

A Profile of Sleep Architecture and Sleep Disorders in Adults with Chronic Traumatic Brain Injury

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Abstract

The primary acceleration-deceleration mechanism of traumatic brain injury (TBI) leaves the brain structures that regulate sleep and wakefulness vulnerable to pathological changes, and there are external secondary factors experienced post-injury that can contribute to the development of difficulties initiating or maintaining sleep, early morning awakening, and/or dissatisfaction with sleep.

Patients with TBI are at risk for developing chronic sleep-wake disturbances, and complaints of insomnia and hypersomnia are commonly reported. The objective of this study was to examine sleep architecture and explore the presence and types of sleep disorders in adults with chronic TBI.

Method: Participants (N=13, mean time post injury 4.5 years) underwent polysomnography and the Maintenance of Wakefulness Test. Polysomnographic findings were compared to age and sex normative data. Sleep disorders were diagnosed according to the criteria of the International Classification of Sleep Disorders, 2nd edition.

Results: Compared to normative data, 92% had abnormal sleep architecture with increased N1 ($p=.002$), reductions in REM sleep ($p=0.017$) and total sleep time, and poor sleep efficiency. All were diagnosed with a treatable sleep disorder according to the ICSD-2.

Conclusion: These exploratory findings add to a growing body of evidence that TBI is associated with a high prevalence of sleep disorders which underlie alterations in sleep architecture including increased arousability, greater amounts of transitional sleep stages, and altered REM latency and duration.

These results highlight the importance of regular screening and assessment of sleep-wake disorders early in the rehabilitation stage for this population in order to prevent the development of chronic sleep disorders.

Keywords Sleep; Sleep disorders; Traumatic brain injury; Polysomnography; Sleep architecture

Introduction

The primary acceleration-deceleration mechanism of traumatic brain injury (TBI) leaves the brain structures that regulate sleep, wakefulness and arousal vulnerable to pathological changes [1]. In addition to the TBI, there are external secondary factors experienced by many individuals post-injury that may contribute to the development of disturbed sleep over time such as changes in, or reductions in, activity, mobility, and lifestyle.

These may result in alterations to the sleep-wake schedule, mood and/or weight due to reduced mobility and activity. All of these can contribute to the development or exacerbation of pre-existing sleep disturbances.

Accordingly, patients with TBI have been found to be at high risk for developing chronic sleep-wake disturbances (SWDs) [2] and up to 70% are reported to have complaints of insomnia and hypersomnia across the continuum of recovery [3-7]. Symptoms of insomnia, including difficulty falling asleep, staying asleep, difficulties with early awakening, as well as fragmented sleep are reported in 50-70% of those with TBI [8-13].

A recent meta-analysis and review further highlights the incidence of sleep disturbances after TBI [6]. For those with moderate-severe TBI, evidence from polysomnography (PSG) studies suggests that excessive daytime sleepiness (EDS) and post-traumatic hypersomnia or post-traumatic pleiosomnia, specifically an increased sleep tendency per 24 hours, are most typically reported [14-17].

Studies involving polysomnography (PSG), an objective measure of sleep, report that 50% of those with moderate-severe TBI present with

treatable sleep disorders other than insomnia, such as obstructive and central sleep apnea, restless leg syndrome (RLS), periodic leg movement disorder (PLMD), post-traumatic hypersomnia and circadian rhythm abnormalities [9,18-20].

Sleep disturbances have been found to begin in the early acute stage of injury and a recent PSG evaluation conducted in an acute care trauma centre found that compared to patients with orthopaedic and or spinal cord traumatic injuries, acute TBI patients showed a significantly longer duration of nocturnal sleep and earlier night-time sleep onset [21].

During the inpatient rehabilitation stage of recovery, results from actigraphy have identified that 67% of participants had a sleep-wake cycle disturbance, co-existing with self-report of difficulty with initiating and maintaining sleep. Other studies using self-report measures have also reported sleep disruptions amongst those in an inpatient rehabilitation setting [22, 23].

In the chronic stage of TBI (>1 year), preliminary polysomnographic findings have identified changes in sleep architecture, in comparison to the general population.

