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Sleep–wake disturbances 6 months after traumatic brain injury: a prospective study

Christian R. Baumann,[1] Esther Werth,[1] Reto Stocker,[2] Silke Ludwig[2] and Claudio L. Bassetti[1]

Departments of [1]Neurology and [2]Traumatic Surgery, University Hospital, Zurich, Switzerland

Correspondence to: Dr Claudio Bassetti, Department of Neurology, University Hospital of Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland
E-mail: claudio.bassetti@usz.ch

Sleep–wake disturbances (SWD) are common after traumatic brain injury (TBI). In acute TBI, we recently found decreased CSF levels of hypocretin-1, a wake-promoting neurotransmitter. In the present study, we aimed to delineate the frequency and clinical characteristics of post-traumatic SWD, to assess CSF hypocretin-1 levels 6 months after TBI, and to identify risk factors for posttraumatic SWD. A total of 96 consecutive patients were enrolled within the first 4 days after TBI. Six months later, out of 76 TBI patients, who did not die and who did not move to foreign countries, we included 65 patients (86%, 53 males, mean age 39 years) in our study. Patients were examined using interviews, questionnaires, clinical examinations, computed tomography of the brain, laboratory tests (including CSF hypocretin-1 levels, and HLA typing), conventional polysomnography, maintenance of wakefulness and multiple sleep latency tests (MSLT) and actigraphy. Potential causes of post-traumatic SWD were assessed according to international criteria. New-onset sleep–wake disturbances following TBI were found in 47 patients (72%): subjective excessive daytime sleepiness (EDS; defined by the Epworth Sleepiness Scale $\geq$10) was found in 18 (28%), objective EDS (as defined by mean sleep latency $<$5 min on MSLT) in 16 (25%), fatigue (daytime tiredness without signs of subjective or objective EDS) in 11 (17%), post-traumatic hypersomnia 'sensu strictu' (increased sleep need of $\geq$2 h per 24 h compared to pre-TBI) in 14 (22%) patients and insomnia in 3 patients (5%). In 28 patients (43% of the study population), we could not identify a specific cause of the post-traumatic SWD other than TBI. Low CSF hypocretin-1 levels were found in 4 of 21 patients 6 months after TBI, as compared to 25 of 27 patients in the first days after TBI. Hypocretin levels 6 months after TBI were significantly lower in patients with post-traumatic EDS. There were no associations between post-traumatic SWD and severity or localization of TBI, general clinical outcome, gender, pathological neurological findings and HLA typing. However, post-traumatic SWD correlated with impaired quality of life. These results suggest that sleep–wake disturbances, particularly EDS, fatigue and hypersomnia are common after TBI, and significantly impair quality of life. In almost one out of two patients, post-traumatic SWD appear to be directly related to the TBI. An involvement of the hypocretin system in the pathophysiology of post-traumatic SWD appears possible. Other risk factors predisposing towards the development of post-traumatic SWD were not identified.

Keywords: sleep; sleep–wake disorder; traumatic brain injury; excessive daytime sleepiness; hypersomnia

Abbreviations: EDS = excessive daytime sleepiness; SWD = sleep–wake disturbances; TBI = traumatic brain injury

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Introduction

Post-traumatic sleep–wake disturbances (SWD) such as insomnia, hypersomnia 'sensu strictu' (defined as increased sleep need per 24 h), and excessive daytime sleepiness (EDS) are common in clinical practice (Rao, 2002; Cohen *et al.*, 1992). However, only a few, mostly retrospective studies have examined SWD after traumatic brain injury (TBI).

Insomnia

In their prospective study based on sleep questionnaires, Fichtenberg and collaborators (2002) found a high prevalence (30%) of insomnia and poor sleep quality in 50 patients after TBI. In a retrospective study comprising a heterogeneous population of 184 somnolent subjects suffering from TBI or head–neck trauma (whiplash injury),

45% of the patients reported insomnia ('disturbed nocturnal sleep'), mostly due to nocturnal pain (Guilleminault *et al.*, 2000). A recent study examined sleep–wake diaries of 63 TBI patients and 63 healthy controls; the authors found an increased number of night-time awakenings and higher sleep onset latencies in TBI patients, particularly in those with mild injuries, anxiety and depression (Parcell *et al.*, 2006). Insomnia has been shown to persist 3 years after TBI (Kaufman *et al.*, 2001).

In a questionnaire study by Ouellet and colleagues (2006a), more than 50% of 452 TBI patients reported insomnia symptoms, and insomnia was a severe and chronic condition remaining untreated in almost 60% of cases. The authors explained this high prevalence by clinical characteristics associated with insomnia symptoms such as higher levels of fatigue, depression and pain. In the same direction, 14 TBI patients were compared to 14 healthy good sleepers by the same group, and all subjective measures of sleep as assessed by questionnaires revealed significant sleep disturbances in the TBI group (Ouellet *et al.*, 2006*b*). The authors found, however, that TBI patients with insomnia have a tendency to overestimate their sleep disturbance compared to polysomnographic measures of sleep. Together, these studies, which are based on subjective reports from patients, suggested that insomnia may be common but overestimated after TBI.

