

Sleep disturbance after pediatric traumatic brain injury: critical knowledge gaps remain for the critically injured

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Traumatic brain injury (TBI), the alteration of brain function or brain pathology following external force, is common in children. TBI affects the sleep of victims, and poor sleep itself can impair recovery from TBI. Due to the developing brains of children, it is especially important to understand the complex interactions between sleep and TBI. Such understanding could lead toward optimizing recovery from TBI in children. Thus, here, we introduce the main issues in this field with a specific focus on the pediatric population and point out the important gaps in knowledge that need to be filled.

TBI accounts for 60,000 pediatric hospitalizations in the USA annually.¹ Half of these children require critical care admission for serious injuries such as skull fractures and intracranial hemorrhage (critical TBI).² Injury and critical care hospitalization leave survivors with physical, cognitive, and psychosocial morbidities encompassed by the postintensive care syndrome.³ Few studies have assessed these important morbidities in survivors of pediatric critical TBI, and interventions to improve outcomes are limited. Sleep wake disturbances (SWD) are increasingly recognized as an important morbidity following TBI and as a barrier to recovery in adult TBI and in concussion (the mildest form of TBI without identified intracranial pathology). SWD in pediatric survivors of critical TBI have been under-appreciated by clinicians and under-evaluated by researchers but may be key to improving the important myriad of sequelae suffered by these children.

Sleep is integral to many physiologic systems, and in children, it is critical for brain maturation and development.^{4,5} SWD during childhood brain development, through effects on synaptic plasticity and memory consolidation, may be particularly impactful on long-term pediatric health.^{6,7} SWD in otherwise healthy children are associated with physical, cognitive, and psychosocial impairments and may substantially compound the negative health consequences of pediatric diseases.⁸⁻¹⁰ SWD of any type are reported in over half of all TBI survivors, occur across all spectrums of severity and location of TBI, and persist for years after injury.^{7,11} SWD including insomnia, awakenings, daytime fatigue, and sleep disordered breathing are reported in adult TBI survivors though to date are poorly quantified in children.^{12,13} SWD after TBI are associated with impaired functional outcomes, decreased participation in activities, and reduced quality of life.^{14,15} Data from our Pediatric Neurocritical Care follow-up clinic show multiple types of SWD complicate recovery in more than half of survivors of pediatric

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critical TBI months after hospital discharge.¹⁶ However, most pediatric critical TBI survivors do not receive this type of specialized follow-up that includes systematic evaluation of sleep or postintensive care syndrome. Currently, clinicians have little data guiding methods to identify SWD or to support therapeutic interventions for SWD following pediatric critical TBI.

While there has been a recent upswing in pediatric sleep literature, variable methodology is used in these studies and few focus on TBI.¹⁷ Polysomnography is the gold standard for the diagnosis of some SWD but is not always feasible in clinical and research populations and may fail to diagnose disorders such as insomnia and excessive daytime sleepiness.¹⁸ A recent review of available pediatric sleep questionnaires resulted in 183 tools reported, but only two fulfilled all appropriate psychometric criteria and only 11 fulfilled most criteria.¹⁹ Actigraphy is increasingly utilized in children for sleep research providing objective data that have been validated against polysomnography for some SWD and also lacks standard methodology or accepted normative data for many measures in children.²⁰ It is likely that the combination of well-validated questionnaires and actigraphy is needed to evaluate the multidimensional aspects of SWD in pediatric critical TBI.

SWD literature is dominated by concussion patients in pediatric TBI cohorts, and available reports are often secondary evaluations of data not designed to collect sleep outcomes.¹³ A systematic review in 2015 of SWD after pediatric TBI identified only eight studies exclusive of case reports that included children with critical TBI.¹³ Only one study of 15 patients with critical TBI included objective actigraphy data evaluating sleep,²¹ and only three studies used a validated sleep questionnaire.^{8,21,22} A 2017 study evaluating fatigue after pediatric critical TBI showed that it remained a significant problem 12 months after injury but was not evaluated in conjunction with sleep measures.²³ Most prior reports do not delineate the specific type of SWD or the severity of SWD in the analysis. Additionally, prior reports stratifying injury severity by Glasgow Coma Scale did not find a significant association with SWD.^{13,24} Glasgow Coma Scale fails to incorporate other concurrent injuries, such as extremity fractures and abdominal trauma, that occur in the majority of pediatric critical TBI patients and have implications for sleep outcomes such as pain, medications, and casting.

