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Letter to editor Open Access

Study of Sleep Patterns Might Advance Our Knowledge on Alertness in Traumatic Brain Injury

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Traumatic brain injury (TBI) is defined as "an alteration in brain function, or other evidence of brain pathology, caused by an external force" [1]. Although the precise incidence and prevalence of TBI is not known due to the lack of consistent epidemiological data [2], between 3.6 and 5.3 million individuals in the United Statesare living with TBI-related consequences [3]; sleep-wake neurobehavioral impairments (i.e., diminished alertness and inability to sustain attention) are among the most commonly reported [4,5]. Thus far, significant advances in sleep and TBI researchhas uncovered an association between brain injury and the delineation of the arousal system, with a raised interest in the past few years to the pattern of sleep-wake organization.

Lossofconsciousness(LOC)inTBIoccursdueto electrophysiological disruption of the ascending reticular activating system, a fundamental structure that maintains tonic arousals as a prelude to alertness [6]. Urakami simultaneously used electroencephalography (EEG) and magnetoencephalography in patients with chronic diffuse axonal injury (i.e. a pattern of brain damage characterized by lesion in the corpus callosum and dorsolateral brain stem accompanied by widespread damage in the white matter in patients with LOC) [7] and found that, in the acute stage post injury, both the frequency of fast spindles and cortical activation source strength were significantly lower in patients with TBI than in healthy controls; the alpha activity reflected the severity of disturbed consciousness [8]. In that study, the presence of sleep spindles was found to serve as an indicator of recovery in the chronic phase after injury [8]. Similarly, Cologan and colleagues proposed that the presence of EEG patterns resembling normal human sleep [9] (i.e. well-structured patterns of non rapid eye movement and/or rapid eye movement (REM) sleep)can be markers of a favorable outcome after brain injury [10]. Moreover, the quality and quantity of spindles can provide a new index of the severity of thalamocortical injury, in accordance with brain imaging studies showing the correlation between the extent of thalamus damage and behavioral disability and outcome in disorders of consciousness [10-13].Gosselin and colleagues observed increased delta and decreased alpha activity during wakefulness in patients with mild TBI and proposed sleep intrusions in the waking state might indicate continuous sleep inertia, manifesting as fatigue and impaired functioning [14]. The clinical significance of the utility of EEG in TBI is reflected in a recent study by Teel et al. [15].While concussed participants passed all clinical concussion testing tools, they showed path physiological dysfunction with evaluation of EEG variables,supporting the hypothesis of diminishedbrain resources to compensate appropriately during activity [15].The results of the study areparticularly relevant to clinicians who make return-to-play or return-to-work decisions (i.e. in sport, first respondents, and other occupations requiring sustained attention). Advanced study of sleep and wake EEG offers new opportunity to define the robust sleep parameters of different patient populations.

Another important advancehas been made by studies exploring the role of neurotransmitters involved in arousal regulation after TBI. Several neurotransmitters, including noradrenergic, serotoninergic, cholinergic, histaminergic, hypocretin/orexin, and dopamine systems,are known to be involved in this process [16]. Recent findings suggest that severe brain injury can affect the hypothalamic system to such an extentthat neuropeptides hypocretin-1 and hypocretin-2 (also known as orexin-A and orexin-B) are altered, either transiently or permanently [17-19]. Hypocretins play an essential role in promoting wakefulness. Nardone and colleagues recently studied cortical excitability in patients affected by different sleep-wake disturbances after TBI to determine whether changes in cortical excitability are associated with the development of post-traumatic excessive daytime sleepiness [20]. They reported that, similar to that in patients with narcolepsy [21, 22], cortical hypo excitability in patients with TBI might reflect deficiency in the excitatory hypocretin/orexin-neurotransmitter system [20].Though not experimentally tested yet in the TBI population, the pre-existing level of alertness should be factored into the conclusions. This is highly relevant to the study of alertness in the TBI population, when taking into account symptom overlap between impaired alertness and daytime sleepiness; nearly half of patients with excessive sleepiness report automobile accidents, with half reporting occupational accidents and other life threatening situations [23] which can result in a TBI outcome.

Studies have focused on understanding how factors other thanthose associated with TBI, including sleep disorders, psychiatric comorbidity, and medications, can impact the ability of TBI patients to maintain alertness during the day [24-26]. Sleep disorders such as sleep apnea (SA), narcolepsy, insomnia, and circadian rhythms disorders are of particular interest at present, since their incidence in TBI has been shown to be significantly higher compared to thegeneral populations[27,28]. Of particular interest is REM sleep behavior disorder (RBD) which is characterized by dramatic REM motor activation resulting in dream enactment, often with violent or injurious results. Verma et al. [29] examined the spectrum of sleep disorders in chronic TBI patients and reported complaints of parasomnia in 25% of participants, with RBD as the most commonly reported disorder (13%). It has been proposed that the increased RBD incidence relative to that of the general population after brain injury is attributed to damage to brainstem mechanisms mediating descending motor inhibition during REM sleep [29]. RBD seems to be a premonitory sign of synucleiopathies such as Parkinson's disease (PD) [30] and as TBI is also a poorly understood risk factor for PD [31], it is difficult to discard the relationship as accidental. Electromyography (EMG) activity

