Research Paper:
Identification of Imaging and Clinical Markers Predicting Chronic Sleep Disturbances After Traumatic Brain Injury in Adults

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ABSTRACT

Background and Aim: We aimed to determine the prognostic imaging and clinical markers of chronic Post-Traumatic Sleep-Wake Disorders (PTSWDs) with a special focus on the early cognitive and executive dysfunctions following Traumatic Brain Injury (TBI). The prevalence rate of Post-Traumatic Psychiatric Disorders (PTPDs) in various sleep disorders was also investigated.

Methods and Materials/Patients: In the present longitudinal study, 165 qualified patients with closed TBI were studied. Demographic, imaging and clinical characteristics of the subjects were recorded. The presence of acute post-traumatic cognitive deficits, anxiety, depression, and headache were measured by standard scales at discharge. Executive functioning was scored by the verbal fluency test. Several subjective questionnaires were applied to screen the chronic PTSWDs at 6 months after the onset of TBI. All variables were compared between the patients as well as those with and without PTSWDs using appropriate statistical tests.

Results: Of 146 patients remaining in the follow-up study, 35% manifested PTSWDs, with insomnia and Excessive Daytime Sleepiness (EDS) as the most prevalent types. A poor executive functioning was observed in all PTSWDs patients, compared to those without PTSWDs, with only insomnia and hypersomnia patients demonstrating acute depression. Hypersomnia was also significantly related to bilateral brain contusion. The insomnia mostly comorbid with fatigue was predicted by mild injury, cortical lesions in the frontal lobe and acute severe headache. However, the patients who experienced the brain stem and diffusion lesions of right hemisphere were prone to EDS that was mainly accompanied by aggression.

Conclusion: The predictive role of acute executive dysfunction has been clarified in this study. It is suggested that early neurorehabilitative interventions targeting the impaired neural circuits of executive functioning and mood processing may accelerate and facilitate the optimal neurofunctional recovery leading to minimizing the persistent sleep disturbances.

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Highlights

- The prevalence of post-traumatic sleep-wake disorders is about 35%.

- Insomnia is the commonest sleep problem after Traumatic Brain Injury (TBI) and co-occurs with fatigue.

- Chronic insomnia was followed by mild TBI, acute severe headache, and frontal lesion.

- Predictors of excessive daytime sleepiness were diffuse lesions of right hemisphere.

- Executive function was poorer in patients with sleep problem.

Plain Language Summary

Circadian Rhythm Sleep Disorders (CRSDs) are among common post-traumatic complications which may be persistent in most cases. These disorders may differ in affected patients. The injured area in the brain has a role in developing a specific type of sleep disorder. CRSDs is following a trauma-induced event, which disrupt the active participation of patients during rehabilitation interventions and interfere or delay their neurological and functional improvement. Considering the patients with traumatic brain injury (TBI), as population with heterogeneous physical, cognitive, and psychological complications, the aim of this study is to identify the severity and location of lesions related to TBI and clinical factors associated with imaging findings in them in order to predict the occurrence of CRSDs after trauma. In this regard, 165 patients with TBI admitted to the hospital were enrolled in the study, and their demographic, clinical and para-clinical data were recorded using a questionnaire. The patients were examined for cognitive, psychological, and physical function through standard tests during discharge. The follow-up evaluation for a variety of CRSDs was conducted six months later. 146 of 165 patients were participated in the follow-up examinations, and 35% of them had a variety of CRSDs six months after TBI, where the most common types were "insomnia" and "daytime sleepness". Those with a poorer cognitive function during discharge were more prone to sleep disorders. The hypersomnia was found to be more frequent in patients with bilateral cerebral lesions. Insomnia was associated with chronic fatigue, and was found mostly in people with mild localized lesions in the frontal cortex and severe headaches during the hospitalization period. On the other hand, daytime sleepness, mostly accompanied by aggressive behaviors, was more common in patients with disseminated lesions in the right-brain hemisphere, especially in the brainstem. In general, cognitive and psychological disorders and headache happening immediately after TBI in hospitalized patients as well as the type, severity and location of brain injuries affect the occurrence of sleep disorders and their types. Therefore, identifying the population exposed to risk factors and early interventions to remove them is a vital priority in the treatment of sleep disorders after TBI.

1. Introduction

Traumatic Brain Injury (TBI) mainly results in various sensorimotor, cognitive, psychological, and emotional disabilities in survivors. Some complications of TBI remain consistent in the longterm [1-6]. Post-Traumatic Sleep-Wake Disturbances (PTSWDs) are among the most common undesirable outcomes of TBI, with various prevalence rates reported by different studies [7-12]. Various categories of PTSWDs, including insomnia, hypersomnia, Excessive Daytime Sleepiness (EDS), parasomnia, obstructive sleep apnea, and Periodic Limb Movement Disorder (PLMD) and Circadian Rhythm Disorder (CRD), have been observed with varying frequency in the TBI population [7, 8, 10, 13, 14]. Obviously, a normal sleep-wake cycle involves a balance between arousal stimulatory and inhibitory systems and functional coordination between them. Therefore, the disruption of the neural circuits regulating sleep-wake cycle caused by TBI creates sleep disorders, and a specific type of PTSWDs occurs depending on the affected area of brain [15, 16].

