Sleep Wake Disorder after Traumatic Brain Injury-A Comprehensive Update

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Abstract

Sleep plays an integral role in several physiologic functions such as cognition and functional ability of an individual. Sleep-wake disturbances are frequent after traumatic brain injury (TBI). More than 50% of TBI patients suffer from sleep wake disorders. The pathophysiology remains unclear; however, it can interfere with rehabilitation and recovery leading to poor neurobehavioral outcome. Nonpharmacological and pharmacological treatment exists with variable outcomes. This review will focus on sleep wake disorders, pathophysiology, treatment options, prognosis and outcome in terms of cognition and quality of life in this subset population who had TBI in the past or recovering from it.

Keywords: Sleep; Sleep-Wake Disorder; Post Traumatic Brain Injury; Pathophysiology; Treatment

Abbreviations

EEG: Electroencephalogram; EDS: Excessive Daytime Sleepiness; PAP: Positive Airway Pressure; CPAP: Continuous Positive Airway Pressure

Introduction

A traumatic brain injury (TBI) is defined as a blow to the head or a penetrating head injury that causes an alteration of the normal function of the brain. It can be mild, moderate or severe, depending on the extent of damage to the brain. About 1.7 million cases of TBI occur in the U.S. every year and approximately 5.3 million people live with a disability caused by TBI in the U.S. alone. Over 50 million TBIs occur internationally each year [1]. Recent data suggest, TBI represents 30 to 40% of all-injury related deaths, and neurological injury is expected to remain the most important cause of disability from neurological disease till 2030. TBI costs the international economy approximately US $400 billion annually.

TBI is a public health issue, with a huge economic and societal burden of unrecognized proportions. The epidemiology of TBI is changing, in high income countries, falls is the most common cause in elderly population whereas in middle- and low-income countries road traffic accident is the main culprit. Treatment guidelines are not individualized and are based on “one size fits all” approach which are insufficiently targeted to the needs of individual patients when severity of injury is considered.

Sleep is considered as a major cause of physical and mental health well-being and understanding sleep-health relations is of prime necessity. Sleep wake disorders (SWDs) on the other hand may comprise of many entities like difficulties in falling or staying asleep, excessive daytime sleepiness, an increased need for sleep or changes in sleep-wake circadian rhythms and the causes can be numerous like...
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Sleep wake disturbances (SWDs) are quite common after traumatic brain injury (TBI) in any age group. Commonest disturbances include hypersomnolence, excessive day time sleepiness, insomnia etc., which can be due to TBI itself or sleep disorders caused by TBI like pleiosomnia, sleep related breathing disorders and even hypersomnia. SWDs can have a negative outcome on the quality of life as well as brain recovery after injury. Both can influence each other thereby leading to neurobehavioral impairment. Psychological problems like depression and anxiety, fatigue, pain, cognitive dysfunction can be exacerbated post TBI if SWDs are not properly controlled and treated.

SWDs post TBI can be due to interaction among social conditions, psychological factors, environmental factors and pathophysiological processes happening at cell level which includes brain as well as other organs responsible for sleep wake cycle [6,7]. SWDs can be present in any type of TBI severity [8,9] and can arise early right after injury or late during the inpatient hospitalization or rehabilitation process in home [10]. SWDs can persist for many years after injury [13-15]. Impact of traumatic brain injury on sleep structure, electrocortico-graphic activity and transcriptome in mice was studied [87].

Pathophysiology of post-traumatic SWDs

Many independent factors that can cause post TBI SWDs are psychiatric sequelae (anxiety, depression, post-traumatic stress disorder) from the primary injury, neuroendocrine disturbances, pain, medications, psychosocial integrity, genetic background, body and brain temperature [16], motor behavior [17]. Loss of histaminergic neurons in tuberomammillary nucleus post TBI can be the reason behind sleep-wake regulatory problem [18]. Impaired melatonin synthesis might contribute to circadian rhythm SWDs [19]. Hypothalamic injury was found to be associated with SWDs [20,21]. Shortened latency to rapid eye movement (REM) sleep has been seen in narcoleptic like occurrence [22]. Hypo excitability of the cerebral cortex and dysregulation in the excitatory hypocretin-neurotransmitter system is seen in people with excessive daytime sleepiness after TBI than in healthy controls [23]. White matter abnormalities in the para hippocampal region may be associated with SWDs [24,25]. Other neuroanatomical structural dysintegrity is also shown by researchers related to sleep problems [26]. Increased proportion of non-rapid eye movement (NREM) stage N1 and N2 sleep, decrease in REM sleep seen in the first 6 months post injury. Increase in slow waves also seen in EEG [27]. Several frequency bands in both NREM (lower delta, higher alpha, and beta power) and REM (lower beta and higher delta power) is also seen in sleep study [27,28].

Diagnosis of post-traumatic sleep-wake disorders

Non validated questionnaire can be used in diagnosis keeping TBI in mind [29]. Large epidemiological study showed that up to half of those suffering TBI endorsed insomnia symptoms of some type [30]. Objective testing with polysomnography (PSG) and multiple sleep latency testing (MSLT) can be helpful in the workup of these patients [31,32].

