Long-lasting sleep patterns of adult patients with minor traumatic brain injury (mTBI) and non-mTBI subjects

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Abstract

Background: Sleep disturbance is a common subjective complaint of minor traumatic brain-injured (mTBI) patients, but little is known about the characteristics of sleep disturbance in adults years after the injury.

Methods: Polysomnographic (PSG) and multiple sleep latency test (MSLT) records of 26 mTBI adult patients with normal brain computerized tomography and negative encephalographic studies, no past history of CNS pathology, no premorbid or present major psychiatric diagnosis, and no sleep apnea syndrome were compared to a matched group of apparently healthy individuals (controls).

Results: Sleep patterns were disturbed in the mTBI patients. Their sleep architecture was altered, with significantly higher light-sleep non-rapid eye movement (NREM) stage 2 scores compared to controls (54.5 ± 13.4% vs. 46.6 ± 10.4%, respectively, \(p = 0.03\)) and significantly lower REM sleep scores (21.2 ± 8.4% vs. 25.4 ± 4.5%, respectively, \(p = 0.05\)). The MSLT findings documented significant excessive daytime episodes of falling asleep.

Conclusions: Sleep disturbances of adult patients with chronic mTBI may manifest characteristic alterations in both timing and architecture of their sleep patterns. Sleep lab evaluations may help identify subgroups of mTBI patients who would probably benefit from treatment.

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Keywords: Adults; Minor traumatic brain injury (mTBI); Multiple sleep latency test (MSLT); Polysomnography (PSG)

1. Introduction

Traumatic brain injuries (TBIs) cause more deaths and disabilities than any other neurological disorder before the age of 50 years [1,2]. The majority of victims are young, causing the cumulative number of patients to continuously rise. The victims of TBI often suffer long-lasting mental as well as physical impairments [3,4]. Minor TBI (mTBI) is a brain concussion that can cause a short (up to 30 min) transient loss or impairment of consciousness, accompanied by vomiting and some
degree of amnesia (either anterograde or retrograde or both). Diagnosis can be difficult because patients with mTBI do not necessarily suffer evident structural brain damage, and emergency room Glasgow Coma Scale (GCS) scores are 13 or higher [5]. Therefore, the condition is frequently defined by the presence of several non-specific mental symptoms following brain concussion [6]. It has been suggested that even a mild brain trauma may cause neuronal damage, both in humans [7] and in animal models [8], in addition to other common long-lasting symptoms that include headaches, dizziness, sleep difficulties [9], cognitive disturbances (executive dysfunction, variable amnesia), affective symptoms (mostly depression, apathy and anxiety) and behavioral disturbances [10,11]. Although most mTBI cases resolve within 6–12 months, as many as 20–30% of the patients present with a protracted or even permanent array of complaints [12], the most prominent of which are headache and sleep disturbances. The benefit of most pharmacological or psychiatric therapies for TBI sequelae is uncertain, and even less so for mTBI [13].

Sleep difficulty is a common complaint of both TBI [12,14,15] and mTBI patients [16]. Sleep interruption and impaired sleep quality were included in a subjective questionnaire survey of 75 patients following TBI, but there was no mention of the percentage of patients experiencing sleep–wake complaints [14]. In another study, Hibbard et al. [15] found sleep disturbances and other chronic health problems to be significantly more common in individuals with TBI living in the community (10 years post-onset on average) than in individuals without disabilities who were matched for age, sex and urban/suburban/rural living environments [15]. In a recently published study, Ouellet and Morin [17] compared subjective (questionnaires) and objective (2 nights of polysomnography [PSG]) sleep complaints and patterns of 14 patients with mild to severe TBI and sleep disturbances, and a matched group of healthy good sleepers. TBI patients were found to have a tendency to overestimate their (subjective) sleep disturbances; however, the PSGs of 10 out of the 14 patients with TBI could be defined as having objective insomnias and the researchers conclude that the findings are similar to those found in patients with either primary insomnia or depression [17].

