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Sleep-Wake Disturbances in Mild Traumatic Brain Injury: Meta analysis of Literature and Modeling of Cerebral Tissue Vulnerability

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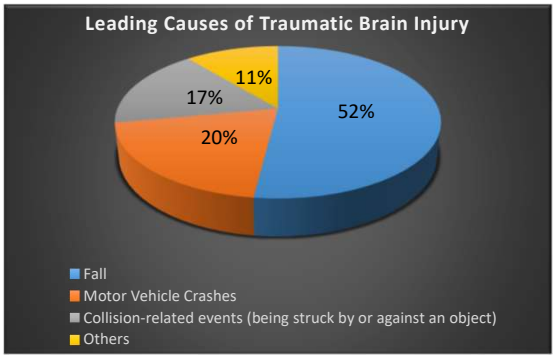
Introduction

Mild traumatic brain injury (mTBI) is defined by the Management of Concussion/mTBI Working Group as Normal imagining; a brief period of loss of consciousness (LOC) less than 30 minutes; post-traumatic-amnesia (PTA) less than a day; and with Glasgow Coma Scale (GSC) of 13-15.

Every year an estimated 55.9 million people worldwide suffer from mTBI [3]; yet due to its lack of reliable diagnosis tools, the exact damage it has on the brain is a mystery. Especially with sleep disturbance, one of the most frequent complaints by patients with mTBI, it contributes to prolong recovery and worsen other secondary damages of mTBI. The common types of sleep disturbance of mTBI include insomnia, daytime sleepiness, and obstructive sleep apnea.

The objective of this work is to suggest possible etiologies of sleep disturbances as a result of mTBI. Based on our laboratory models sleep disturbance could be caused by abnormal CSF dynamics while we acknowledge prior works along with the accumulation of tau protein, a decrease of melatonin and serotonin as well as oxidative damage to structures in the midbrain region.

Fig 1. Centers for Disease Control 2019 statistic on leading causes of Traumatic Brain Injury



Hypothesis

Mild traumatic brain injury causes altered CSF flow in the third ventricle inducing mechanical and functional damages to the Pineal gland located at the roof of the third ventricle in the brain that is responsible for sleep disturbances.

Methods

We have evaluated approximately 50 published works from year 1990-2020 containing keywords such as mild traumatic brain injury, sleep disorders/issues, and biomarkers and have identified 10 articles that have observed in human or animal mild head injury models changes in at least one suspected serum or CSF biomarker implicated in mTBI. Our work has proposed a model that connects possible contributory factors of sleep disturbance as a result of mTBI.

Cerebrospinal Fluid Dynamics Model

Our model incorporates three principal changes in anatomy and function due to the impact of altered CSF flow in the brain stem and the third ventricle causing the following plausible changes in Pineal gland functions:

1) The direct impact between the tentorium and the pineal gland could cause pineal gland injury and disruption of melatonin production that regulates the sleep-wake cycle. [5]

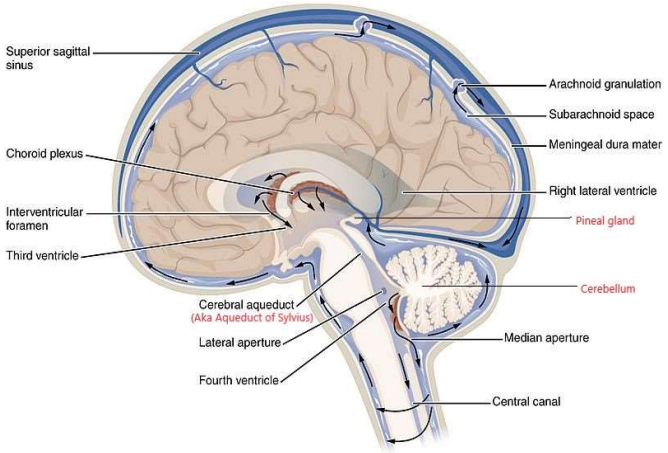
2) CSF dynamics through the Aqueduct of Sylvius and the third ventricle could be sensitive to tissue deformation in the cerebellum and basal ganglia during and immediately after the head is impacted in minor head trauma (Fig. 2).

3) Serotonin (5-HT) is a precursor of melatonin and its relationship with sleep is well-researched. A study has revealed TBI could cause disruption of the serotonergic system causing the reduction in 5-HT reuptake and decreased 5-HT neurotransmission [4]. This defect is possibly related to the key role CSF plays in transporting those chemical compounds away from Pineal surfaces. We propose possible Pineal surface damage by the dynamic load from CSF during and after shaking of midbrain tissue.

Discussion

The production and transportation of hormones secreted by the Pineal gland depend heavily on CSF pressure on Pineal surfaces. Our argument is based on the findings that the shape and pressure of venous blood in internal jugular vein change drastically by simple posture change [2]. Although conventional imaging tools often detect no abnormality in mTBI, it has been found that vascular injury at vessel wall membranes occurs in mTBI [2]. Since tau protein is predominantly found in neuronal axons, studies have shown that total tau in CSF could be a promising biomarker of mTBI [6]. Alteration of tau has also been observed to wreckage sleep structure [1]. A progression that is also discovered in patients with Alzheimer's disease.

Fig 2. Functional anatomy of CSF circulation



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