Fatigue, hypersomnia and EDS

Fatigue as assessed by validated scales appears to be common among patients with TBI (LaChapelle and Finlayson, 1998). Also using questionnaires, Stulemeijer and collaborators (2006) observed fatigue in one out of three patients 6 months after mild TBI. Furthermore, they found a clear negative impact of fatigue on quality of life. In a recent review, Belmont and collaborators (2006) summarized that post-traumatic fatigue is common, independent of TBI severity, and may be related to insufficiency in the hypothalamic-pituitary axis. Masel and colleagues (2001) found EDS (defined as abnormally low mean sleep latencies in multiple sleep latency tests, MSLT) in almost half (33 of 71) of their patients described as having different types of brain injury (traumatic, ischaemic, haemorrhagic, anoxic). In 21 patients (30%), 'post-traumatic hypersomnia' (defined as EDS in the absence of narcoleptic symptoms, pathological sleep apnea or periodic limb movement indices) was diagnosed. Latency between onset of TBI and sleep recordings, however, varied considerably between subjects. Furthermore, 49 patients were on medication at the time of the study; laboratory examinations aimed at ruling out other reasons for sleepiness were not performed. On the other hand, Castriotta and co-workers performed polysomnography and MSLT in 10 patients with TBI and EDS and found sleep–wake disorders such as sleep apnea and periodic limb movement syndrome in all tested patients (Castriotta *et al.*, 2001). In a retrospective study comprising 20 patients with post-traumatic EDS and based on sleep questionnaires and electrophysiological examinations (polysomnography, MSLT), eight subjects were found to suffer from sleep apnea syndrome (Guilleminault *et al.*, 1983).

In summary, fatigue, hypersomnia and EDS have been reported to be frequent after TBI. Retrospective assessments and methodological shortcomings of previous studies, however, make it impossible to draw clinical relevant conclusions.

Circadian sleep–wake disorders

The findings pertaining to circadian sleep–wake disorders are also rather inconclusive. Anecdotal reports on a post-traumatic delayed sleep phase syndrome have been published, but a recent study of 10 patients failed to provide evidence of any shift in circadian timing of sleep subsequent to TBI (Quinto *et al.*, 2000; Steele *et al.*, 2005).

The neurobiological bases for post-traumatic SWD are unknown. In a recent study, we found significantly decreased CSF hypocretin-1 levels in patients with acute TBI (Baumann *et al.*, 2005). Since this hypothalamic neuropeptide is involved in sleep–wake regulation (Nishino *et al.*, 2000), it is reasonable to assume that hypocretin neurotransmitter deficiency could contribute to the pathophysiology of post-traumatic SWD.

In summary, the frequency and characteristics of post-traumatic SWD have not been systematically examined in spite of their high prevalence and their medical, social, economic and medicolegal implications. The primary aim of this study was to assess frequency, clinical characteristics and causes of sleep–wake disorders after TBI. Secondly, we sought to identify risk factors as well as parameters prognostic for the development of post-traumatic SWD. Third, we tested whether hypocretin deficiency might be associated with post-traumatic SWD.

Material and Methods

The protocol for this prospective study was approved by the ethics committee of the University Hospital of Zurich.

Patients

The study comprised 96 consecutive patients (75 males, mean age ± SD 38 ± 16 years, range 16–72) with acute, first-ever TBI, admitted to our hospital between July 2003 and June 2006 immediately after the injury. Patients with sleep–wake and/or psychiatric disorders diagnosed prior to TBI were excluded. Informed consent for study participation was obtained from all patients before participation (in comatose patients after regaining of the consciousness). For the execution of a lumbar puncture, additional written informed consent was mandatory.

Definitions

Sleep–wake disorders and symptoms were identified by the means of interviews, questionnaires and sleep studies (Table 1).

Table 1 Definitions of sleep–wake disturbances and symptoms in this study

Sleep–wake disturbance/symptom		Definition
Subjective excessive daytime sleepiness	S-EDS	Epworth Sleepiness Scale (ESS) ≥10
Objective excessive daytime sleepiness	O-EDS	Mean sleep latency on multiple sleep latency test (MSLT) <5 min
Sleep attacks		Involuntary, short episodes of unwanted sleep
Post-traumatic hypersomnia	PH	Increased sleep need per 24 h (at least 2 h more than before TBI)
Fatigue		Tiredness reported at interview, ESS <10 and mean sleep latency on MSLT >10 min
Insomnia		Chronic inability to fall or remain asleep for an adequate length of time at night, associated with daytime tiredness
Behaviourally induced insufficiency sleep syndrome	BIISS	Difference in sleep time per 24 h between weekdays and weekends/holidays ≥2 h

Note: Specific sleep disorders such as narcolepsy, obstructive sleep apnea syndrome or restless legs syndrome, were diagnosed according to the international criteria (American Academy of Sleep Medicine, 2005).

Specific sleep–wake disorders were diagnosed according to the international criteria (American Academy of Sleep Medicine, 2005).

Severity of TBI

Severity of TBI was assessed (i) clinically using the Glasgow Coma Scale (13–15 = mild, 9–12 = moderate and 3–8 = severe) and (ii) by cerebral computed tomography (CT) using the Marshall criteria (I = no visible intracranial pathology, II–IV = midline shift and V = mass lesion) (Marshall *et al*., 1992).