They include decreased sleep efficiency (amount of time asleep divided by amount of time in bed) [24]; increased percentage of stage 1 sleep [9]; reduced percentage of both slow wave sleep [24, 25], and REM sleep [25]; as well as increased awakenings and number of arousals [25]. However, there has been a lack in formal diagnoses of underlying sleep disorders which may be contributing to these findings.

Despite the increasing awareness regarding post-traumatic sleep and wake disturbances, sleep is not routinely assessed amongst this population.

Many patients, therefore, may go undiagnosed and thus are ineffectively managed or not treated. Moreover, given that this increased awareness is a relatively recent trend, there is a paucity of information regarding the sleep of individuals in the chronic stage post injury.

The aims of this study are as follows: 1.To objectively examines sleep architecture via overnight PSG in a sample of adults with chronic TBI; 2.To diagnose any underlying sleep disorders that result in symptoms of insomnia or hypersomnia and disturbed sleep architecture.

We hypothesized that we would find alterations in sleep architecture as previously reported [9, 24, 25] in comparison to age norms. We further hypothesized that some participants would have underlying sleep disorders that caused their symptoms of insomnia or hypersomnia.

Materials and Method

The study was approved by the local research ethics review boards. This cross-sectional study was conducted in accordance with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for case-control studies [26]. This study was part of a longitudinal study examining the impact of treatment for sleep and arousal disorders on outcomes for adults with chronic traumatic brain injury. The findings specific to outcomes are published elsewhere [5].

Setting and participant recruitment

Participants were assessed in the Sleep Disorders Clinic and Brain Sciences Program at a teaching hospital affiliated with the University of Toronto.

Participants were recruited over a 2-year period from across Southern Ontario by means of clinicians working in major rehabilitation centres in Toronto, community-based rehabilitation practitioners, and an announcement on the Brain Injury Association of Canada website. Follow-up and clinical care was provided to all participants in the study.

Participants

Eligible participants had to meet the following criteria: 1. Be between the ages of 18-60 years; 2. Have a diagnosis of moderate-severe traumatic brain injury or mild traumatic brain injury with persistent symptoms; 3. During the initial interview, have self-reported post-traumatic sleep and/or wake disturbance (e.g., excessive daytime sleepiness), with dissatisfaction with sleep such that it was a cause of significant distress and/or a score of 15 or greater on the Insomnia Severity Index (ISI), which represents "Clinical Insomnia" (see Measures), those with night-time sleep problems, or a score of 8-14 which represents "Sub-threshold Insomnia" or those with adequate or excessive night time sleep and excessive daytime sleepiness [27]; 4. Be able to speak and read English; and 5. Provide informed written consent to participate. (See table 1)

Individuals were excluded from the study if they: 1. had a history of psychosis; 2. were actively using substances such as alcohol or non-prescription drugs; 3. had pre-injury sleep disturbances as determined during the initial assessment; 4. had ingested alcohol and/or caffeine in the 24-hour period previous to the PSG appointment. The sample size is consistent with that used in previous studies of TBI (range N=7-14 subjects with TBI per study) [5, 9, 21, 25, 28].

All eligible participants completed the Insomnia Severity Index (ISI) [27], and participated in the Diagnostic Interview for Insomnia [27], and provided a list of current medications.

Following a comprehensive clinical evaluation of sleep and wakefulness by a neurologist who was also a diplomate of the American Board of Sleep Medicine, an Epworth Sleepiness Scale (ESS) score was also obtained [29].

Where indicated, participants were referred for blood work to evaluate endocrine function, ferritin levels, and vitamin B12 to disentangle possible alterations in endocrine function, in particular, full or partial hypo-pituitarism, which is common following TBI, as well as assess other common medical contributors to sleep-wake disorders [30].

Overnight polysomnography (PSG) was performed followed by a Maintenance of Wakefulness Test (MWT) the following day where clinically indicated [31]. The PSG and MWT test were scored by a registered PSG technologist.