Post traumatic pleiosomnia

After TBI, patients sleep significantly more than carefully matched controls [33,34]. Increased sleep need of 2 hours or more per 24 hours compared with pre-TBI conditions slightly different from hypersomnia. Six months post trauma, pleiosomnia is present in about 20 - 25% of TBI patients. Excessive daytime sleepiness (EDS) is not universally present in all pleiosomnia patients but increased slow-wave sleep (SWS) appears to be common in this condition. The severity of TBI, as assessed by the presence of intracranial hemorrhage, is a predictor for the development of post-traumatic pleiosomnia [35]. Noain D and colleagues found out in a rat model that closed diffuse traumatic brain injury caused increased sleep need one month after trauma and sleep was more consolidated. They also found a reduced
number of histamines immunoreactive cells in the tuberomammillary nucleus, potentially related to increased neuroinflammation [36]. No treatment option exists for posttraumatic pleiosomnia at this moment.

**Post-traumatic excessive daytime sleepiness**

Post-traumatic excessive daytime sleepiness can be diagnosed in patients who suffer from daily episodes of irrepresible need to sleep [37]. It may occur in about 25% to 60% of TBI patients, irrespective of trauma severity [40-42]. Pain is considered as an important factor in nocturnal sleep disruption and consecutive sleepiness [38,39]. Sleep apnea and periodic limb movements can also be an issue related to this issue [38,39]. Multiple sleep latency tests revealed EDS in 57% of patients post TBI. Psychiatric symptoms in patients admitted to ICU following trauma may exacerbate these symptoms [43]. Botchway, *et al.* found sustaining TBI in childhood can increase risk of SWDs in young adulthood, particularly following moderate TBI [44]. Severe and protracted sleep disruptions in mouse model of post-traumatic stress disorder post TBI was found [45]. Aggravation of EDS concurrent with aggravation of an injured ARAS (ascending reticular activating system) was demonstrated in a patient with mild TBI using DTT (diffusion tensor tractographies) [46]. Moderate TBI in mice reduces wakefulness and increases NREM sleep during the dark period, effects that may be mediated by hypocretin-producing neurons and/or downstream cholinergic effectors in the basal forebrain [47].

In proportion of TBI patients, EDS is linked to underlying sleep-wake comorbidities such as obstructive sleep apnea (OSA) syndrome and periodic limb movements during sleep (PLMS), however on contrary to pleiosomnia, severity of TBI is not associated with the development of EDS. Modafinil significantly improved subjective EDS, as assessed with the ESS, and increased mean sleep latencies on the maintenance of wakefulness test [48,50]. Jha, *et al.* did not observe such an effect of modafinil in patients with TBI [49]. Positive effects of blue light therapy on sleepiness after TBI is described too [51].

**Post-traumatic insomnia**

These problems occur at least 3 times per week, have been present for at least 3 months, and cannot be attributed to inadequate sleep opportunities or circumstances [37]. Prevalence of insomnia of about 30 - 70% in TBI patients is showed in many studies but some showed lower frequencies too [52]. Lot of disparity among researchers is believed to be caused by insomnia symptoms which prevail shortly after TBI, but over time fade and unmask enhanced sleep pressure [53]. Evidence suggest that TBI might overestimate insomnia symptoms, when comparing objective with subjective assessments [31]. Post-traumatic insomnia is most likely of multifactorial origin [54]. Questionnaires such as the Pittsburgh Sleep Quality Index (PSQI) or the Insomnia Severity Index (ISI) are helpful. Psychological distress and its associated factors among informal care givers of disabled young adults with traumatic brain injuries have a bad outcome on patients [55]. Somatic symptoms are associated with insomnia disorder traumatic brain injury [56]. Individuals with persistent post-TBI insomnia had poorer psychosocial outcomes [58]. Orexin signaling as a potential therapeutic target in insomniac disorders caused by TBI [57]. Recently Moore, *et al.* manualized cognitive behavioral program to modify the CBT-I treatment program for treatment of insomnia in children of age group 6 - 10 years who sustained traumatic brain injury [59]. Nonpharmacological treatment and good sleep hygiene have been recently studied by Ford, *et al.* [60]. Benzodiazepine receptor agonists are effective to treat disrupted sleep, but these drugs should be used only during short periods (i.e., up to 2 weeks) [61]. It has been observed that 1 out of 5 patients use hypnotics on average 9 years after TBI [62].

**Post-traumatic circadian rhythm sleep-wake disorders**

Delayed sleep phase syndrome and irregular sleep-wake pattern is common after TBI and these disorders might be misdiagnosed as insomnia by inexperienced clinicians in this field [63]. Decreased evening melatonin production may lead to disruption of circadian regulation of melatonin synthesis in TBI patients [19,68]. Post-traumatic circadian rhythm disorders such as delayed sleep-wake phase disorder or non-hour sleep-wake rhythm disorder also reported post TBI [64,65]. Abnormal expression levels of circadian clock genes like
Per2, Clock and Bmal1 were detected in patients with TBI-related sleep disorders [66]. Wickwire EM., et al. has studied about interplay between sleep disorders, and circadian health following mTBI in Adults [67]. PERIOD3 polymorphism is associated with sleep quality recovery after a mild traumatic brain injury [69]. No specific studies for the treatment of post-traumatic circadian sleep-wake disorders. Evening melatonin replacement and bright light exposure in the morning might be tried in future.