While most published studies have focused on the TBI spectrum of severity population as a whole (Ouellet and Morin [17] have studied a mixed group of adult patients, with only 4 mild and 1 mild to moderate TBI out of 14 patients; Prigatano et al. [18] studied a group of 10 patients, only 3 of them with mild TBI), mTBI studies have focused mainly on recent-onset cases [19] or on infants, young children or adolescents [20,21]. A high incidence of sleep disturbance was reported both in hospitalized patients with recent-onset (median of 3.5 months) TBI (72.7%) and in discharged patients with a median of 29.5 months post-TBI (51.9%) [22]. In addition, sleep disturbances have been shown to contribute to poor daytime performance and a poor individual sense of well-being in this population [23]. Long-term sleep disturbances have been documented in adolescents three years after having sustained an mTBI without any discernible clinical sequelae, and these complaints have been confirmed by both PSG and actigraphic monitoring [21].

There are only few data on the long-lasting sleep disturbances and other health issues in adults who underwent mTBI. One of those studies attempted to separate the effects on sleep complaints of the mTBI per se from those of chronic pain following other concomitant injuries. When comparing the incidence of sleep complaints of patients with mTBI to those of patients with orthopedic injuries who were matched for age, sex, distribution and time from injury, the former reported more difficulty in initiating and maintaining sleep at night and greater difficulty with sleepiness during the day than the latter [24]. A number of case reports suggest an association between circadian rhythms disorders or a narcolepsy-like disorder and mTBI [25–30], but our literature search failed to uncover any study addressing these phenomena.

In order to characterize the long-term sleep patterns of adult patients with chronic mTBI and sleep complaints, we compared their PSG and multiple sleep latency test (MSLT) findings with sleep lab findings of an age- and sex-matched convenience group of apparently healthy subjects who served as the control group.

### 2. Methods and materials

This study was approved by the Institutional Review Board at the Tel Aviv Sourasky Medical Center (No. 6/06-014).

#### 2.1. Setting

The Neuropsychological Unit for Treatment & Rehabilitation is accredited for clinical neuropsychological rehabilitation by the Israeli Ministry of Health.

#### 2.2. Study group

Patients who present with the complaint of poor sleep are routinely referred for a sleep lab evaluation, the extent of which often varies depending upon each patient’s medical insurance (HMO) coverage. Data were collected from the Unit’s files for all patients admitted consecutively to ambulatory rehabilitation programs between 1996 and 2001, for whom there were any data from the sleep lab. The inclusion criteria were age between 21 and 50 years, documented and non-recent (one year or more) mTBI, no structural imaging findings...
on brain computerized tomography (CT) scan or magnetic resonance imaging (MRI), and negative electroencephalographic (EEG) studies. The exclusion criteria were a past history of any central nervous system (CNS) pathology, past or present axis I major psychiatric diagnosis, and a suspected or established diagnosis of sleep apnea syndrome and/or periodic limb movements (restless legs syndrome).

2.3. Control group

The control data were taken from the sleep-lab’s files on age- and sex-matched job-seeking individuals (non-patients) who had been referred for a sleep evaluation as part of a routine pre-employment assessment procedure required by many hi-tech companies in Israel. The control group data was recorded during the same period of time as the study group, using the same methods and protocol.

2.4. PSG recording and scoring

PSG was performed as previously described [31]. In short, PSG recordings included the following: EEG (C3-A2; C4-A1), electro-oculogram (EOG), electromyogram (submental and tibialis EMGs), electrocardiogram (ECG), measurements of airflow (thermistors placed on the nasal and oral cavities), respiratory movements, body movements, and arterial oxygen saturation (SaO2; BIOX 3740, Ohmeda, Louisville, CO). The PSG recordings were made on an EEG-4214 (NihonKohden, Kogyo Co. Ltd., Tokyo, Japan). All records were scored in 30-second epochs using standard criteria [32]. Sleep-onset latency was measured from “lights out” to the first of three consecutive minutes of stage 2 sleep. Rapid eye movement (REM) latency was measured as time from sleep onset to the first period of REM sleep. Sleep period time (SPT) was measured from “lights out” (in the morning). Total sleep time (TST) was measured by subtracting awake time, movement time, and stage 1 from the SPT. Wake time was calculated by summing all recordings (30 s each) scored as “awake” (at least 15 s of alpha waves in the particular 30-s epoch). The number of awakenings during the night was divided into those lasting 15–60 s, 1–3 min, and over 3 min. Movement time included episodes of up to one minute of increased muscle tone and body movement without arousal.