Clinical outcome 6 months after TBI

Six months after TBI, patients were examined by the first author. The interview comprised questions about social status and residual symptoms since TBI. Thereafter, patients were given a comprehensive neurological examination. Neuropsychological functions were assessed using a standardized protocol that tapped verbal and visuospatial memory functions and fluency, speed of information processing and the affective state; the Folstein Mini-Mental State Examination was part of the protocol (Schmidgen *et al*., 1994). Outcome was classified according to the Glasgow Outcome Scale (GOS; 1 = dead, 2 = vegetative state, 3 = severe disability, 4 = moderate disability and 5 = good recovery). To detect depression, all patients were given the Beck Depression Inventory, a self-report rating inventory measuring characteristic symptoms and severity of depression (Beck *et al*., 1961).

We assessed quality of life using the SF-36, a questionnaire aimed at capturing the relative impact of disease on physical and social functioning, role activities due to physical/emotional functioning, bodily pain, vitality (energy and fatigue), mental health and general health perception (Findler *et al*., 2001).

SWD 6 months after TBI: interviews and questionnaires

During the interviews, we assessed changes in sleep habits, sleep quality, daytime vigilance (e.g. do you feel tired/sleepy during the day since TBI?) and insomnia symptoms. All patients filled out an extensive sleep questionnaire that comprised validated scales such as the Epworth Sleepiness Scale (ESS; ≥10 suggests EDS) (Johns, 1991), the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ ≥32 for females or ≥36 for males suggests sleep-related breathing disorders) (Douglass *et al*., 1994), the Ullanlinna Narcolepsy Scale (≥14 suggests narcolepsy) (Hublin *et al*., 1994) and the Swiss Narcolepsy Scale (<0 suggests narcolepsy) (Sturzenegger and Bassetti, 2004).

SWD 6 months after TBI: sleep studies

Conventional overnight polysomnography (PSG, using a 16-channel recording system: Embla A10) was performed from 11 p.m. to 7 a.m. Sleep-stage scoring was performed visually by the first author according to standard criteria (Rechtschaffen and Kales, 1968). PSG was followed by a modified Maintenance of Wakefulness Test (MWT; one single test at 8 a.m., measuring the ability to stay awake for 20 min while sitting quietly in a dark room) and subsequently by a Multiple Sleep Latency Test (MSLT; 4–5 sleep opportunities every 2 h, objectively measuring EDS under standard conditions in the absence of external alerting factors) (Littner *et al*., 2005). Mean sleep latency in the MWT and the MSLT was defined as the time from light-off to the first epoch of any sleep stage. A drug washout for 10 days prior to recordings was performed in all patients.

In 27 patients, sleep and physical activity levels were recorded over 14 days with sleep logs, and verified with wrist actigraphy (on the non-dominant wrist; light sensor data included, Actiwatch, Neurotechnology) (King *et al*., 2005). With this software the determination of 'time asleep' and 'time awake' relies on an algorithm using the activity data recorded by the Actiwatch in a series of linked calculations.

Laboratory studies

Within the first 4 days after TBI, whenever possible, we measured hypocretin-1 levels in CSF, obtained by intraventricular catheters, inserted for continuous intracranial pressure monitoring, or by lumbar puncture ($n = 27$, contaminated with blood in five patients) (Baumann *et al*., 2005). Six months after TBI, we determined CSF hypocretin-1 determinations in a subset of patients ($n = 21$) who gave informed consent to undergo a lumbar puncture. Hypocretin-1 levels below 320 pg/ml

are considered low (detection limit at 40 pg/ml) (Baumann *et al.*, 2004).

Serum laboratory tests 6 months after TBI included haemoglobin levels, parameters of thyroid function and iron metabolism. HLA typing was performed to detect narcolepsy-associated alleles.

Post-traumatic SWD: identification of potential causes and of risk factors

In all patients with post-traumatic SWD, we searched for the presence of underlying causes such as specific sleep–wake disorders (e.g. sleep-related breathing or movement disorders, narcolepsy or behaviourally induced insufficiency sleep syndrome), or the presence of other sleep-modifying disorders including substance abuse. Furthermore, we examined whether demographic, residual clinical symptoms or TBI characteristics were associated with post-traumatic SWD.

Statistical analyses

Statistical analyses were performed by correlation analyses (Pearson and Spearman), Student's *t*-tests, Mann–Whitney U-tests, Chi-square tests and multivariate regression analyses.

Results

Patients

Fifteen out of the 96 patients (16%) died (GOS 1) within the first 4 weeks after injury (moderate TBI in 3, severe TBI in 12). Five of the surviving 81 patients were abroad 6 months after the injury (TBI mild in 3, moderate in 1, severe in 1; GOS not available), and 11 patients refused to participate in the follow-up (TBI mild in 6, moderate in 2, severe in 3; GOS 5 in 7, GOS 4 in 4). Sixty-five patients participated in the present study (86% of 76 patients who did not die and who did not move to foreign countries; 53 males, 12 females, mean age 39 years, range 16–72).

Severity of TBI

TBI was mild in 26 (40%), moderate in 15 (23%) and severe in 24 (37%) patients (Fig. 1). Median GCS was 11 (mean 10.2, range 3–15). Twenty-five patients (38%) sustained an injury to multiple organs. Lesions on brain CT scans were observed in frontal ($n = 29$, 45%), parietal ($n = 19$, 29%), temporal ($n = 24$, 37%), occipital ($n = 18$, 28%) and in brainstem/midbrain ($n = 10$, 15%) locations. Brain CT was normal (Marshall I) in 21 (32%) patients. Intracranial haemorrhage was found in 34 (52%) patients (subarachnoidal haemorrhage in 14 patients).

