Suitability of Neuroimaging in Diagnosis of Sleep, Fatigue, Perfusion and Metabolite Deficits after Mild Traumatic Brain Injury

Subhendra N Sarkar[1]*, Xiang Fu Zhang[1], Mary Alice Browne[1] and John Claude Krusz[2]

[1]Department of Radiologic Technology & Medical Imaging, New York City College of Techology, City University of New York, New York, USA

[2]Anodyne Headache and Pain Care, Dallas, USA

*Corresponding author: Subhendra N Sarkar, Department of Radiologic Technology & Medical Imaging New York City College of Techology, City University of New York, A414, 300 Jay St, Brooklyn, NY, USA.

Abstract

The objective of this review is to summarize the findings of promising imaging approaches that may provide mechanistic understanding of mild traumatic brain injury (mTBI). Imaging in mTBI has so far explored brain tissue damage or physiologic changes involving perfusion and metabolite distribution. Clinical manifestations of sleep, visual disturbances and associated fatigue observed in a substantial number of mTBI patients have not been diagnosed at all. Although the association of TBI with sleep disorders is being recognized, the mechanistic relation is far from clear. The association of fatigue and sleep with mTBI raises the question which one comes first. This has been addressed to some extent in this review. Patients with mTBI and persistent post-concussive symptoms have a high incidence of medial temporal lobe injury leading to altered hippocampal, caudate and insular perfusion. The mTBI literature discusses the importance of oxidative stress and BBB disruption. Although SPECT is very sensitive in this regard, various imaging modalities with tools to map perfusion, metabolite and functional deficiencies are showing significant promise. It is a concern that MR spectroscopic abnormalities in mTBI go mostly undetected. We could not find any work that addresses secondary metabolite levels like GABA, Glutamate and so on or explores the whole brain to assess mTBI induced global metabolite abnormalities. Further mechanistic understanding to link sleep and fatigue is necessary. In conclusion, combining tissue biology to model the impact of oxidative stressor and injury localization with tracer imaging and functional connectivity mapping is preferred as well as global perfusion/metabolite measurements. Multi-modal approaches hold more promise than advanced applications of single modalities. Focal surgical procedures as in the placement of neurological shunts or neuroimplants offer excellent templates to study the deficits from static loads in pre-planned locations and may help mechanistic evaluation of mTBI that usually involves dynamic and global loads.

Keywords: Mild TBI; mTBI; Head trauma; Fatigue; Perfusion imaging; SPECT; MRI in TBI; Functional MRI in TBI; MR Spectroscopy in TBI; Metabolite imaging in TBI

Abbreviations: TBI: Traumatic Brain Injuryl; mTBI: Mild Traumatic Brain Injury; SPECT: Single Photon Emission Computed Tomography; PET: Positron Emission Tomography; MRI: Magnetic Resonance Imaging; CT: Computed Tomography; MEG: Magnetoencephalography; DTI: Diffusion Tensor Imaging (Diffusion Tractography); fMRI: Functional MRI; LOC: Loss of Consciousness; PTA: Post Traumatic-Amnesia; GSC: Glasgow Coma Scale; CDC: Center for Disease Control; PCD: Post Concussive Disorder

Introduction

Mild traumatic brain injury (mTBI) is defined by the Management of Concussion/mTBI Working Group as Normal appearance in imaging; a brief period of loss of consciousness (LOC) less than 30 minutes; post traumatic amnesia (PTA) for less than a day; and with Glasgow Coma Scale (GCS) between 13-15. The injury is usually as a result of the head being struck by an object or undergo a whiplash motion. Consistent with the prevalence of Mild TBI, an estimation of 42M people worldwide and more than 1.2M in USA suffer from mTBI or concussion every year [1]. The exact damage it has on the brain is largely a mystery due to the lack of reliable diagnostic tools. Most patients with mTBI have impaired or absent cerebral autoregulation within 48 hours of injury [2], especially, sleep disorder, being one of the main complaints on the same day as mTBI [3]. Still neurocognitive deficits are reported

only in 10% of cases, significantly underestimating the long-term burdens associated with it [3-6]. CDC has recently included sleep disturbances as a common effect of mTBI. The chronic stage of mTBI involves a complex and, linked/mix of symptoms including headaches, fatigue and sleep disorders for which the diagnostic and treatment options are inadequate [4].