2.5. Multiple sleep latency test (MSLT) recording and scoring

MSLT was performed according to the standard protocol on the day between the two nocturnal recordings and was given at two-hour intervals starting at least 1.5 h after awakening [33]. For each latency test, the patients lay down on a bed in a quiet and dark room and were instructed to try to go to sleep. They remained in bed for 20 min after three consecutive epochs of stage 1 sleep or one epoch of another sleep stage, or after 20 continuous min of being awake. Sleep latency was scored as the amount of time (in minutes) of the first epoch of sleep, and the mean latency of the four tests was the primary dependent measure.

2.6. Data collection

PSG was performed throughout two entire nights (not during weekends), and only data from the second night were used. Data from the MSLT performed on the day between the two PSG nights were collected and evaluated for all patients who underwent this evaluation.

2.7. Data analyses

Statistical analyses were done using the SPSS-13 software package, and the retrieved data on the mTBI and control groups were compared. The χ² or Fisher’s exact test analyzed the differences in proportions of categorical variables between the groups. Continuous variables of differences between the groups were analyzed using analysis of variance (ANOVA). Multivariate analyses (GLM) for comparing groups and snoring were done including all the variables that were significantly (p < 0.05) different between groups.

3. Results

Twenty-six patients who fulfilled study entry criteria underwent both a complete two-night PSG study and MSLT evaluation, all performed in the same sleep laboratory and with the same protocol.

The mTBI group and controls were similar in mean age (31.6 ± 8.8 and 33.8 ± 7.8 years) and other demographic parameters but not in education (the control group had significantly higher mean years of education) (data not shown).

3.1. PSG and MSLT

There were no significant differences in sleep latency and REM latency values between the groups: both falling asleep and the appearance of the first REM epoch were not disturbed in the study group compared with the control group, and both were within normal limits.

The proportion of stage 2 NREM sleep was significantly higher (p < 0.05) and the proportion of REM was significantly lower (p < 0.05) in the mTBI group compared with controls, with no difference in the proportion of stage 3–4 NREM sleep between the groups (Fig. 1). In other words, the mTBI patients spent a longer proportion of their sleep in the “superficial” or
“light” sleep phase than the controls and had a much shorter proportion of REM sleep than the controls, but there was no difference in the “deep” sleep phase between them.

Total sleep time was significantly lower in the mTBI group compared with controls (354.69 ± 60.83 min for patients, 441.0 ± 25.93 min for controls, \( p < 0.05 \)), although there was only a trend toward lower net sleep time (excluding times of wakening) (339.26 + 78.7 min patients, 371.1 + 38.94 min controls). The number of wakening times was significantly higher in the controls than in the mTBI patients (specifically, the 1–3 and >3-min time awakenings) (the 1–3 min wakenings were 6.7 ± 3.4 for controls and 2.4 ± 2.2 for patients, \( p < 0.05 \); the >3-min awakenings were 4.0 ± 3.3 for controls and 2.0 ± 2.5 for patients, \( p < 0.05 \)). This means that the mTBI patients used their sleep time less effectively than the control group.