**Post-traumatic sleep-related breathing disorders**

Obstructive sleep apnea (OSA) do emerge in a large proportion of TBI survivors as a de novo post-traumatic feature. The prevalence of OSA after TBI ranges from 11% to 36%. Nakase-Richardson R., et al. used American Academy of Sleep Medicine (AASM) and Centers for Medicare and Medicare (CMS) scoring rules in moderate to severe TBI undergoing inpatient neurorehabilitation. OSA was prevalent using the AASM (66%) and CMS (41.5%) criteria, chronic morbidity after moderate to severe TBI, the impact of CMS policy for OSA diagnosis for persons with chronic disability and young age are considerable to AASM [70]. Sleep disturbances among older adults following traumatic brain injury was studied [71]. A retrospective cohort study was performed to find the association of insomnia and sleep apnea with deployment and combat exposure in the entire population of US army soldiers from 1997 to 2011, extraordinary increases in incidence of insomnia (652%) and OSA (600%) was seen [72]. Perceived sleep quality was markedly disrupted in mTBI military personnel and sleep-wake disturbances were prevalent [73,74]. Webster., et al. reported central sleep apnea in adults in one of his study [75]. The negative consequences of sleep apnea across health, functioning, disability, and economic outcomes are well documented and may contribute to chronic health outcomes following TBI [76,77]. Presence of sleep apnea is underexplored as a mediator of TBI outcome. A dose-response relationship has been demonstrated between treatment and outcomes in non-TBI sleep apnea [78]. Sustained use of PAP has been shown to slow deterioration of cognition, preserve sleep quality, and enhance mood in older dementia patients with sleep apnea [79]. More studies are required in Post TBI patients who develops OSA as a complication.

**Post-traumatic sleep-related movement disorders**

In a study of adolescents with a history of chronic mild head injury, parasomnias were reported by 42% of head injured patients (compared to 19% of controls). Adolescents reported increased rates of sleep enuresis (involuntary urination; 21% versus 0%) and sleep bruxism (teeth grinding; 42% versus 6%) in head-injured subjects compared to non-injured control subjects [79]. In 60 adult patients with chronic TBI (3 months - 2 years from injury), 25% presented with parasomnia as their primary sleep complaint, the most frequent of which was REM sleep behavior disorder (RBD) [42]. There is also emerging evidence that trauma exposure e.g., TBI is associated with risk of disruptive nocturnal behaviors along with increased electromyographic (EMG) tone during both REM and NREM sleep, among the military population [80].

**Treatment**

Cognitive behavioural therapy (CBT) has shown good efficacy in SWDs in different subset of population in long term [82]. Acupuncture [83], CPAP [84], blue light therapy etc. has shown benefit in different settings as non-pharmacological treatment [89]. Benzodiazepine receptor agonists has been used to treat SWDs to be used in short periods only [90]. Amitryptiline and melatonin has been studied with mixed benefits [85]. Combination of prazosin with behavioural sleep counselling showed some success in reducing sleep disturbances [86]. Methylphenidate has also shown to be efficacious in some studies [87]. Recent pharmacological treatment also discussed. Association with an autoimmune inflammatory process, corticosteroids may serve to stabilize the blood brain barrier leading to the successful and sustained resolution of TBI induced sleepiness [88].

**Discussion**

Disrupted sleep is common after TBI. Sleep hygiene is a feasible, nonpharmacologic intervention to treat disrupted sleep in a TBI inpatient rehabilitation setting [91]. Piantino., et al. reported about the role of the glymphatic system as a potential link between TBI, sleep,
and headaches [92]. Cognitive impairment is associated with worse health-related quality of life after TBI and partially mediates the effect of depressive symptoms on emotional role functioning [93]. Set interval scoring is the most efficient method to determine the rest interval in TBI patients [94]. A complex interaction exists between post TBI fatigue, sleep disturbance, and other correlates, which needs more evidence in evaluating the potential benefits of interventions at what stage according to severity of brain injury [95]. Hormonal alterations in relation to sleep impact cognitive and functional outcome after TBI [96].

**Conclusion**

Regulation of sleep wake and hormonal balance dysfunction is responsible for sleep issues post TBI. Proper diagnosis and apt management is responsible for brain recovery post insult stage and failure to do so can cause cognitive problems and impaired activities of daily living. Nonpharmacological treatment like CBT and sleep hygiene followed by drugs can be the treatment. However, at this moment there is no single set of guidelines which can address all the SWDs in a post TBI patient. Future research should continue to find neuroimaging or protein markers related to brain injury. Management of pain, fatigue and its pathophysiological role in SWDs need further research.

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