ID	Age	Sex	TBI Severity	Time Post injury (years)	Onset of Sleep disturbance	Sleep Architecture	ESS	Insomnia Severity Index	Prescribed Medications
1	18	F	Severe	2	Post-injury	Normal	13	17 (moderate)	Quetiapine
2	19	M	Severe	1	Post-injury	Abnormal	7	22 (severe)	None
3	21	M	Moderate	4.5	Post-injury	Abnormal	13	17 (moderate)	Escitalopram
4	28	F	Severe	2	Post-injury	Abnormal	16	26 (severe)	Trazadone Zopiclone Sertraline Doxycycline Acetaminophen Codeine
5	29	M	Severe	22	Post-injury	Abnormal	15	14 (sub-threshold)	Bupropion Risperidone Desvenlafaxine
6	31	M	Severe	1	Post-injury	Abnormal	14	17 (moderate)	Modafinil Bupropion Escitalopram
7	32	M	mTBI with persistent symptoms	2	Post-injury	Abnormal	15	21 (moderate)	None
8	37	F	Severe	2	Post-injury	Abnormal	8	13 (sub-threshold)	Synthroid Clopidogrel Escitalopram Atorvastatin Propranolol
9	47	M	mTBI with persistent symptoms	2	Pre-existing mild OSA, exacerbated post-injury	Abnormal	15	22 (severe)	Topiramate Methlyphenidate Duloxetine Meloxicam Tramadol Pregabalin Puprenorphine
10	49	M	Severe	1	Post-injury	Abnormal	14	25 (severe)	Citalopram Nortriptyline Amlodipine Metoprolol
11	53	F	Severe	3	Post-injury	Abnormal	15	23 (severe)	Lamotrigine
12	55	F	Severe	18	Post-injury	Abnormal	12	17 (moderate)	None
13	58	F	Severe	1.5	Post-injury	Abnormal	6	10 (sub-threshold)	Metoprolol Amiodarone Fluoxetine Atrovastin Levothyroxine Warfarin

Table 1: Participant demographics and characteristics, TBI=Traumatic Brain Injury.

Variables of interest

The following variables were examined: insomnia severity, excessive daytime sleepiness (by self-report standardized measures); sleep onset latency (SOL), total sleep time (TST), sleep efficiency (SE), arousal index (the number of spontaneous arousals per hour; SAI), Wake After Sleep Onset (WASO), percentage of stage N1 sleep, percentage of stage N2 sleep, percentage of stage N3 sleep, Rapid Eye Movement (REM) latency, REM percentage of total sleep (as measured by PSG), apnea hypopnea index (AHI), lowest oxygen saturation (lowest SaO₂) and periodic limb movement index (PLMI); normality of sleep architecture and the ability to remain awake while resisting the desire to sleep during the day (as measured by a MWT).

Study measures

Insomnia Severity Index (ISI) [27]. This index is designed to be both a brief screening measure of insomnia and an outcomes measure for use in treatment research. Its reliability and validity have been established and it has also been found to be sensitive to change following pharmacologic and/or behavioral intervention for primary insomnia

Polysomnography: All PSGs were recorded on digital equipment (Compumedics, Australia) using standard recording and scoring methods [32]. During each study, monitoring of the following took place: Electroencephalogram (EEG), electro-oculogram (EOG), surface electromyography (EMG), respiratory measures (abdominal and thoracic effort [measured with respiratory inductive plethysmography belts], nasal/oral pressure [measured with a nasal/oral pressure transducer], nasal/oral flow [measured with a thermistor]), oxygen saturation, and a 2-lead ECG.

Expanded EEG or EMG montages were used if nocturnal seizures or parasomnias were suspected. All studies were videotaped and audiovisual recordings were time-synchronized to the remainder of the data. Sleep was manually scored according to the American Academy of Sleep Medicine [AASM] criteria [32]. Sleep disorder diagnoses were made after clinical assessment according to the International Classification of Sleep Disorders (ICSD-2) [33].

Maintenance of wakefulness test (MWT) [31]: This test involves giving the participant four opportunities to maintain wakefulness during the day at 9am, 11am, 1pm, 3pm, for 40 minutes each time. They are placed in a slightly reclined position, in a dimly lit room, with the instructions "Please sit quietly and try to remain awake". The latency to sleep onset was recorded.

The MWT was used to quantify EDS, as well as to provide an indicator of future risk of accidents [31, 34]. Patients with TBI are typically administered the Multiple Sleep Latency Test (MSLT) [35]; however the MWT may identify different aspects of alertness for those with severe TBI [36]. Furthermore, EDS impairs function and puts patients at risk of sustaining further injury [34].