The objective of this review is to summarize the findings of promising imaging approaches that may provide mechanistic understanding of mild traumatic brain injury (mTBI). Imaging in mTBI has so far explored brain tissue damage or physiologic changes involving perfusion and metabolite distribution. Clinical manifestations of sleep, visual disturbances and associated fatigue observed in a substantial number of mTBI patients have not been diagnosed at all. We feel that clinical manifestations of sleep, visual disturbances and associated fatigue in a substantial number of mTBI patients that do not recover fully after mTBI may now be explained by multi-modal neuroimaging that carry complementary information.

Routine clinical modalities like MRI or CT performed immediately after mTBI usually do not reveal structural damage of the brain tissues. Even when MR or CT is positive, the findings are subtle, such as petechial hemorrhage, mild edema or small contusions, considered 'minor' findings needing no neurosurgical intervention. The majority of mTBI survivors recover fully within 3-4 weeks. However, a significant minority (10-20%) continue to experience symptoms for several months (including subacute post-concussive disorder, PCD) or often years (chronic PCD) [5]. Hence, there is a growing consensus that routine structural imaging tools do not fully reflect the underlying microscopic environment or the chronic progression of neurobiological effects of mTBI [3,6-8]. It is claimed on the other hand that, the positive predictive value of the physiologic tools like radiotracer SPECT or PET increases as mTBI progresses from acute to chronic stage and the negative predictive value also reaches nearly 100% at the chronic stage for SPECT [9]. This adds sensitivity for SPECT imaging in terms of cell membrane permeability at the level of functional blocks in vascular endothelium with impaired cerebrovascular autoregulation after TBI [10]. However, there might be other biomarkers present in mTBI to which SPECT is not differentially sensitive enough resulting in loss of specificity.

It is worth noting that analogous to minor brain trauma, when controlled, surgical intervention for placing Deep Brain Stimulation (DBS) electrodes has created increased global cerebral perfusion [11] and have been verified to produce moderately increased MR signal from whole brain tissue even under low Power MRI techniques [12]. Hence the perfusion results after minor head trauma have to be carefully assessed and global insult originating from perhaps oxidative stress model based on whiplash or dynamic blunt load should be taken into account.

Although the association of TBI with sleep disorders is being recognized, the mechanistic relation is far from clear [5,8]. The association of fatigue and sleep with mTBI [13] raises

the question should the mTBI patients with fatigue and sleep disorders be assessed for chronic fatigue, given the prevalence of neuropsychological symptoms in many of them [14]. The conversion from acute to chronic symptoms in TBI that accompanies fatigue among young patients [15] requires further study. Similarly, the local blood-brain barrier (BBB) disruption in the microvasculature [16] and the distal spread of injury due to the cerebral vulnerability as demonstrated in minor blast-induced TBI [17] are inadequate to create a mechanistic model as claimed by radiotracer imaging [18]. Of interest to note that repetitive blast-induced injury in war zones often causes fatigue as well as sleep disorders along with long-term cognitive deficits although somewhat differently than other forms of mTBI [19].

Patients with mTBI and persistent post-concussive symptoms have a high incidence of medial temporal lobe injury leading to altered hippocampal, caudate and insular perfusion [20]. Quantification of altered hippocampal and medial temporal lobe perfusion requires sensitivity to small perfusion changes. Radiotracers like 99m-Tc work well when there exist reliable control regions in the contralateral side (internal control) or by comparing with age-matched control subjects. In routine clinical setting it is difficult to obtain baseline controls using healthy controls for isotope-based SPECT or PET, both being high radiation modalities. Radiation-free perfusion methods like arterial spin labeling MRI are promising but suffer from high inter-subject variability and low resolution [21,22].

Discussion

We have evaluated published works (from 1995- pre-prints from 2020) containing keywords such as mild traumatic brain injury, sleep disorders/issues, fatigue and neuroimaging and have identified 40 articles that have conclusively observed or discussed at least one dominant damages due to mTBI or investigated similar situations to contribute to mechanistic understanding of mTBI. The goal was to summarize common, contributory factors detectable by various modalities in a complementary fashion instead of requiring several modalities to agree on a single issue post mTBI.