Clinical outcome 6 months after TBI

187 ± 17 days after TBI, outcome was 'good' in 31, 'moderate disability' prevailed in 30 and 'severe disability' in 4 patients (GOS; median 4, mean 4.4, range 3–5; Fig. 1). Twenty-eight (43%) patients reported subjective memory impairment after TBI, and 26 (40%) concentration problems. Increased headache compared to pre-TBI state was reported by 15 (23%) patients.

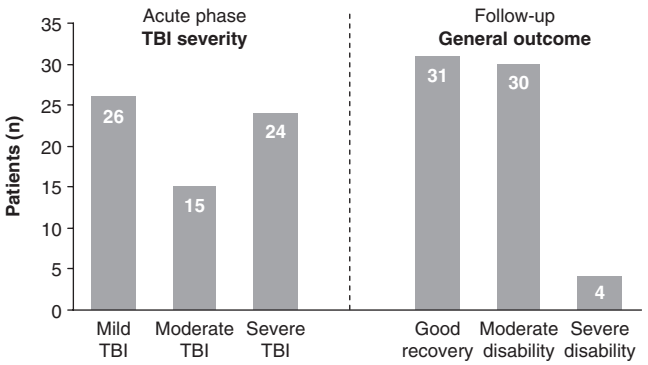

Fig. 1 Though many patients had a moderate or severe TBI, clinical outcomes were generally good. TBI severity in the acute phase (as assessed by the Glasgow Coma Scale; left side), and general outcome (as assessed by the Glasgow Outcome Scale; right side) 6 months after TBI (right side).

Pathological findings in the neurological examination were found in 36 (55%) patients. The most common pathologies were cranial nerve dysfunctions ($n = 19$, 29%), loss of sensation ($n = 9$, 14%) and limb paresis ($n = 9$, 14%). Memory functions were objectively impaired in six patients. In the Mini-Mental Status Examination, a mean score of 29 points was achieved (median 30, range 24–30, <27 in five patients).

On the Beck Depression Inventory, six patients qualified for mild to moderate depression, and two patients for moderate to severe depression.

Fifty-four patients resumed work. In evaluating the quality of life by the SF-36 questionnaire the lowest scores (most severe problems; maximum: 100) were found with respect to vitality (60.3 ± 18.9) and general health perception (61.7 ± 25.1). The highest scores (least problems) were obtained with respect to bodily pain (87.6 ± 20.6).

SWD 6 months after TBI: interviews and questionnaires

Post-traumatic hypersomnia was diagnosed in 14 patients (22%), and insomnia in three patients (5%). Two (3%) patients reported sleep attacks. Mean time spent in bed per 24 h was 8.0 ± 1.5 h (median: 8, range 6–14 h). Regular ($\geq 3\times$/week) daytime naps were reported by 12 patients (18%). Symptoms suggestive of circadian sleep–wake disorders such as advanced/delayed sleep phase syndrome were not reported during interviews. Cataplexy-like events were reported by one (2%) patient, but they did not fulfill the criteria of definite cataplexy (Anic-Labat *et al.*, 1999; Bassetti *et al.*, 2003). Sleep paralysis was reported by three (5%) and hypnagogic hallucinations by three (5%) patients. New parasomnias after TBI were not reported. Sleeping pills were taken regularly by four patients, antidepressants by seven patients.

Table 2 Polysomnography, MSLT and MWT findings in 65 patients at 6 months after TBI

	Mild TBI ($n = 26$)	Moderate TBI ($n = 15$)	Severe TBI ($n = 24$)	All TBI ($n = 65$)	*P*
Demographics and TBI					
Age*	40 ± 15	44 ± 19	36 ± 18	39 ± 17	0.34
Male gender	22 (85%)	10 (67%)	21 (88%)	53 (82%)	0.32
GOS#	5 (5, 4–5)	4 (4, 3–5)	4 (4, 3–5)	4 (4, 3–5)	0.60
Polysomnography					
Sleep efficiency (%)*	92 ± 6	91 ± 8	88 ± 11	91 ± 9	0.21
Sleep latency (minutes)*	15 ± 13	23 ± 16	21 ± 19	19 ± 16	0.27
Sleep-onset REM period	3/26	1/15	3/24	7/65	0.23
Mean arousal index*	9 ± 7	8 ± 10	8 ± 6	9 ± 6	0.95
AHI (per hour)*	6 ± 12	7 ± 14	4 ± 7	5 ± 11	0.74
AHI > 10*	3/26	1/15	3/24	7/65	0.88
PLMI (per hour)*	6 ± 10	4 ± 8	5 ± 9	5 ± 9	0.71
PLMI > 15	2/26	1/15	3/24	6/65	0.72
REM sleep (%)*	20 ± 8	19 ± 5	20 ± 5	20 ± 6	0.79
NREM I sleep (%)*	12 ± 6	10 ± 8	11 ± 5	11 ± 6	0.74
NREM II sleep (%)*	49 ± 10	47 ± 9	41 ± 7	45 ± 9	***0.02***
NREM III/IV (%)*	15 ± 9	17 ± 10	17 ± 9	16 ± 9	0.62
MSLT					
Mean sleep latency (minutes)*	8 ± 5	10 ± 4	10 ± 5	9 ± 5	0.30
Mean sleep latency <5 min	9/26	2/15	5/24	16/65	0.23
≥2 Sleep-onset REM periods	3/26	1/15	2/24	6/65	0.81
MWT					
Mean sleep latency (minutes)*	15 ± 4	13 ± 11	12 ± 6	13 ± 5	0.70
NREM I achieved	7/26	2/15	6/24	15/65	0.78
NREM II achieved	1/26	0/15	2/24	3/65	0.37

Note: GOS: Glasgow Outcome Scale; PLMI: periodic limb movement index; AHI: apnea-hypopnea-index; *: mean ± SD; #: mean, median, range.