Epworth sleepiness scale (ESS) [29]: This 8-question scale was designed to evaluate daytime sleepiness, and asks the respondent the likelihood that he/she would fall asleep under various scenarios.

This questionnaire was administered as part of the routine clinical evaluation of sleep. Most rested individuals have a score under 10. The reliability and validity of the ESS has been well established [37].

Analysis

Sleep was manually scored according to the American Academy of Sleep Medicine [AASM] criteria [32]. The following variables were derived: total sleep time, sleep efficiency (amount of time asleep as compared to amount of time in bed), arousal index (per hour), percentages of each sleep stage and REM latency (time to first REM period).

Variables were compared to age and sex-based normative data [38]. Sleep disorders were diagnosed following clinical assessment according to the ICSD-2 [33].

Statistical analysis

Descriptive statistics are reported using means and standard deviations. Paired t-tests were used to compare sleep architecture variables to matched published age and sex normative values. Significance was set at $p \leq 0.05$. All analysis was performed with SPSS version 22.

Sleep disorder diagnoses

The ICSD-2 classification was used that lists 84 sleep disorders under 7 major categories, including: 1 - insomnias; 2 - sleep-related breathing disorders (SRBD); 3 - hypersomnias; 4 - circadian rhythms sleep disorders; 5 - parasomnias; 6 - sleep-related movement disorders; and 7 - other sleep disorders and isolated symptoms [38].

Results

Sleep study results and PSG parameters

Table 2 provides the sleep parameters of the 13 participants. We documented reductions in total sleep time (mean=343.8 minutes \pm 92.6), reduced sleep efficiency (mean=74.9 \pm 15.7) and increased incidence of wake after sleep onset (mean=73.9 \pm 53.7). Further, all severe TBI participants exhibited sleep fragmentation (multiple arousals or awakenings); increased arousal index (mean=13.28 \pm 7.7) as well as alterations in sleep staging in comparison to published age and sex norms.

We further identified increased stage N1 ($p=0.002$), which indicates transitions in state, and alterations in REM percentage ($p=0.017$) and or REM onset latency (Table 2) compared to normative values of same age and sex [38]. All the insomnia group participants who completed the ESS (4 out of 5) were excessively sleepy with a mean score of 12.53 \pm 3.4.

Two of five participants who underwent MWT had abnormal findings (criterion: one epoch of sleep considered as failure due to risk of driving accident). Of the three participants with sleep-related breathing disorder (SRBD), two (66.7%) had abnormal MWT findings. Of the three with relatively "normal" (i.e., considered as mildly abnormal) polysomnographic data, two were unable to maintain alertness as per MWT and one had MWT findings considered normal with modafinil taken at the time of assessment. For this individual a modafinil washout was tried however he was unable to function without the medication.