The mTBI patients had a significantly higher number of falling asleep episodes during the MSLT compared to the controls (3.4 vs. 1.9, \( p < 0.05 \)) and a significantly shorter time to fall asleep than the controls (6.4 vs. 17.3, \( p < 0.0005 \)) (Fig. 2). Moreover, in four of the patients sleep-onset REM periods (SOREMPs) were evident (in one patient – during 4 out of 5 episodes of falling asleep, in another patient 2 out of 5 such episodes, in a third patient 1 out of five episodes and in the fourth patient – 1 out of 4 episodes of falling asleep). With respect to snoring (Table 1), half of the mTBI patients (\( n = 13 \)) compared to only two (10%) of the controls did not snore at all, and the proportion of those with the most severe snoring was also lower in the mTBI group (4 [15.4%] compared with 9 [45%] controls).

### 3.2. Multivariate analyses

In the multivariate analyses model that included all the variables that were different between the groups in univariate analyses (\( p < 0.05 \)), those that significantly differed between the mTBI patients and the controls

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<tr>
<th>mTBI</th>
<th>Controls</th>
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<tr>
<td>26 (100)</td>
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<td>13 (50)</td>
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<td>9 (34.6)</td>
<td>6 (30)</td>
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<td>4 (15.4)</td>
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mTBI, minor traumatic brain injury.

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<th>mTBI mean ± SD</th>
<th>Controls mean ± SD</th>
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<td>Stage 2%</td>
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NREM, non-rapid eye movement; REM, rapid eye movement; mTBI, minor traumatic brain injury; ANOVA, analysis of variance; SD, standard deviation.

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were the number of wakenings of a 1–3 min duration, total time in bed, and time to fall asleep during the MSLT. Interactions between snoring and groups were demonstrated in stage 2 NREM sleep (%) \( (F = 3.6, p = 0.006) \) and REM sleep (%) \( (F = 2.8, p = 0.03) \). Specifically, in the highest snoring grade (III), the mean stage 2 NREM sleep (%) proportion was lowest among mTBI patients and highest in the controls, and the mean REM% was highest in the mTBI patients and lowest in the controls (Table 2).

4. Discussion

The general objective of this study was to explore objective sleep lab findings of adult patients with chronic mTBI and sleep-related subjective complaints (“not sleeping well”, “getting out of bed in the morning tired”, “sleepy during the day”), in comparison with a convenience sample of non-patients. Using PSG and MSLT, we found that from 12 months to 21 years after having sustained an mTBI, patients who continue to complain of significant sleep disturbances have objective sleep lab findings. The two-night PSG recordings revealed a significantly higher proportion of stage 2 sleep and a significantly lower proportion of REM in the mTBI group compared with controls, and a significantly lower total sleep time in the mTBI group compared with controls (in spite of significantly lower wakening times in the mTBI group). Moreover, the mTBI patients presented a prominent daytime tendency to fall asleep (the number of episodes of falling asleep during the MSLT was significantly higher and the time to fall asleep was significantly shorter) than the controls. Interestingly, although none of the patients or controls were diagnosed with sleep apnea syndrome (such a diagnosis would have excluded them from the study), 50% of the mTBI and 90% of the controls snored, and the proportion of those with the most severe snoring was lower in mTBI (15.4%) compared with the controls (45%).

The significant increase in the stage 2 (light sleep) phase accompanied by a decrease in REM sleep suggests a cycling back to stage 1 or 2 after disruption of sleep. This pattern of sleep disturbances may account for some of the cognitive alterations generally found in chronic mTBI patients (not evaluated in our sample), particularly memory difficulties [34]. Numerous studies demonstrated that the processes of learning and memory consolidation and integration are in part sleep-dependent (for review, see [35–37]).

Other interesting data emerging from the current study is that our chronic mTBI adult patients manifested a significant daytime tiredness with a tendency to fall asleep, as found by the MSLT evaluation, and three of them even had “a narcolepsy-like pattern” (with SOREMPs during some episodes), a rather rare disturbance in the general population. However, excessive daytime sleepiness has already been described in adult patients 10–20 months after head trauma, but without grouping patients by different types of head and neck traumas [38].