The clinical manifestations of PTSWDs may appear in different phases of the disease [17]. The occurrence of PTSWDs in the acute phase is harmful to the nervous system restoration and interferes with primary neural improvement and may prolong neuroplasticity [15]. Also, sleep problems occurring in subacute and chronic

phases prevent the active participation of the patients in the rehabilitation program and delay their functional recovery [15, 17]. Additionally, it negatively affects the various aspects of health and quality of life, and challenges return to healthy lifestyle [7, 13, 18, 19]. Thus, better understanding of the factors involved in the onset or durability of PTSWDs is of importance in preventing the persistence of this complication, making decision for an early therapeutic intervention, and accelerating and facilitating optimal recovery in patients' daily activities.

Previous studies reported a clear relationship between the occurrence of PTSWDs, mood disorders, daytime fatigue and nighttime pain [20-22]. Some studies have supported the association between chronic insomnia and headache, anxiety and depression following TBI. Likewise, TBI severity could be associated with the risk of chronic hypersomnia [10]. However, there are contradictory findings on the prognostic role of severity, location, and type of lesion in the occurrence of new-onset sleep-wake cycle problems in TBI [7, 8, 10, 13, 18, 22, 23]. In addition, there is little information available on neuropathological and neuropsychological factors involved in the development of different types of PTSWDs.

The clinical and paraclinical characteristics in patients prone to chronic PTSWDs remain undiscovered. These information gaps demand further prospective investigations. Furthermore, the relationship between Post-Taumatic Psychiatric Disorders (PTPDs) and the various types of consistent PTSWDs is unclear. Moreover, post-TBI sleep disorders negatively impact the cognitive and emotional functions [17, 24]. As one of the risk factors for chronic traumatic encephalopathy, PTSWDs contribute to the onset and exacerbation of symptoms, including poor cognition, aggression, and impulsivity [25, 26]. Sleep disorders may be the cause of cognitive impairment and Alzheimer disease [27, 28]. Therefore, it is useful to clarify whether the early post-TBI executive and cognitive functions evaluated at the discharge are associated with disrupted sleep in the chronic phase.

In this regard, the present study aimed to determine the clinical and imaging markers predicting the occurrence of various types of PTSWDs. We also explored the role of early post-TBI executive and cognitive functions in developing various categories of PTSWDs, in particular. Furthermore, the prevalence of PTPDs was investigated in the different types of post-traumatic sleep disorders.

2. Methods and Materials/Patients

In this prospective longitudinal study, 165 qualified patients with closed TBI participated. The subjects aged between 18 and 65 years and were admitted to the Neurosurgery ward of Poursina Hospital in Rasht City, Iran. They were enrolled in the study after providing a written consent. The inclusion criteria were as follows: intracranial injuries determined in primary neuroimaging findings in adult patients with primary TBI, experiencing amnesia for 20 minutes or more, being conscious during neuropsychological examinations (discharge phase), and having a functional outcome score of 3 or higher according to Glasgow Outcome Scale (GOS) [29], having at least 4 years of education. Exclusion criteria were the patients in a vegetative state, or with severe loss of consciousness at discharge who were unable to perform the cognitive tasks, those with normal neuroimaging findings but a history of TBI and previous sleep and psychiatric disorders, patients with preexisting cognitive dysfunctions, substance abuse, neurological or orthopedic disorders, patients with malignant diseases, intellectual disability, or sensory disabilities, as well as individuals receiving sedative medications.

The demographic, clinical and paraclinical characteristics of patients were recorded by a separate questionnaire. The family history of sleep and psychiatric disorders were identified by evaluating the presence of these disorders in first-degree relatives of patients. Type, size and location of lesions were determined using neuroimaging techniques within 24 hours after brain trauma. The obtained data were reported by a neuroradiologist unaware of the neurological and neuropsychological outcomes. The data about the brain lesion side, site and type were recorded. The injury types were classified according to lesion morphology [29], including hematoma, contusion, edema, pneumocephalus and Diffuse Axonal Injury (DAI). Lesion site consists of the cortex, subcortex, epidural, subdural, subarachnoid spaces, ventricles, and brain stem. For the multifocal damages, the most intense and wide site on brain scans were considered as an analyzable lesion site. TBI severity was ranked according to the post-resuscitation Glasgow Coma Scale (GCS) score and the duration of Post-Traumatic Amnesia (PTA) [29].

Persian version of the Hospital Anxiety and Depression Scale (HADS) [30] was applied to assess self-reported mood status. The presence and severity of headache was subjectively evaluated using the Numerical Pain Rating Scale (NPRS), which assigns numbers 0-10 to the amount of pain. According to the NPRS, zero means no

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pain. Mild pain is specified by 1-3, moderate pain by 4-6, and severe pain by 7-10. The executive functioning was measured by verbal fluency test as previously described [6]. Cognitive impairment was objectively diagnosed using the standard Persian version of Mini-Mental State Examination (MMSE) after the patient's discharge [31].

