated imaging reading using CNNs and multimodality models, there are several preclinical TBI imaging strategies being developed to more accurately model TBI under experimental conditions. For example, some animal studies have shown that using fMRI to better characterize structural and functional changes in gray and white matter may provide a novel way to diagnose low grade TBI that cannot be efficiently classified with traditional CT and MRI scanning. When used alongside other imaging, these methods can provide data on diffusivity and fractional anisotropy in specific regions of the brain, as well as the degree of diffuse axonal injury, based on myelin and diminished microstructural integrity of the brain [63]. In 2014, one of the first animal studies to establish that interrupted networks and functional connectivity abnormalities between neural tissue injured during TBI and specific brain regions were associated with functional status post-TBI was conducted [64]. More recent animal studies have built upon this to demonstrate how fMRI and DTI can be used to track diffused and persistent neural damage post-TBI, based on neuronal connectivity, axonal integrity, and neurovascular function. fMRI-based resting-state functional connectivity (RSFC) was used in one study to measure neural connectivity and further showed that decreased RSFC strength in the cortex, hippocampus, and thalamus, as well as an increase in interhemispheric asymmetry, were more common in rat models with fluid percussion injury reminiscent of TBI [65]. Recent animal studies have also shown that using microarrays to detect long non-coding RNA (lncRNA) can be helpful in further understanding the pathophysiology of the TBI. Rats with induced TBI were shown to have alterations in messenger RNA (mRNA) and microRNA (miRNA) in their neural tissue, shortly following the injury. While these pieces of genetic material do not directly correspond to protein, they can induce the expression of molecules that may be involved in the progression of injury after the initial insult. One study found that the most common pathways that were aberrantly activated

by lncRNA following surgically-induced, TBI-like injury in rats were inflammation and apoptosis, two of the major processes that contribute to secondary, long-term TBI morbidity. Energy metabolism, chemokine activation, hypoxia, and DNA transcription were also significantly altered in the experimental rats. Using animal models to study the genetic implications of TBI can provide a physiological rationale on which to base future imaging and treatment modalities [66].

5. Conclusions

This review provided an overview of some of the recent imaging improvements seen in the diagnosis and treatment of TBI. With the massive quantity of information available and the promise of even more knowledge from future advancements, it seems that one of the primary concerns moving forward is implementing multimodality imaging and developing reliable algorithms for the automated processing of this data through CNNs. It is also apparent that the use of certain imaging modalities such as NIRS and TCD is not standardized, and that consensus regarding acceptable ranges of certain parameters such as fractional anisotropy and mean diffusivity is lacking. Early TBI imaging can be an immensely powerful tool for acute treatment, but with recent literature revealing the potentially debilitating long-term effects of even low severity TBI, such as sports-associated concussions, advancements in TBI imaging could be an equally important tool for preventing chronic injuries that manifest long after the patient leaves the clinic.

Author Contributions

Conceptualization and overview by BLW. AA selected the relevant references and made substantial contributions to the conception and design of this manuscript. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

Brandon Lucke-Wold and Amelia Alberts are guest editors of the special issue of Pathophysiological Mechanisms, Biomarkers, and Treatments for Traumatic Brain Injury (TBI). We declare that Brandon Lucke-Wold and Amelia Alberts did not participate in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Gernot Riedel.

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