Mean ESS 6 months after TBI was 7.5 (median 6.5, range 2–20). Subjective EDS (S-EDS) defined as ESS ≥ 10 was found in 18 (28%) patients. ESS was ≥14 in 5 (8%) patients. The mean Ullanlinna Narcolepsy Scale score was 5.0 (range 0–18), and ≥14 in 3 patients. Swiss Narcolepsy Scale values were normal in all patients. Mean SA-SDQ score was 24.4 (range 16–49), ≥36 in 8 (15%) male patients and ≥32 in one (8%) female patient. The mean body mass index was 24.0 (range 18–35).

SWD 6 months after TBI: sleep studies

Sleep efficiency in PSG was below age-adjusted 25% percentile values in three patients (mild TBI: $n = 2$, severe TBI: $n = 1$) (Danker-Hopfe *et al.*, 2005) (Table 2). On modified MWT, 15 patients fell asleep. On MSLT, objective EDS (O-EDS; mean sleep latency <5 min) was found in 16 (25%) patients. There was no significant correlation between mean sleep latency on MSLT and ESS. S-EDS and/or O-EDS were found in 25 patients (38%); the concurrence of both S-EDS and O-EDS was found in 9 patients. Fatigue was diagnosed in 11 patients (Fig. 2). In 8 PH patients, post-traumatic hypersomnia was not associated with fatigue or EDS.

Actigraphy monitoring and sleep logs documented an increased mean time 'asleep', i.e. ≥9 h per 24 h, in 14 of 27 (52%) patients. There were no correlations between mean time 'asleep' and measures of excessive daytime sleepiness (ESS, MSL on MSLT), fatigue (by history) or depression (Beck Depression Inventory). Actigraphy and sleep logs did not reveal circadian sleep disorders in any patient.

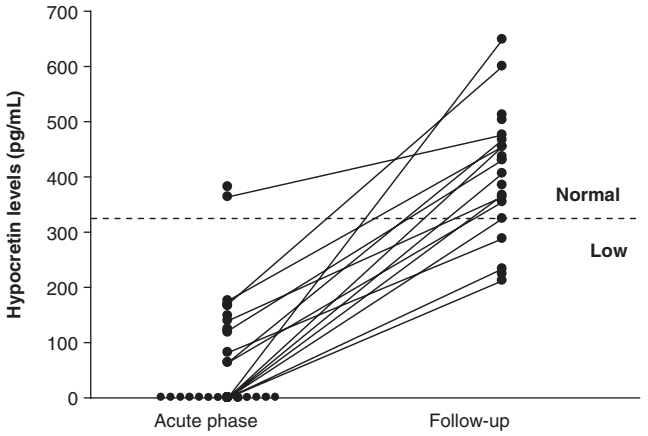

Fig. 2 Low or undetectable CSF hypocretin levels were observed in most patients in the acute phase of TBI, but levels increased to low and normal levels 6 months later. Cerebrospinal (CSF) hypocretin-1 levels in 27 patients with acute TBI (left side), and in 21 patients 6 months after TBI (right side). Lines connect hypocretin values from the same patient ($n = 15$). The dotted horizontal line indicates the border between normal and low hypocretin levels. Undetectable hypocretin levels are plotted as 0.

Laboratory studies

In the acute phase after TBI, CSF hypocretin-1 levels were undetectable in 13, low (<320 pg/ml) in 12, and normal in 2 patients. Six months later, undetectable levels were not observed (Fig. 2). Levels remained low in four patients (range 211–289 pg/ml; see later), and were normal in 17 patients. An increase ('recovery') of hypocretin-1 levels between acute phase (79 ± 103 pg/ml) and follow-up (406 ± 121 pg/ml) was observed in all patients, in whom CSF was available at both time points ($n = 15$, $P < 0.001$).

Thyroid function was normal in all patients. Mild iron deficiency was found in two, and mild anaemia in five patients. HLA DQB1*0602 was positive in 12 (18%) patients, and HLA DRB1*15 was positive in 9 (14%) patients.

Identification of potential causes of post-traumatic SWD

Forty-seven patients were diagnosed with post-traumatic SWD (S-EDS: $n = 18$, O-EDS, $n = 16$, post-traumatic hypersomnia: $n = 14$, fatigue: $n = 11$, insomnia: $n = 3$); potential causes are summarized in Fig. 3. In 28 patients (43% of the study population), we could not find a potential cause underlying post-traumatic SWD (Table 3).

Identification of risk factors for post-traumatic SWD

Sleep efficiency was significantly lower in patients ≥50 years ($P < 0.005$). Apart from these differences, gender and age did not influence the development of post-traumatic SWD.