HADS, NPRS, MMSE and verbal fluency test were performed after discharge. The duration of post injury when patients were synchronically evaluated with the duration of hospitalization was 10 days on average. All examinations of discharge phase were performed by a trained research assistant. Six months after the TBI occurrence, the samples were divided into 2 groups of with and without chronic PTSWDs. A differential diagnosis of PTSWDs and psychiatric disorders was conducted through a structured interview using a clinical checklist by a psychiatrist and according to the Diagnostic and Statistical Manual of Mental Disorders-V [32].

Subjective standard evaluations were also performed to determine the nature and severity of PTSWDs. For this purpose, the Persian version of Pittsburgh Sleep Quality Index (PSQI) [33], the Insomnia Severity Index (ISI) [34], and the Epworth Sleepiness Scale (ESS) [35]

were used. In this study, daytime fatigue is reported in individual interviews with an ESS score of more than 10 as fatigue, scores less than 10 in the ESS as EDS, scores less than 7 in the ISI as insomnia, and an increased need for sleep (at least 2 hours more than before TBI occurrence) per 24 hours as hypersomnia. Psychiatric symptoms developed 6 months after the occurrence of TBI were considered as chronic PTPDs. In the discharge assessments, early cognitive impairments were diagnosed with a score of less than 23 in MMSE.

Acute anxiety and depression were determined with a score of more than 7 in the HADS. The obtained data were analyzed using SPSS. After evaluating the normal distribution of quantitative variables by Kolmogorov-Smirnov test, Independent Samples t test and Chi-squared test were applied to analyze the quantitative and qualitative demographic, clinical and paraclinical data between the study groups. The scores of sleep indexes, HADS anxiety and depression subscales, cognitive and executive functions in various types of PTSWDs and non-PTSWDs were compared using One-way ANOVA (analysis of variance) and Scheffe post hoc test. To determine clinical and imaging markers predicting the
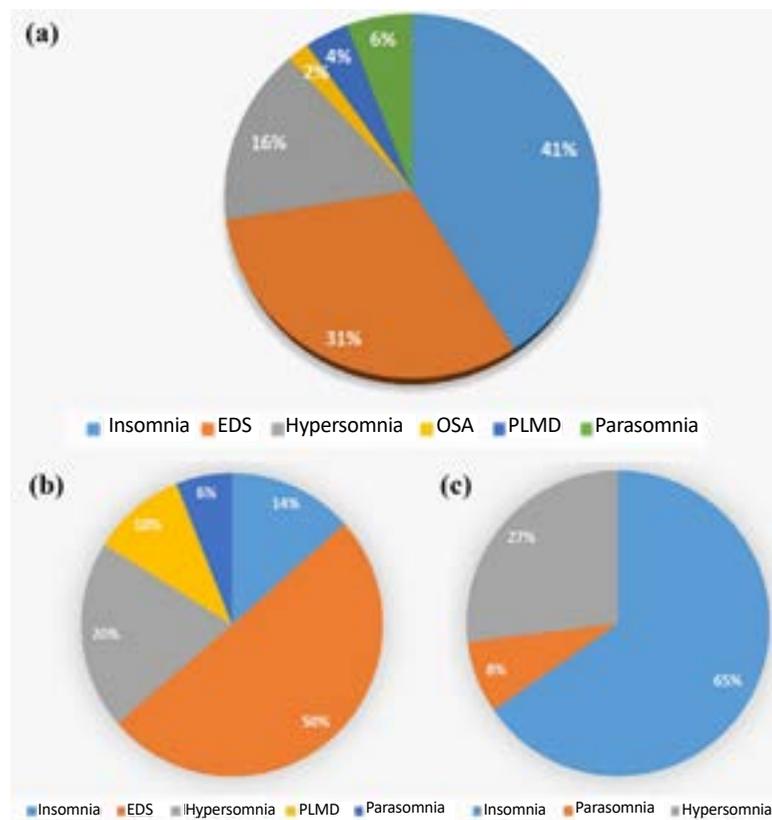

Figure 1. (a) Distribution of PTSWD types in all TBI patients with sleep problems, in PTSWDs patients with comorbid chronic PTPDs, (c) and fatigue at 6 month follow-up

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PTSWDs at 6 months after the TBI onset, a multiple logistic regression using Backward method was used in a multivariate analysis. Two-tailed test was used and 3 significance levels including P<0.05, P<0.01 and P<0.001 were considered.

3. Results

Of 165 patients enrolled in the primary sampling, 146 patients were remained in follow-up assessments, of whom 51 (34.93%) patients had PTSWDs. According to Table 1, the Mean±SD age of the subjects was 35.5±11.04 years. The ratio of male to female was approximately 3.4:1. Their Mean±SD GCS score was 9.4±2.13. About 73% of TBI patients reported a good recovery according to GOS. Moderate and severe disabilities were observed in about 36% and 13% of all TBI patients, respectively. According to neuroimaging findings, hematoma and pneumocephalus were the most frequent lesion types in the studied TBI patients.