The pathophysiology of SWD after critical TBI is unclear but has been attributed to structural and functional disruptions of sleep circuitry, circadian rhythm disturbances, hormonal

dysfunction, and comorbidities such as pain and psychological disorders.⁷ However, evaluation of disease mechanisms remains in its infancy, despite a rapidly growing body of literature.⁷ A variety of neural networks, neurotransmitters, and neuropeptides are linked to normal and disordered sleep. After a critical TBI, many of these sleep-related systems are affected either through the primary injury or through the secondary injury related to inflammation and physiologic derangements.

Secondary injury related to inflammation has been under-evaluated in TBI with regard to sleep outcomes. TBI induces an acute systemic inflammatory response that increases neuroinflammation and directly injures the brain.^{25–28} Interleukins (ILs) and other proinflammatory cytokines, including IL-1 β , IL-6, and tumor necrosis factor alpha (TNF α), are elevated in serum and cerebrospinal fluid after TBI, cross the blood–brain barrier freely after injury, and are evaluated as mediators of other TBI outcomes.^{25–28} Levels correlate with injury severity, increased intracranial pressure, increased mortality, and worsened Glasgow Outcome Score in TBI survivors.²⁸ Chronic elevations of TNF α , IL-6, and IL-1 β levels weeks to months after TBI correlate with significantly worse Disability Ranking Scale, Glasgow Outcome Score, and slowed trajectory of cognitive recovery.^{29–31} The same inflammatory cytokines elevated after TBI influence sleep through damaging neurons in the hypothalamus, modifying astrocyte and microglial function, altering levels of melatonin and orexin, and impairing circadian regulation.^{32–36} SWD also potentiate chronic inflammation, and this is a proposed mechanism leading to many of the negative health consequences linked to SWD.^{33,34} Despite overlap between inflammation after critical TBI and inflammation in SWD reported separately in the literature, prior studies have not assessed the link between inflammation and SWD following critical TBI.

In sum, SWD after pediatric critical TBI are an important morbidity. There remain substantial gaps in available knowledge due to limited data. Research is needed to identify the incidence, risk factors, and pathophysiologic mechanisms underlying SWD. Untreated SWD delay recovery and compound other morbidities encompassed by postintensive care syndrome, including physical, neurocognitive, and psychosocial dysfunction after pediatric critical TBI (Figure 1). Understanding the burden of SWD in critical TBI survivors is the first step toward identifying effective interventions for SWD and evaluating sleep as a modifiable target for other important morbidities plaguing pediatric survivors of critical TBI.

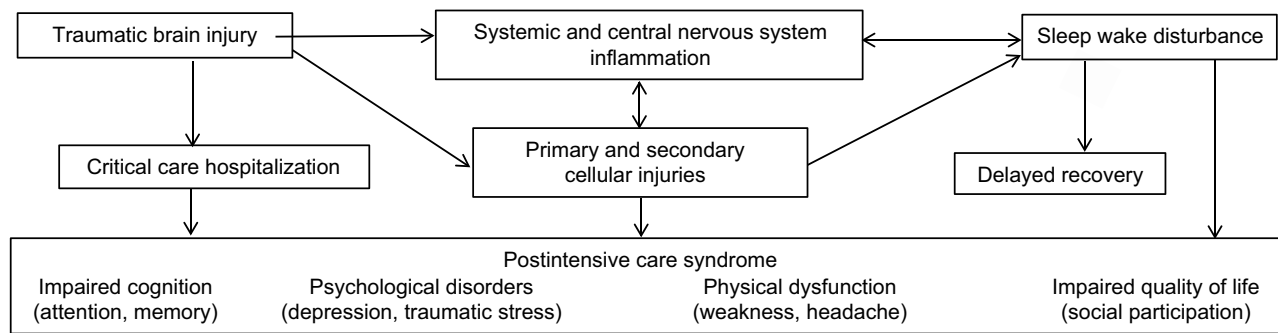


Figure 1 Proposed relationship between traumatic brain injury, inflammation, sleep wake disorders, and postintensive care syndrome.

Disclosure

The authors report no conflicts of interest in this work.

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