Severe TBI was associated with the development of post-traumatic hypersomnia ($P = 0.02$), but not with the presence, characteristics and severity of other post-traumatic sleep–wake disorders. Similarly, there were no associations between severity of TBI as assessed by CT scans and sleep outcome parameters. There were no associations between localization of TBI and post-traumatic SWD. Neurological and sleep-related outcome in patients with visible lesions in the hypothalamus or in the brainstem ($n = 10$) did not differ from other patients.

Pathological findings in the neurological examination 6 months after TBI were not associated with post-traumatic SWD. There were no associations between HLA typing, initial CSF hypocretin levels and post-traumatic SWD. However, significantly decreased CSF hypocretin-1 levels were observed in EDS patients, compared to patients without post-traumatic EDS, 6 months after TBI (Table 4). Furthermore, low CSF hypocretin-1 levels 6 months after TBI were associated with poorer clinical outcome as assessed by GOS (Table 5).

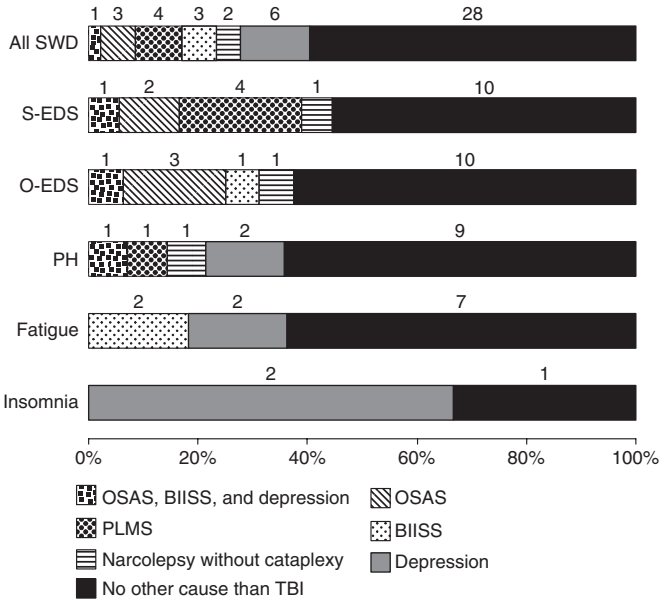

Fig. 3 In 28 patients (43% of 65), we could not identify potential causes other than TBI underlying post-traumatic sleep–wake disturbances (SWD). Forty-seven patients suffered from SWD including S-EDS, O-EDS, PH, insomnia and/or fatigue (all SWD group). S-EDS (subjective excessive daytime sleepiness, as assessed by Epworth sleepiness scale ≥10) was observed in 18, O-EDS (objective excessive daytime sleepiness, as assessed by mean sleep latencies on MSLT <5 min) in 16, PH (post-traumatic hypersomnia: increased sleep need per 24 h ≥2 h compared to pre-TBI conditions) in 14, fatigue (tiredness, reported at interview, without measures of EDS) in 11 and insomnia in 3 patients. For each of these SWD, potential causes including OSAS (obstructive sleep apnea syndrome: AHI > 10), PLMS (periodic limb movements at sleep: PLMI > 15), BIISS (behaviourally induced insufficiency sleep syndrome: difference in sleep time per 24 h between weekdays and weekends/holidays ≥2 h), narcolepsy and depression, were assessed. Other causes were not identified. Each bar represents the total of patients with a specific post-traumatic SWD, and is divided into the possible causes underlying the respective SWD.

Sleep–wake disturbances and quality of life

General outcome (GOS) was significantly worse in patients with subjective EDS ($P = 0.02$). Similarly, there were weak correlations between general health perception and ESS ($r = -0.38$, $P = 0.04$) and sleep efficiency on PSG ($r = 0.31$, $P = 0.03$), respectively. There was, however, no correlation between quality of life and MSLT findings. Furthermore, there were no correlations between Beck Depression Inventory scores and post-traumatic SWD.

Single patient reports

In two male patients (18 and 26 years old), MSLT revealed ≥2 SOREM's and abnormally short mean sleep latencies (6.3 and 2.9 min, respectively). ESS scores were 13 and 9, respectively. In both patients, Ullanlinna and Swiss Narcolepsy Scales were normal. Neither patient had cataplexy-like episodes, hypnagogic hallucinations, or sleep paralysis. CSF hypocretin-1 levels in the acute phase were

Table 3 Patients with post-traumatic hypersomnia (defined as increased sleep need per 24 h ≥ 2 h compared to pre-TBI conditions) at 6 months after TBI

	Hypersomnia	No hypersomnia	*P*
n	14	51	
Age (years)*	32 ± 16	42 ± 17	0.07
Male gender	12	41	0.49†
GCS#	8 (7, 3–14)	11 (12, 3–15)	***0.02***
GOS#	5 (5, 4–5)	4 (4, 3–5)	***0.04***
Sleep hours/night*	9.0 ± 1.9	7.9 ± 1.4	0.44
ESS#	8, 7, 3–16	8, 7, 2–20	0.94
PSG sleep efficiency (%)*	90.0 ± 6.6	90.5 ± 9.0	0.86
PSG REM%	20 ± 8	20 ± 6	0.94
PSG NREM I%	11 ± 8	11 ± 6	0.83
PSG NREM II%	42 ± 9	46 ± 9	0.12
PSG NREM III/IV%	20 ± 7	15 ± 9	0.08
PSG apnea-hypopnea-index*	5.4 ± 16.2	5.2 ± 18.9	0.95
PSG periodic limb mov. index*	5.1 ± 8.3	5.3 ± 9.2	0.95
MSLT mean sleep latency (mins)*	8.8 ± 4.1	9.4 ± 5.0	0.69
Initial CSF hypocretin-1 levels	124 ± 139 (*n* = 11)	58 ± 73 (*n* = 16)	0.17
CSF hypocretin-1 levels at 6 months	467 ± 97 (*n* = 7)	380 ± 117 (*n* = 14)	0.10
Actigraphy: "time asleep" (hours)	12 ± 4 (*n* = 8)	8 ± 2 (*n* = 18)	0.20