The occurrence of lesion in subdural or epidural or subarachnoid spaces were more than other lesion sites. About 62% and 37% of TBI patients represented single and multiple lesions on brain scans, respectively. About 30%, 36% and 32% of TBI patients had right, left and bilateral brain damage, respectively. More details are presented in Table 2. Figure 1 A shows the distribution of different types of PTSWDs at 6 months after the onset of a lesion in people with closed TBI. Insomnia (41%) and EDS (31%) were the most common chronic sleep disorders in the subjects. About 16% of the study participants experienced hypersomnia. Parasomnia, PLMD, and OSA composed a low proportion of PTSWDs.

Based on Table 1, there was no significant difference between the groups with and without PTSWDs in terms of age, gender, educational level, family history of psychiatric disorders, and functional outcomes at discharge (P>0.05). Neurosurgical intervention for managing brain lesions in TBI patients did not have a significant effect on PTSWDs appearance (P>0.05). Furthermore, an identical percentage of people who underwent neurosurgery was observed between PTSWDs and non-PTSWDs groups. However, the family history of sleep disorders seems to increase the risk of PTSWDs occurrence (P<0.03).

The obtained results suggested that TBI severity was significantly different between the 2 groups (P<0.01). Moreover, a high percentage (72.54%) of people with sleep problems showed early cognitive deficits after TBI, while about 37% of non-PTSWDs had a cognitive impairment. This difference was statistically significant between the 2 groups (P<0.01). In addition, the PTSWDs group had significantly lower executive functioning scores than non-PTSWDs group at the discharge (P<0.003). There was mostly anxiety alone, and mild or moderate headache in half of non-PTSWDs that was significantly different from the prevalence of acute anxiety and or depression (75%) and headache (92%) in the people with PTSWDs. Most patients with PTSWDs experienced severe headache during the acute phase of TBI, while none of the patients without Chronic Sleep Disturbances demonstrated severe headaches during the same phase (Table 1).

The results revealed a significant difference in chronic fatigue between the 2 groups (P<0.001). A high percentage (about 90%) of people without sleep difficulties did not complain of fatigue, but half of the patients with PTSWDs suffered from chronic fatigue. Also, the occurrence of chronic PTPDs in the PTSWDs group was significantly more than that in non-PTSWDs group (P<0.001). Half of the patients with PTSWDs that had comorbid PTPDs were classified in the EDS category (Figure 1 B).

According to Figure 1 C, among the types of PTSWDs, chronic fatigue was more prevalent in patients with insomnia, ranked after TBI (65%). In patients with insomnia, comorbid PTPDs were not very common (20%); however, insomnia patients with comorbid PTPD showed more PTSD symptoms than the other types of PTPDs. Moreover, about 93% of patients with EDS suffered from PTPDs, including aggression, as the most common symptom (56.25%). In total, 75% of patients with hypersomnia had comorbid PTPDs, predominantly with symptomatic depression (87.5%). PTPDs were concurrently observed in all patients with PLMD and parasomnia, which were mainly manifested with symptoms of PTSD and aggression (Figure 2).

Based on the data presented in Table 2, there was a significant difference between the 2 groups regarding the brain injury type (P<0.003), locus (P<0.001), lobe (P<0.001), side and plurality. All TBI patients diagnosed with DAI according to primary brain scans represented the chronic PTSWDs. Among all types of brain lesions, pneumocephalus was more prevalent in the group without sleep problems. In addition, PTSWDs patients demonstrated a high frequency of cortical (37.52%), subcortical (21.56%) and brain stem (19.6%) injuries compared to those without PTSWDs. Furthermore, in 50% the PTSWDs that displayed cerebral lobe damages, the most commonly affected lobe was frontal. Frontal lobe lesions were more prevalent in the group with sleep

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Table 1. Demographic and clinical characteristics of TBI patients according to PTSWD presence

Variables		All TBI Patients (n=146)	Non-PTSWD (n=95)	PTSWD (n=51)	P
Age at injury (Mean±SD)		33.5±11.04	36.5±8.15	30.11±9.8	NS
Formal Education (Mean±SD)		9.8±2.27	8.87±1.92	10.97±2.03	NS
Gender, n (%)	Male	113(77.39)	64(75.78)	36(80.35)	NS
Family psychiatry history, n (%)	Yes	9(6.76)	6(6.89)	3(6.52)	NS
Family SWD history, n (%)	Yes	28(19.17)	9(9.47)	19(37.25)	0.031
TBI severity, n (%)	Mild	43(29.45)	14(14.73)	29(56.86)	0.017
	Moderate	52(35.61)	47(49.47)	5(9.8)	
	Severe	51(34.93)	34(35.78)	17(33.33)	
Neurosurgical intervention for current TBI, n (%)	Yes	52(35.61)	36(37.89)	21(41.17)	NS
ICU duration, days (Mean±SD)		2.94±1.68	1.79±1.3	2.05±1.16	NS
Length of hospitalization, days (Mean±SD)		9.6±2.43	10.84±2.26	13.2±2.11	NS
Functional outcome at discharge, n (%)	Good recovery	73(50)	44(46.31)	23(45.09)	NS
	Moderate disability	53(36.3)	38(40)	21(41.17)	
	Severe disability	20(13.69)	13(13.68)	7(13.72)	
Acute cognitive deficit, n (%)	Yes	73(50)	36(37.89)	37(72.54)	0.011
Acute anxiety or/ and depression, n (%)	No	61(41.78)	48(50.52)	13(25.49)	0.022
	Only anxiety	43(29.45)	31(32.63)	12(23.52)	
	Only depression	20(13.69)	8(8.42)	12(23.52)	
	Anxiety & depression	22(16.43)	8(8.42)	14(27.45)	
Acute executive function score, (Mean±SD)		58.39±10.63	74.03±11.16	32.47±9.51	0.003
Acute headache, n (%)	No	54(36.98)	50(52.63)	4(7.84)	0.004
	Mild	23(15.75)	15(17.64)	8.(15.68)	
	Moderate	44(33.08)	30(31.57)	14(27.45)	
	Severe	25(26.31)	-	25(49.01)	
Chronic PTPD, n (%)	Yes	61(41.78)	31(32.63)	30(58.82)	0.001
Chronic fatigue, n (%)	Yes	35(23.97)	9(9.47)	26(50.98)	0.001