ID	Sex	Stage N1 % (Norm) * p=0.002	Stage N2 % (Norm)	Stage N3 % (Norm)	REM Latency Norm=90-120 Mins	REM (Mins) %age (Norm) *p=0.017	Total SleepTime (Mins)	Sleep Effic (%)	Wake After Sleep Onset (Mins)	Arousal Index	AHI	Lowest SaO2 (%)	PLMI	ESS	MWT Latency (Mins)	Sleep Diagnosis ICDS-II
1	F	3 (3.74)	50 (49.3)	27 (23.43)	29.5	20 (22.12)	457	95	12.5	3	0.1	96	0	13	8.13	HS
2	M	9.2 (3.74)	52.4 (57.8)	19.3 (23.04)	128.5	19.1 (22.12)	390	88	18.5	18.7	0.2	93	0	7	Not performed	MD and OSA
3	M	19.7 (4.18)	36.8 (45.54)	19.7 (21.09)	252.2	23.8 (28)	294	61.5	121	7.3	0.2	91	1.4	13	18.3	Insom
4	F	4.5 (4.18)	43 (52.7)	41.8 (17.69)	87.5	10.7 (25.23)	201	50.8	88.5	6.9	0.3	93	2.4	16	Not performed	Insom
5	M	10.3 (4.17)	71.2 (56.89)	12.9 (12.46)	251	5.6 (23.47)	329	87.3	35	21.7	1.1	90	11.8	15	Not performed	MD
6	M	10 (4.17)	58.9 (56.89)	21.1 (12.46)	286	10.7 (23.47)	505	73	58	11	2.6	92	3.3	14	Normal with (modafinil)	HS
7	M	9.9 (4.17)	58.2 (56.89)	3.7 (12.46)	83	27.6 (23.47)	326	91.6	30	6.6	0.1	92	2.7	15	23.8	HS
8	F	16.3 (4.17)	57 (53.77)	26.7 (14)	No REM	Absent (22.15)	260	65	63	14.3	0	93	16.6	8	Normal	CRSD and MD
9	M	11 (5.64)	59.7 (54.75)	19.2 (8.85)	121	10.1 (22.85)	462	88.2	59	9.6	20.1	78	0	15	8.1	OSA, CSA and Insom
10	M	33.2 (5.64)	50.8 (54.75)	3.9 (8.85)	119.5	12.1 (22.85)	280	53.4	198	16	1.5	97	31.2	14	Normal	MD, OSA
11	F	7.3 (4.85)	51 (57.8)	19.9 (10.63)	117	21.8 (21.77)	389	90	36	6.2	4.2	88	0	15	14.4	HS and OSA
12	F	25.3 (4.85)	49.6 (57.8)	5.1 (10.83)	66	20 (21.77)	237	60.5	127.5	24.1	3.5	88	0	12	Normal	OSA
13	F	30.4 (4.85)	40.1 (57.8)	0.4 (10.63)	70	29.1 (21.77)	339	70.3	114	27.3	53.1	79	0	6	26	OSA

Table 2: Age and sex-related norms from Williams, R.L., Karacan, I., and Hirsch, C.J. (1974). *Electroencephalography (LEG) of Human Sleep: Clinical Applications*. Chichester, Sussex: John Wiley.

AHI=Apnea/Hypopnea Index, SaO2=Oxygen Saturation, PLMI=Periodic Limb Movement Index, HS=Hypersomnia, Insom=Insomnia, CRSD=Circadian Rhythm Sleep Disorder, MD=Movement Disorders (PLMD, RLS), SA=Sleep Apnea (Obstructive or Central), OSD=Other Sleep Disorders

Note: In this sample 70% (N=9) have a diagnosis in the insomnia family: 23% (N=3) insomnia, 8% (N=1) CRSD, 31% (N=4) MD, 39% sleep-related breathing disorder (N=5); 31% (N=4) have a diagnosis of hypersomnia; 39% (N=5) have more than one diagnosed sleep disorder

Clinical findings: Diagnosis of sleep disorders

All participants were diagnosed with a treatable sleep disorder as per the ICDS-2 criteria and 5 of 13 (38.5%) had co-morbid sleep disorders. We refer the reader to Tables 1 and 2 for specifics. Among the sample, participants were diagnosed with sleep apnea (Obstructive Sleep Apnea (OSA) N=4 and Obstructive and Central Sleep Apnea (OSA and CSA) N=1) 39%; Hypersomnia (N=4) 31%; Sleep-related movement disorders (N=4) 31%, Circadian rhythm sleep disorder (N=1) 8%, Insomnia (N=3) 23%, and Other sleep disorder (N=2) 15.5%.

While the sleep diagnoses varied, all participants had a diagnosis of TBI, ten in the severe category, and one in moderate-severe and two in the mild category with persistent symptoms.

When sleep was considered according to individual sleep diagnosis, we identified that the group with SRBD, RLS and/ or PLMD displayed greater amounts of lighter stages of sleep of (i.e., stage 1).

Discussion

The aims of this study were to objectively examine sleep architecture via overnight PSG in a sample of adults with chronic TBI as compared to normative data by age and sex, and to describe any underlying sleep disorders that resulted in symptoms of insomnia or hypersomnia.