Key publications in mTBI seem to stress on the importance of oxidative stress and BBB disruption. Although ECD SPECT is very sensitive for mTBI, with advancements in various imaging modalities other perfusion, metabolite and functional imaging tools could be used for early detection and treatment planning.

Effects on both frontal and temporal lobes: injury translation

The microvascular damage in mild to moderate TBI has been well staged by susceptibility weighted MRI in terms of hemorrhagic lesions commonly in frontal and temporal regions indicating local mechanical strain and microvasculature rupture. However, skull anatomy plays a significant role in translating the focal injury to distal regions by bony ridges and fasciculi [23]. Since anterior fossa structures are more mobile compared to posterior fossa structures, undersurface of the frontal and temporal lobes undergoes more

frequent deformity when colliding with skull protuberances. Frontal and temporal lobes are interconnected by arcuate and uncinate fasciculi that often are affected by TBI. This may be the primary reason for dysfunction of both lobes and is revealed by perfusion imaging [18] (injury translation).

Sleep disturbance observed across all patients

Coup-contrecoup brain injury following mTBI usually occurs at the skull base around bony irregularities like the sphenoid ridges [24] and could explain the sleep disturbances that are observed for almost all patients in an affected mTBI group [4,5]. The inferior frontal lobe is one of the important regions involved in sleep initiation [25]. This may also indicate that not only medial temporal and frontal lobes are vulnerable in mTBI where the SPECT hypo perfusions were noted, the inferior frontal and anterior temporal regions also should be considered that are often difficult to image due to large intensity attenuation. A recent work with diffusion tensor imaging [26] found that a significant number (39%) of patients with mTBI had diffusional changes (decreased Fractional Anisotropy) of the arcuate fasciculus although due to significant bony susceptibility in this region diffusion MRI may not be reliable.

Mechanism of tracer hypoperfusion in mTBI SPECT imaging

Microvascular membrane functions in the frontal and temporal regions change in mTBI leading to imperfect tracer retention and washout. An ideal "trapping" of 99m-Tc ECD happens if both the esterase ligands are used when ECD crosses the BBB and forms a polar ECD complex that stays away from lipid membrane and is trapped in the parenchyma [6]. TBI generates abnormal influx of Ca^{+2} causing acidosis [20] with subsequent rise in oxidative stress affecting cell membrane permeability. Qualitatively, acidic environment from oxidative stress reduces esterase production and enzymatic action [6] and hence could explain the tracer hypo-retention in frontal and temporal lobes in mTBI.

What comes first: sleep issues or fatigue

It is unclear what causes sleep issues. Using the same concept of oxidative stress affecting endothelial junction proteins we think that SPECT perfusion mechanics in mTBI may be due to bilateral cerebral injury seen by functional MRI [27]. None of these explain the mechanistic source of injury by itself. However, significantly elevated levels of F2-isoprostanes translated from frontal to occipital lobes may indicate late effects of oxidative stress for TBI [28], particularly when there is fatigue [13] accompanying mTBI. The sequence of oxidative stress leading to altered homeostasis in mTBI [2] might cause peroxidation of membrane lipids and generate excess intracellular calcium disrupting homeostasis and increasing membrane permeability. Since increased reactive oxidation species (ROS) in mTBI affect endothelial cells and alter cerebral autoregulation including ATP generation, a systemic fatigue often accompanying mTBI seem to get worse several months after emergence of sleep issues.

Oxidative stress and effects of mTBI on endothelial tight junctions

The blood–brain barrier consists of the cerebral microvascular endothelium, pericytes, astrocytes and neurons, out of which the endothelial changes seem to be best suited for imaging by perfusion measurements. Neuroimaging presents a unique opportunity to understand BBB disruption when mTBI precedes fatigue. Perhaps one may identify the effects of oxidative stress on the tight junctions (TJ) in vascular endothelium under three inter-dependent events: impaired autoregulation after mTBI [10,16], during local ischemic injury and a widespread occurence of metabolite deficits in addition to perfusion abnormalities [28].