TBI: Traumatic Brain Injury; PTSWD: Posttraumatic Sleep & Wake Disorders; PTPD: Posttraumatic Psychiatric Disorders; SD: Standard Deviation; NS: Not Significant

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Table2. Neuropathology after TBI based on the initial neuroimaging data according to PTSWD presence

Variables		All TBI Patients (n=146)	Non-PTSWD (n=95)	PTSWD (n=51)	P
Brain lesion type, n (%)	Hematoma	47(32.19)	30(31.57)	17(33.33)	0.003
	Contusion	18(12.32)	6(6.31)	12(23.52)	
	Edema	22(15.06)	15(15.78)	7(13.72)	
	Pneumocephalus	49(33.56)	44(46.31)	5(9.8)	
	DAI	10(6.84)	-	10(19.6)	
Brain lesion locus, n (%)	Cortex	31(21.23)	12(12.63)	19(37.52)	0.001
	Sub-cortex	18(12.32)	7(7.37)	11(21.56)	
	Epidural/subdural/ subarachnoid spaces	62(42.46)	54(56.84)	8(15.68)	
	Ventricles	22(15.06)	19(20)	3(5.88)	
	Brain stem	13(8.9)	3(3.15)	10(19.6)	
Brain lesion locus, n (%)	Cortex	31(21.23)	12(12.63)	19(37.52)	0.001
	Sub-cortex	18(12.32)	7(7.37)	11(21.56)	
	Epidural/subdural/ subarachnoid spaces	62(42.46)	54 (56.84)	8(15.68)	
	Ventricles	22(15.06)	19(20)	3(5.88)	
	Brain stem	13(8.9)	3(3.15)	10(19.6)	
Damaged cerebral lobes, n (%)	Frontal	46(31.50)	24(25.26)	22(43.13)	0.001
	Temporal	30(20.54)	25(26.31)	5(9.8)	
	Parietal	11(7.53)	11(11.57)	-	
	Occipital	6(4.1)	6(6.31)	-	
	None	53(36.3)	29(30.52)	24(47.5)	
Lesion plurality, n (%)	Single	91(62.32)	68(71.57)	23(45.09)	0.004
	Multiple	55(37.67)	21(22.1)	28(54.9)	
Brain lesion side, n (%)	Right	45(30.82)	22(23.15)	23(45.09)	0.004
	Left	53(36.3)	37(38.94)	16(31.37)	
	Bilateral	48(32.87)	36(37.89)	12(23.52)	

TBI – Traumatic Brain Injury; PTSWD–Posttraumatic Sleep & Wake Disorders; DAI – Diffuse Axonal Injury; ICH–Intracranial Hemorrhage; IVH– Intraventricular Hemorrhage; SDH– Subdural Hemorrhage; EDH– Epidural Hemorrhage; SAH– Subarachnoid Hemorrhage; NS – Not Significant

problems (43.13%), than those without sleep problems after TBI (25.26%). The multiple lesions and right side damage of brain were more frequent in PTSWDs group, compared to non-PTSWDs ones (P<0.004).

Figure 3 shows the ANOVA results. Based on the obtained data, the mean score of PSQI in insomnia group was significantly higher than that in non-PTSWDs (P<0.001), EDS and hypersomnia groups (P<0.01). Pa-

tients with EDS obtained a higher mean ESS score than other groups. The highest mean ISI score was observed in the insomnia group, which was statistically significant (P<0.001). The mean MMSE and executive function scores in TBI patients with insomnia and those without PTSWDs were higher than those in EDS and hypersomnia (P<0.01). There was no significant difference in mean MMSE and executive function scores between the EDS

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Table 3. The final step results of multiple logistic regression to determine the predictors of PTSWD types

PTSWDs Types	Predictors	OR (CI95%)	P
Insomnia	Frontal lobe damage	2.04(1.07-4.15)	0.047
	Acute severe headache	4.59(1.27-6.53)	0.019
	Cortical lesion	5.96(2.02-9.05)	0.002
	Mild TBI	8.38(3.19- 13.4)	0.004
EDS	Right side damage	8.41(1.48-10.58)	0.012
	Brain stem lesion	9.78(2.03-12.75)	0.002
	DAI	9.91(2.18-13.59)	0.004
	Severe TBI	12.73(2.64-15.6)	0.004
Hypersomnia	Contusion	3.27(1.04-5.33)	0.001
	Acute depression	8.62(1.25-10.5)	0.004
	Bilateral damage	9.85(2.7-13.03)	0.004