The generators of the patterns of distribution of REM and NREM within sleep are not known. Multiple sleep-promoting factors have been proposed, and some have been identified (e.g., melatonin). Their roles in the determination of sleep state are poorly understood. The finding of specific sleep disturbances in patients with a history of mTBI suggests that the functioning of some of the key structures involved in normal sleep, particularly the brainstem, basal forebrain, and hypothalamus, might be affected to some degree in mTBI [39].

Our group of patients is not necessarily representative of all chronic mTBI patients; however, our findings may indicate that insomnia and some degree of excessive daytime tiredness/sleepiness may be common following mTBI and may persist for extensive periods of time after trauma occurrence. Since sleep-wake disorders are prevalent in the general population mainly after the age of 45–50 years, with a pattern of a high prevalence of the “superficial-sleep” NREM stages 1 + 2 even being characteristic of old age, we chose a young adult population to show a more direct association between mTBI and these persisting symptoms. However, our findings suggest that a possible “premature-like aging” of the brainstem structures may exist not only in severe TBI patients (as suggested by George et al. [40]) but also in mTBI patients as well.

Another intriguing issue, and one for which we have no explanation, is the sleep patterns found in the non-symptomatic (“non-patients”) control group. PSG results of our control group were not entirely within the normal values as stated in the literature [41]. Since none of them complained of any sleep disturbance (neither spontaneously nor when questioned explicitly), we accepted their sleep data as suitable for comprising the controls in this study. However, it is possible that being evaluated in the sleep lab as part of the requirements for employment in a rather desired and very well paid workplace (the high-tech industry), candidates tended to minimize or deny any medical/physical condition that might have prevented their admittance, thus not reporting any existing sleep difficulties.

There are two states of sleep, NREM and REM, each of which has its own distinct neuroanatomic, neurophysiologic, and neuropharmacologic mechanisms and behavioral features. No single anatomic site is responsible for all the manifestations of a given state. The percentage of sleep in the REM state decreases rapidly, from about 50% of total sleep time at birth to about 20% by age 3–5 years, with this percentage persisting for the remainder of the life span. During adult life, there is a very slow and gradual reduction of slow-wave sleep (stages 3 + 4, the deepest stages of NREM sleep).
from about 40% in late adolescence to very low percentages in senescence combined with a parallel increase of ‘light sleep’ (stages 1 + 2), from about 40% at young adulthood to 70% in senescence [41–43]. It is possible that “normal values” of sleep as defined in the literature represent “ideal values” of sleep architecture and timing that are not very common in our present, hectic, Western culture society, marked by frenetic over-working, insufficient sleep, shift work, overweight-induced snoring, and environmental pollution [44]. That said, the finding of chronic sleep architectural changes resembling age-related sleep changes in mTBI might suggest that the neurodegenerative damage in this type of injury is much more profound than what is discernible structurally [45,46]. The possibility that TBI exacerbates neurodegenerative processes is also supported by both our mouse model of mTBI [47] and by the epidemiological finding of increased risk for Alzheimer’s type dementia years after TBI, a clinical finding supported by basic studies in transgenic mice as well [48].

This study has several methodological limitations, which must be taken into consideration. First, the patients were evaluated in the sleep lab between 12 months and 21 years post mTBI. It is somewhat difficult to affirm after an interval of 21 years that all or most of the presentation is related to the initial trauma (even when sleep complaints are documented repeatedly in the patient’s file throughout the years). A more uniform group of mTBI patients would have been better. Second, the study of mTBI patients’ sleep was performed on two successive nights, and the data of the second night was used. However, the control group slept only one night in the laboratory. Some bias may derive from the comparison of these two groups of data.

It is difficult to draw clinical implications from these results; however, there should be a high index of suspicion for objective sleep disturbances in mTBI patients in the presence of sleep disturbance complaints. Several questions remain unsolved. Are the changes treatable? If so, how and when should they be treated: pharmacologically (maybe with melatonin)? Behaviorally? With light therapy? Are they all preventable? Do the findings of the current study correlate with findings in various neuropsychological evaluations? Or with functional brain imaging findings? The answers to these questions await further study.

Acknowledgement

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References