Endothelial junctional (tight junction, TJ) proteins play important roles in vascular permeability, and toward in-vitro stretch model of TJ proteins for mild-blast brain trauma [29]. We think the TJ stretch model can be applied to the increased permeability of microvasculature in the frontal and temporal lobes to explain the reduced esterase activity for ECD tracer in mTBI just because there may be greater Red-ox activity post mTBI in this region) [18]. The effects of biaxial stretch were characterized at 5, 10, 15, 25, and 50% deformation (mild to moderate in trauma scale in the stretch model) that induced a deformation-dependent increase in LDH release, cell death, and activation of caspase 3/7, suggesting the induction of apoptosis. For mTBI with small deformations, an increase in TJ proteins is expected as a compensation mechanism [29] that might generate imperfect "polar" ECD forms in the vulnerable, frontal temporal lobes enabling ECD to early washout [18].

mTBI at chronic phase: utility of multimodal approach

If and when the effects from mTBI enters chronic phase more resources need to be allocated, due to additional complexity, to diagnose and treat to preserve quality of life and offer suitable preventive treatment. As MRI begins to look at the acute to chronic transition, routine clinical imaging perhaps should be avoided. However, a recent fMRI work to detect fatigue in patients with previous TBI [27] has demonstrated altered striato-thalamic-cortical functioning in caudate and anterior thalamus. Multimodal brain imaging may start with a sensitive tool like SPECT followed by a non-invasive research tool like resting state connectivity fMRI or Magnetoencephalography or MEG to detect altered memory and executive functions [30]. MRI based diffusion tractography [31] and neurometabolite spectroscopy [32,33] could also advance the understanding of chronic components. There is a growing consensus [34] that an effective treatment plan would benefit from combined structural, physiologic and functional assessments both at acute and at chronic phases [35].

Conclusion

This review emphasizes the following three main findings of imaging in mTBI:

A.   Mild traumatic brain injury causes mechanical damage that often indirectly leads to perfusion heterogeneity in the

frontal and temporal lobes and perhaps over time by oxidative stressor or vascular effects translate the injury to occipital lobe.

B.   Deficits in the occipital region, not observed by routine MRI or nuclear SPECT or PET contribute to visual problems and perhaps contribute to sleep disturbances. It is not clear if this can change the levels of major metabolites like NAA and be observed by sampling basal ganglia or occipital lobe using MR spectroscopy. A slight reduction of NAA in the occipital lobe has been observed [32] as well as diffusion tract changes [31]. It is also not known if metabolites move around or replenished as some of the mTBI patients recover.

C.   Deficits in the thalamus region bordering the frontal lobe are common for mTBI as often seen by isotope imaging in SPECT or PET [18,32] which is an important region of the brain that helps promote sleep and maintain wakefulness.

It is worth noting that MR spectroscopic abnormalities in mTBI are mostly absent [32,36]. However, this needs to be critically evaluated and confirmed. Mild Trauma and subsequent global oxidative stress could alter Glutamate pathways, particularly if fatigue is to be explained. Measuring major metabolites alone, particularly by localized single voxel measures, seem to be insufficient to conclude about the utility of spectroscopy. One may use the whole brain approach using 3D multi-voxel spectroscopy with emphasis in limbic region and assess with GABA and Glutamate detection to observe patterns of secondary metabolite imbalance in the affected group. To our knowledge, it is not clear if neuro metabolite levels alter over time when mTBI progresses in certain patient groups and get replenished in others. Particular attention may be given for metabolite follow ups in frontal, temporal and occipital regions due to early sleep and visual disturbances presumably originating in basal ganglia and tentorium.

Further mechanistic understanding to link sleep and fatigue is necessary. Also combining tissue biology to model impact of oxidative stressor and injury localization with tracer imaging and functional connectivity mapping [30] could be performed as well as perfusion/metabolite measurements. Multi-modal approaches hold more promise than advanced applications of single modalities like repeat CT for Hounsfield unit changes [37] or susceptibility MR for micro-hemorrhages [33] or PET/SPECT with new tracer designs. Repetitive minor blast trauma [17] as well as focal surgical procedures as in the placement of neurological shunts or implants [11,12] may act as templates to study effects of controlled, static loads in pre-planned locations to offer useful mechanistic evaluation of mTBI that usually involves dynamic and global loads.

Acknowledgement

Conflict of Interest

The authors do not have any direct or indirect conflict of interest.

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