TBI – Traumatic Brain Injury; PTSWD–Posttraumatic Sleep & Wake Disorders; DAI – Diffuse Axonal Injury; EDS– Excessive Daytime Sleepiness; OR–Odds Ratio; CI– Confidence Interval

and hypersomnia groups. Although mean MMSE score was not different between the 2 groups of insomnia and non-PTSWDs, the mean score of executive function was significantly higher in non-PTSWDs, compared to insomnia patients (P<0.001). Similarly, the mean depression subscale score was significantly higher in insomnia and hypersomnia groups compared to other groups (P<0.01). There was no significant difference in the mean depression subscale score between individuals with EDS and non-PTSW. However, insomnia patients

obtained higher anxiety subscale scores than the other groups (P<0.001).

To determine the predictors of common chronic PTSWDs types of our study, all significant clinical and imaging variables were included in multiple logistic regression model. In the final modeling processing step (Table 3), mild TBI (OR=8.38; 95% confidence interval=3.19-13.14), cortical damage (OR=5.96; 95% CI=2.02-9.05), acute severe headache (OR=4.59; 95% CI=1.27-6.53), and frontal lobe damage (OR=2.04; 95%
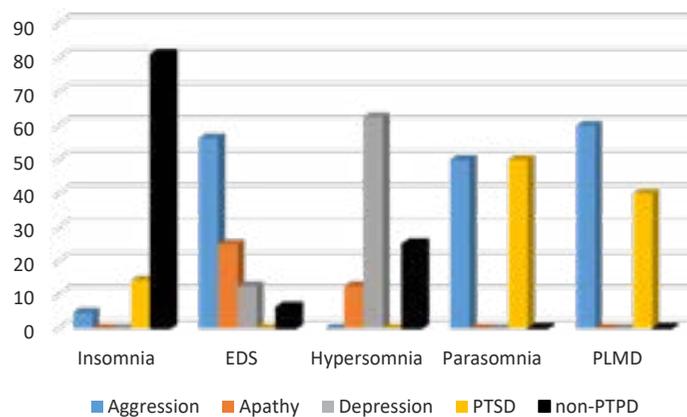

Figure 2. The frequency percentage of comorbid PTPD types in the individual categories of PTSWDs during chronic phase

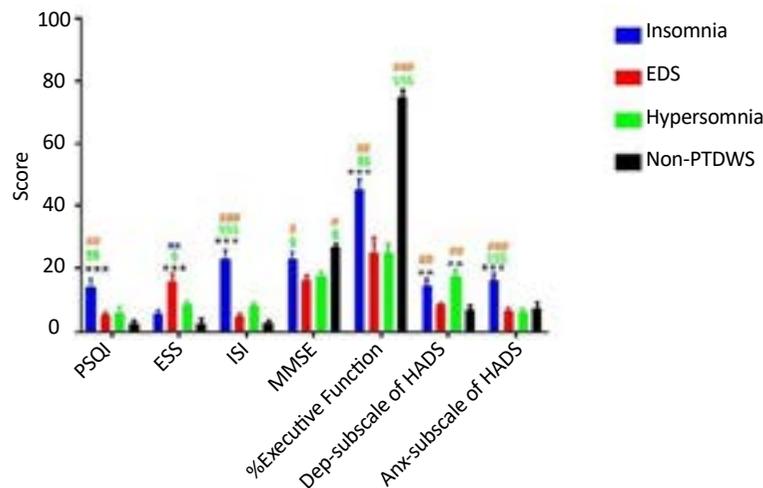EDS: Excessive Daytime Sleepiness; PLMD: Periodic Limb Movement Disorders

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Figure 3. The comparison of sleep indexes, HADS sub-scales, cognitive and executive functions scores between more common PTSWDs observed at 6 month after injury and non-PTSWDs. Data are expressed as mean ± SD. * P< 0.05, ** P< 0.01, *** P< 0.001 compared to the non-PTSWDs; ## P< 0.001, ### P< 0.001 compared to EDS; $ P< 0.05, $$ P< 0.01, $$$ P< 0.001 compared to hypersomnia; ×× P< 0.01 compared to insomnia. PTSWDs Posttraumatic Sleep & Wake Disorders; EDS–Excessive Daytime Sleepiness; PSQI–Pittsburgh Sleep Quality Index; ESS– Epworth Sleepiness Scale; ISI– Insomnia Severity Index; MMSE– Mini-Mental State Examination; HADS– Hospital Anxiety and Depression Scale; Dep: Depression; Anx: Anxiety

CI=1.07-4.15) were considered as strong insomnia predictors. Interestingly, severe TBI was the first variable to remain in the final step of modeling to predict EDS (OR=12.73; 95% CI =2.64-15.6). After that, DAI (OR=9.91; 95% CI=2.18-13.59), brainstem lesion (OR=9.78; 95% CI=2.03-12.75), and right side damage (OR=8.41; 95% CI=1.48-10.58) predicted EDS. In addition, bilateral lesion was identified as the first hypersomnia predicting factor (OR=9.85; 95% CI=2.07-13.03). Acute depression and contusion were the second (OR=8.62; 95% CI=1.25-10.5) and third predictors (OR=3.27; 95% CI=1.04-5.33) of hypersomnia.