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during sleep therefore has implications for biomarker discovery. To elaborate, it has been reported that the masseter EMG activity due to excitability level of the motor neurons is associated with arousal fluctuations within REM and non-REM sleep states [32]. In addition, there are some motor events such as REM twitches, swallowing and rhythmic masticatory muscle activity, whose generation might involve the additional activation of specific neural circuits. While currently the matter as to which neural circuits determine the genesis of RBD in the TBI population as well in the general population remains elusive, the available knowledge on EMG activity recording in polysomnography (PSG) can provide information on a range of neural factors involved in trigeminal motor neurons. Such study can enable determination of the genesis of RBD. Another sleep parameter relevant to this discussion is electrooculography (EOG). Currently, the main purpose of recording eye movements in PSG is to identify REM sleep and distinguish between sleep onset and consolidated sleep. However, because sleep eye movements are controlled by neurons located in the brain stem structures, the study of eye motility in sleep may have greater implications, -for instance, in the study of neurodegenerative disorders. Christensen and colleagues, searching for biomarkers of PD based on the observation that patients suffering from RBD are at high risk of developing the disease, reported that eye movements during sleep as well as muscle activity measured at one EOG channel held information useful in classifying RBD and PD patients[33]. Although this study is the only one of its kind to date, it demonstrates that analysis of EOG and EMG activity during sleep holds potential in the discovery of biomarkers for neurological disorders, including TBI.

Sleep parameters are useful in study of a variety of other sleep disorders, highly prevalent in the TBI population, the majority of which can significantly impair sleep architecture and cause or contribute to excessive daytime sleepiness and impaired alertness. One of the most highly occurring sleep disorders in TBI is sleep apnea (SA), characterized by a cessation of breathing in sleep. Research shows that 30-40% of patients with TBI who complained of daytime sleepiness were diagnosed with this sleep disorder.Although the high incidence of sleep apnea (SA) in the TBI population (i.e. 25 to 35% compared to 4-9% in the general population) is not completely understood, Yin et al. [34] probed the neuromuscular contribution in the pathogenesis of the condition [34], assessing the validity of chin surface EMG in their study of obstructive sleep apnea. Researchers proposed that recording and analyzing chin surface EMG, as part of a routine sleep study, may be a valid method for screening neuromuscular activity. This concept is highly relevant for patients with TBI, as disturbed coordination of upper airway and diaphragmatic muscles due to damage to the brainstem might favor the appearance of SA in TBI. Also, researchers have utilized EMG in an attempt to distinguish central from obstructive sleep apnea (SA) and concluded that the diaphragmatic EMG could be a useful technique in assessing neural respiratory drive and respiratory effort and, therefore, in accurately distinguishing the two forms of sleep apnea (SA). This is particularly relevant to the TBI population as, according to a report by Cologan et al. [10], the majority of the events in their TBI sample were central in nature rather than obstructive, while in the general population, sleep apnea (SA) consists of 90% obstructive and only 10% central events [35].

Study of electrocardiography (ECG) in sleep in persons with brain injury holds new opportunities. Sorensen et al. [36] investigated whether patients with PD with and without RBD and patients with idiopathic RBD had an attenuated heart rate response to arousals or to leg movements during sleep compared with healthy controls [36].The researchers found heart rate response to arousals and leg movements to be significantly lower in both Parkinsonian groups compared with the control group and the idiopathic RBD group. They proposed that the attenuated heart rate response may be a manifestation of the autonomic deficits experienced in PD. This is important for future study of alertness in TBI, pointing to the relationship betweentop-down control processes governing arousal and sustained attention decrement [37, 38]. Interestingly, research that investigated whether sleep-wake variations in the autonomic control of the heart are specifically altered by long-term confinement during a 105-day simulated mission to Mars, observed that autonomic changes during confinement reflected an increase in parasympathetic activity during wake periods [39]. The results from this study may be applicable to our population since the increase in low frequency heart rate variability and high frequency heart rate variability, as seen during confinement, was related to decreased attention processing, an outcome evaluated through an attentional load test. These objective physiological measures can be used to characterize differences in performance efficiency and in ability to adapt to working environments after TBI. In turn, fatigue-related performance decrements caused by sleep loss or sustained attention might be improved with training to regulate responses, including autonomic and central nervous system parameters [39]. Further, psychiatric disorders such as major depressive disorder, anxiety, and substance abuse thataffect sleep and consequently alertness should be further studied, since they can playprimary, contributing, or exacerbating roles. Similarly, while data on the efficacy of pharmacological treatment for impaired alertness in TBI are limited [40], no studies have yet differentiated the effects of medication that TBI patientsare administeredfrom the effect of brain injury on nocturnal sleep, alertness, or both. Moreover, sleep parameters can be beneficial in clarifying the nature of behavior disorders in which postsynaptic dopamine hypersensitivity is thought to be a factor, such as in social phobia, PD, neuroleptic and drug and alcohol dependence to name a few [41], each of which is pertains to our population of interest.

The substrates of diminished alertness in the brain injury population have yet to be determined. However, there has been progress in understanding that the alertness phenomenon as a complex physiological processwith changes in one or many neurotransmitters and /or neuromodulator systems as a result of injury to the brain, with manifestation of these processes in sleep parameters. Consequently, study of sleep remains of high interest in TBI, since it can lead to the elucidation of the relationships between sleep, alertness patterns, and functional neuroanatomy.

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