Note: *: mean ± SD; #: mean, median, range; †: Chi square; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; PSG: Polysomnography; ESS: Epworth Sleepiness Scale; MSLT: Multiple Sleep Latency Test; CSF: cerebrospinal fluid.

Table 4 Patients with S-EDS (ESS ≥10) and O-EDS (mean sleep latency on MSLT <5 min) compared to patients without both S-EDS and O-EDS

	S-EDS and O-EDS	no S-EDS and no O-EDS	*P*
n	9	40	
Male gender	9	35	0.44†
Age (years)*	38 ± 18	38 ± 15	0.94
GCS#	12 (13, 5–15)	10 (10, 3–15)	0.25
GOS#	4 (4, 4–5)	5 (5, 3–5)	0.32
History: sleep hours/night*	7.3 ± 1.1	8.0 ± 1.3	0.18
PSG sleep efficiency (%)*	93 ± 5	89 ± 11	0.29
PSG REM%	22 ± 7	19 ± 5	0.21
PSG NREM I%	13 ± 9	11 ± 5	0.46
PSG NREM II%	51 ± 10	44 ± 10	0.79
PSG NREM III/IV%	11 ± 10	17 ± 9	0.10
PSG apnea-hypopnea-index*	9 ± 20	5 ± 4	0.21
PSG periodic limb mov. index*	5 ± 6	5 ± 9	0.87
Initial CSF hypocretin-1 levels	91 ± 31 (*n* = 4)	96 ± 130 (*n* = 15)	0.95
CSF hypocretin-1 levels at 6 months	289 ± 64 (*n* = 4)	444 ± 113 (*n* = 10)	***0.05***

Note: *: mean ± SD;#: mean, median, range; †: Chi square; (for definitions, see Table 1). S-EDS: subjective excessive daytime sleepiness; O-EDS: objective excessive daytime sleepiness; GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; PSG: Polysomnography; CSF: cerebrospinal fluid.

63 and 83 pg/ml. Six months after TBI, levels were normal (468 pg/ml) and low (289 pg/ml), respectively. HLA typing was negative for both patients. In the younger patient, TBI was mild, but severe in the 26-year-old patient. Brain CT scans did not reveal hypothalamic lesions. These patients were asymptomatic before TBI. Based on the MSLT findings and according to the international classification of sleep disorders, these two patients can be diagnosed as *narcolepsy without cataplexy* (American Academy of Sleep Medicine, 2005).

One male patient (22 years old) reported hypnagogic hallucinations and cataplexy-like episodes (subjective weakness in both knees with laughter), which did not fulfill the criteria of cataplexy (Anic-Labat *et al.*, 1999). ESS was 11, Ullanlinna Narcolepsy Scale 15, Swiss Narcolepsy Scale normal, mean sleep latency 5.6 min and there were no SOREM's. This patient with a *narcolepsy-cataplexy-like phenotype* reported that he had not observed these symptoms prior to TBI. CSF hypocretin-1 was low 6 months after TBI (225 pg/ml).

Table 5 Outcome parameters in patients with low and in patients with normal CSF hypocretin-1 levels 6 months after TBI

	Hypocretin-1 low	Hypocretin-1 normal	*P*
n	4	17	
GCS (mean, median, range)	8 (7, 6–13)	11 (11, 3–15)	0.21
GOS (mean, median, range)	4 (4, 3–4)	5 (5, 4–5)	***0.011***
Increased sleep need/24 h (*n*)	1	4	0.89
ESS (mean, median, range)	8 (8, 4–11)	8 (6, 3–20)	0.92
PSG sleep efficiency (mean ± SD)	93.7 ± 4.6	91.3 ± 7.2	0.53
MSL (mean ± SD)	6.4 ± 5.6	9.1 ± 4.2	0.41
≥2 SOREM periods on MSLT (*n*)	1	2	0.49

Note: GCS: Glasgow Coma Scale; GOS: Glasgow Outcome Scale; PSG: Polysomnography; ESS: Epworth Sleepiness Scale; MSL/MSLT: Mean sleep latency on Multiple Sleep Latency Test; SOREM: sleep-onset REM sleep.

There were two other patients with a low CSF hypocretin-1 level 6 months after TBI (besides one patient with narcolepsy, and one patient with a narcolepsy-like phenotype, see earlier). In a 58-year-old patient (211 pg/ml), PSG revealed a moderate sleep apnea syndrome (apnea hypopnea index: 25/h), and a short mean sleep latency on MSLT (2.5 min). In a 19-year-old patient (234 pg/ml), all findings were normal.

Seven patients in our study (six males, mean age 57 ± 12 years) suffered from obstructive sleep-apnea syndrome, which was severe (AHI >30/h) in three patients. Restless legs syndrome was not diagnosed in any patient, whereas periodic limb movement disorder was found in six patients.