There are several key findings. Firstly, among the participants, twelve of thirteen had abnormal sleep architecture as compared to published age and sex norms. Specifically, increased stage N1 sleep, alterations in percentage of N3 stage and reduced REM percentage which are consistent with previously reported changes in sleep architecture in patients with TBI [9,24,25]. Secondly, all participants were diagnosed with a treatable sleep disorder based on alterations in sleep parameters upon completion of their assessment. Lastly and importantly, sixty percent (6 out of 10) were unable to maintain wakefulness during controlled conditions during the day.

Clinical implications

All participants reported symptoms of insomnia or hypersomnia with increased sleep need, and dissatisfaction with their sleep. Despite the fact that the participants ranged from 1 to 22 years post-injury, only 1 of 13 had undergone specialist investigation of sleep complaints shortly post-injury (at three months). However, all participants were diagnosed according to the ICSD-2, with a treatable sleep and/or wake disorder upon completion of all study investigations.

In this sample, the mean time post-injury was 4.5 years, and two participants were more than 15 years post-injury, yet both had been struggling with trauma-related onset of sleep disturbances.

Two participants, who were actively driving a motor vehicle at the onset of the study, reported severe daytime sleepiness with impaired alertness based on MWT, and subsequently had to stop driving until they were adequately treated. All participants reported that their sleep-wake disturbance had a negative impact on their mood and quality of life.

Thus these findings have implications for those providing clinical management of individuals with TBI. We suggest that routine screening of sleep, assessment of any identified sleep related issues as well as prevention and treatment efforts should be an integral part of any TBI rehabilitation program.

Limitations

Given the heterogeneity of the sample, we were unable to control for medications and therefore the sleep findings must also be considered in light of possible medication effects on sleep [39]. Seventy seven percent of the sample was taking multiple medications at the time of investigation, (see Table 1) some of which are known to enhance sleep, or to compromise or alter sleep. These include selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), known to suppress REM and increase lighter stages of sleep [40, 41] and to cause symptoms of insomnia in a small number of (4 to 18%) of depressed samples. 'Atypical' anti-psychotic agents (e.g., quetiapine) have been reported to increase total sleep time and sleep efficiency.

Adverse effects of anti-psychotic agents however, may also include SRBD, RLS, and circadian rhythm disturbances [43,44]. Pregabalin, a medication used to treat neuropathic pain, has been shown to increase slow-wave sleep as a proportion of the total sleep period, reduce sleep-onset latency and reduce the number of awakenings in healthy volunteers [45,46]. Stimulants are recognized to create difficulties with initiating sleep thus increasing sleep onset latency, as well as being REM-suppressants [47]. Finally, modafinil, is reported to cause insomnia in placebo-controlled trials in some patients [48].

We further recognize that the sample was small, and therefore, the findings although comprehensive, are exploratory and thus may not be representative of the wider TBI population. We also recognize that the normative data is dated; however to our knowledge there are no more recent normative data available.

The majority of participants had severe TBI, and were symptomatic, reporting significant dissatisfaction with their sleep post-injury. All participants were placed on the sleep lab schedule and thus their PSG were not necessarily congruent with their circadian phase. Consequently, these results may not truly represent the habitual sleep-wake schedule of the participants and are not 'free running'.

Conclusion

This study adds to the understanding of persistent sleep disorders in a sample of adults with chronic TBI, utilizing both objective- and self-report measures. To our knowledge, it is the first study to both examine sleep architecture via PSG compared to published age and sex norms, and provide a diagnosis of sleep disorders according to the ICSD-2.

In addition, these findings highlight the heterogeneity and complexities of these multi-faceted disorders, including the possible confounds of medication, an important consideration for this population who are often prescribed multiple medications that may impact sleep. Our results also suggest that currently, significant delays occur in the identification, diagnosis and treatment of sleep disorders associated with TBI.

There is a need for greater awareness and understanding of sleep and sleep disturbances following TBI, streamlined referrals for assessment, and the development of practice guidelines. We recommend that patients with TBI of all severities be screened for disorders of sleep, wakefulness and arousal in the early stage of rehabilitation as this may pre-empt the development of chronic sleep disorders.

These results add to a small but growing body of evidence that sleep-wake disorders associated with TBI are complex and remain highly prevalent many years post-injury. Further research with larger samples and free-running PSG is needed.

Declaration of Interest

The authors report no conflicts of interest.

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