4. Discussion

The overall prevalence of new-onset sleep disturbances in the current study was estimated about 35%, consistent with some previous reports and inconsistent with some others [7, 10-12]. Apparently, insomnia is the most common post-TBI sleep problem, and is strongly associated with mild brain lesions, cortical lesions of frontal lobe, and severe headaches. According to the obtained results, most patients who suffered from PTSWDs had mild brain damages, and experienced frontal lobe cortical hematomas within 6 months after the lesion occurrence. Therefore, a possible reason for the higher incidence of insomnia in our study may be the high prevalence of mild TBI and cortical lesions of frontal lobe in all subjects with PTSWDs. Although high prevalence of TBI-induced insomnia found in our study

was consistent with the results of Hou and colleagues [10], it did not confirm Baumann et al. study reports [7].

We also realized that a high frequency of sleep disruptions after insomnia belonged to EDS. Severe TBI strongly predicts the risk of developing EDS, and the frequency of severe injuries in people with PTSWDs is less than mild TBI. Thus, perhaps this is the reason why EDS was the second most commonly occurring type of PTSWDs in this study. The heterogeneity of TBI population is considered as one of the possible explanation for the discrepancy between the current and previous studies in terms of the prevalence of post-TBI sleep problems and its different types. We used self-reported questionnaires and subjective evaluations instead of objective tests such as polysomnography and multiple sleep latency tests to detect PTSWDs. Such methods might have led to underestimating the occurrence of PTSWDs, especially in people with DAI and severe brain damages who possibly experience an impaired self-awareness [31, 32].

Patients with insomnia obtained higher scores in PSQI and ISI than others, and ESS scores in patients with EDS were more than others. These findings may be due to the high sensitivity of PSQI and ISI for screening insomnia as well as ESS for diagnosing EDS.

Our study revealed that PTSWD patients suffered from acute headache, acute anxiety and depression (sepa-

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rately or together), early poor executive and cognitive functions, as well as chronic fatigue and PTPDs, more than non-PTSWDs ones. These sequels after TBI appear to be a sequence of destructive neurobiological processes resulted from secondary insults, including inflammation, excitotoxicity, abnormal perfusion, ischemia, and apoptotic or necrotic cell death. Additionally, its occurrence is inevitable at all degrees of TBI, although it is found in more severe lesions with worse clinical manifestations [11, 36].

These secondary neural injuries are associated with biomechanical, structural and functional changes in the damaged brain regions and corresponding homologous regions structurally or functionally connected with them [37, 38]. Subsequently, they cause the inefficiency of neural networks and imbalance of neurotransmitter systems regulating affective and cognitive behaviors [39, 40], that seem to contribute in the occurrence of sleep disorders [41, 42]. The patients with chronic sleep problems in comparison with non-PTSWDs ones had DAI and contusion especially in cortical, subcortical and brainstem regions. Therefore, it is believed that the early disruption of neural circuits caused by brain's white and gray matter lesions negatively impacts cognitive and emotional processing [40, 43, 44], and leads to psychiatric [6] and sleep-wake cycle disturbances in the long term.

We also found that chronic comorbid PTPDs are more prevalent in EDS than the other categories of TBI-induced sleep disorders. However, all patients with PLMD and parasomnia and the majority of hypersomnia ones suffered from chronic PTPDs. A possibility to explain this result may be that the total number of patients with EDS is higher than the other types of sleep disorders except for insomnia. Aggression and depression were more prevalent than other PTPD types in patients with EDS and hypersomnia, respectively. Our prior study has highlighted that the most common chronic PTPDs, including aggression, depression, and PTSD, are associated with DAI, severe brain damages, and TBI, respectively [6]. Similarly, the current study revealed that factors affecting the appearance of EDS accompanied with PTPDs, included severe TBI, DAI and brain stem lesions.

The paucity of comorbid chronic PTPDs in insomnia patients may be attributed to the differences in the TBI severity and neuropathology of insomnia, which include mild TBI and cortical lesions. Furthermore, post-TBI new-onset executive dysfunction may trigger aggression, impulsivity and antisocial behavior [45, 46] and could be associated with PTPDs occurrence [6]. Here, a weaker

executive dysfunction was also beholden in those having EDS and hypersomnia. Therefore, it is possible that post-TBI early executive dysfunction predisposes the comorbidity of PTPDs and chronic EDS or hypersomnia.

Specifically, it appears that the simultaneous occurrence of PTPDs and EDS or hypersomnia following TBI and during its chronic phase is probably due to the overlap between the centers controlling cognitive and sleep behaviors and their associated neuropathology. This means that severe brain stem lesions and DAI, especially in axon projections targeting the limbic system and diencephalon, may disrupt the inhibitory projections of monoaminergic nuclei of Arousal-Reticular Ascending System (ARAS), such as raphe nucleus, locus coeruleus on the Ventrolateral Preoptic nucleus (VLPO) of the hypothalamus and create hypersomnolence [16, 47].

Cognitive behaviors are regulated by mesencephalic subdivision of the limbic network, including dorsal raphe nucleus and locus coeruleus projecting the axonal fibers to cortical and subcortical centers of the limbic circuit. Thus, it is conceivable that the lesion of these neural structures and the axonal sharing in relevant white matter tracts lead to PTPDs occurrence [16, 48, 49]. In EDS, aggression is prevalent. Based on evidence, the dorsal raphe nucleus located in the brain stem has serotonergic transmission in the projections areas of prefrontal cortex, a main aggression control site [50], that plays an important role in the management of aggressive behaviors, and a lesion occurring in this nucleus causes antisocial behaviors [51]. Therefore, in patients with EDS, who mainly have brain stem lesions, damages of dorsal raphe nucleus or its serotonergic projections may take part in the occurrence of aggressive behaviors. Furthermore, acute depression was considered as a clinical marker predicting hypersomnia and turned to be chronic in more than half of the patients with hypersomnia.

Depression is associated with a decreased level of norepinephrine and central serotonin that their main sources are locus coeruleus nuclei and dorsal raphe in brainstem, respectively [52, 53]. The frontothalamic and frontostriatal circuits complicated in the modulation of executive functions of frontal lobe, emotional processing, and sleep-wake cycles, are highly vulnerable to TBI [39, 54]. The noradrenergic projections of locus coeruleus in brain stem towards neocortex and the limbic system modulate motivational, cognitive and goal-directed responses [55, 56].

Accordingly, it is believed that following long-lasting secondary neuronal insults caused by DAI and brain stem lesions, an abnormality occurs in the function of common neural networks regulating cognition, emotion, mood and wakefulness. The possibility of aggressive and depressive and hypersomnolence states increases by early cognitive and executive dysfunctions.

Another important result of our study was that the patients with insomnia showed weaker early executive functioning than non-PTSWD group. However, it was significantly better than the executive functioning of the patients with EDS and hypersomnia. This may be due to the higher frequency of mild lesions in insomnia patients, compared to EDS ones. The frontal lobe, especially DLPFC, is involved in the mental processes of executive function [57]. Therefore, executive dysfunction (mostly frontal lobe lesions) is possible in the insomnia group. Many of the white matter microstructural lesions associated with executive dysfunction following mild trauma are not visible on CT scans and conventional MR imaging used in our study [58, 59].

People with insomnia experienced a mild lesion. Thus, they were probably aware of their sustained disabilities and personal, professional and social failures. As a result, they were mainly prone to depression, anxiety, and nocturnal sleep problems. We also found that a high proportion of people with chronic fatigue experienced insomnia. It is evident that adenosine accumulation in the basal forebrain region occurs after prolonged periods of sleeplessness or sleep deprivation [60, 61]. Furthermore, reports indicate that increased plasma adenosine is associated with chronic fatigue syndrome [62]. Therefore, the activation of central adenosine receptors or elevation of its ligand in the basal forebrain of insomnia patients may be a possible mechanism for the occurrence of chronic fatigue in these patients.

Studies on the intrinsic architecture of brain white matter and individual sleep patterns have reported that poorer sleep duration and quality are associated with subtle white matter microstructural changes [60]. Therefore, it is hypothesized that individuals with a family history of sleep disorders are more likely to have an inherited susceptibility of the white matter architecture and susceptible to develop PTSWDs.

5. Conclusion

In this prospective study, we identified the risk factors that predispose the development of chronic PTSWDs. Based on the current results, mild TBI, the presence of cortical lesions, especially in the frontal lobe, and severe acute phase headaches can predict chronic insomnia, the most prevalent type of PTSWDs in the study, which was accompanied by fatigue more than others. Interestingly, the occurrence of EDS, which was mainly associated with chronic PTPDs, and especially aggression, was directly related to the lesion itself. Right lesions, especially DAI and brainstem lesions, were the most prominent markers of imaging. Additionally, severe brain injury was the most important clinical prognostic marker of chronic EDS.

Patients with acute depression and bilateral contusion were more susceptible to hypersomnia, which was associated with chronic depression. The prominent role of early executive dysfunction was evident in the development of common types of chronic PTSWDs. Investigating the efficacy of early neuro-cognitive rehabilitation in TBI patients to reduce the odds of chronic PTSWDs occurrence is recommended for the future studies. Furthermore, the early detection of neural circuits and network dysfunctions provoking various types of PTSWDs using advanced modalities of MRI such as functional MRI is a critical priority for early diagnosis and proper therapeutic interventions in these patients. Importantly, understanding of the neuropathogenesis of all types of PTSWDs may help in applying the noninvasive brain stimulation techniques modulating the pathological neural circuits involved in sleep-wake cycle disorders.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article. The participants were informed about the purpose of the research and its implementation stages; They were also assured about the confidentiality of their information; Moreover, They were allowed to leave the study whenever they wish, and if desired, the results of the research would be available to them.

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Authors' contributions

Conceptualization, investigation, writing of original draft: Sara Ramezani; Critical review: Shahrokh Youse-

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Conflict of interest

The authors declared no conflict of interest.

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