Discussion

General outcome after traumatic brain injury

In this prospective study, we found an overall mortality of 16%, which is in line with predicted values based on CT findings (Marshall classification) (Maas *et al.*, 2005). Compared to large clinical outcome studies of TBI patients, however, the clinical outcome of our patients was favourable (Choi *et al.*, 1991; Narayan *et al.*, 2002; Doppenberg *et al.*, 2004). Still, this good outcome may bias our study; post-traumatic sleep–wake disturbances may be even more frequent in patients with a worse outcome.

Frequency of sleep–wake disorders after traumatic brain injury

We found that SWD are common after TBI. New SWD subsequent to TBI were present in three out of four patients, consistent with previous reports (Betaar *et al.*, 1986; Cohen *et al.*, 1992). The most prevalent SWD were EDS/fatigue (55%) and post-traumatic hypersomnia (22%), but not insomnia or circadian sleep–wake disorders.

Assessment of new SWD after TBI was based on retrospective information from patients about their sleep before TBI. Given that such data may not be entirely reliable, some of the pertinent findings of this study must be interpreted with caution. Furthermore, the relatively small number of patients ($n = 65$) only allows us to draw preliminary conclusions concerning the prevalence of post-traumatic SWD. But as a prospective study, it allows us to estimate the frequency of post-traumatic SWD in a general population for the first time. A supportive feature of the study is the high proportion of consecutive TBI patients participating in all aspects of the study (86% of all surviving patients, who had not moved to foreign countries).

Clinical characteristics and potential causes of post-traumatic sleep–wake disorders

In our population, EDS ($n = 25$, 38%), hypersomnia ($n = 14$, 22%) and fatigue ($n = 11$, 17%) were the most prevalent SWDs following TBI. Subjective EDS, defined as ESS ≥10, was found in 28%, which does not differ from the frequency (35%) in a general population, as reported in a recent study with 556 patients (Mignot *et al.*, 2006). The patients in our study were younger (mean: 37 years) than those of this recent study (mean: 64 years) so that direct comparisons between the two populations cannot be made. In our study, objective EDS (defined as abnormally short mean sleep latencies on MSLT, however, was almost as prevalent (25%) as subjective EDS, compared to 1–6% in a general population (Mignot *et al.*, 2006). The finding of highly prevalent EDS with short mean sleep latencies on MSLT is in agreement with previous studies in TBI patients (Masel *et al.*, 2001; Rao and Rollings, 2002).

Compared to other studies, the prevalence of insomnia ($n = 3$, 5%) in our population was remarkably low (Guilleminault *et al.*, 2000; Fichtenberg *et al.*, 2002; Parcell *et al.*, 2006; Ouellet *et al.*, 2006*a*). This discrepancy in findings is not easily explained. It might be accounted for by the favourable clinical outcome of our patients (lower occurrence of pain and depression may enhance sleep quality). Furthermore, as pointed out initially, there are marked methodological differences between previous studies (e.g. differences in the assessment of insomnia, in intervals between TBI and examinations, in focusing on specific SWD and in population characterization), resulting in unequivocal findings. The finding

of a low frequency of insomnia may, at least in parts, be explained by an overestimation of insomnia symptoms in questionnaire-based studies (Ouellet *et al.*, 2006*b*).

Among patients with post-traumatic SWD, no common clinical pattern could be identified (Fig. 3). In 19 patients, we found potential causes of SWD other than TBI such as obstructive sleep apnea, periodic limb movements at sleep, behaviourally induced insufficiency sleep syndrome and depression. There were, however, no associations between EDS/fatigue/hypersomnia and depression (as assessed by the Beck Depression Inventory). Restless legs syndrome was not diagnosed in our patients (prevalence of 4–10% in the normal population) (Tison *et al.*, 2005). In two patients, the criteria of narcolepsy without cataplexy (severe EDS, $\geq$2 SOREM's on MSLT) were fulfilled. CSF hypocretin-1 level 6 months after TBI was low in one of these patients. Based on the patients' history, we assume that these symptoms were not present before TBI. In one patient with a low CSF hypocretin-1 level 6 months after TBI, a narcolepsy-cataplexy-like phenotype was observed. Post-traumatic narcolepsy-cataplexy, however, was not identified in our patients. In 28 patients (43%), potential causes for SWD other than TBI could not be identified. In other words, post-traumatic EDS, fatigue or post-traumatic hypersomnia appear to be directly related to the neuronal injury itself in almost one of two study patients.

Predisposing factors for post-traumatic sleep–wake disorders

Hypocretin

CSF hypocretin-1 levels were normal in most (17/21) patients 6 months after TBI, but levels were lower in patients with EDS. In agreement with this finding, Bassetti and collaborators (2003) reported hypocretin deficiency in one patient with post-traumatic hypersomnia. Ripley and collaborators (2001) found a low hypocretin-1 level in one TBI patient 7 months after trauma. Data on sleep and wakefulness after TBI, however, were not reported. Belmont and colleagues (2006) reported an association between post-traumatic fatigue and insufficiency in the hypothalamic-pituitary axis, suggesting hypothalamic dysfunction. Furthermore, in our study, lower hypocretin-1 levels were associated with a worse clinical outcome. Although we tested hypocretin in only a subset of patients, we believe that these findings support the hypothesis that hypocretin deficiency may contribute to the development of post-traumatic SWD.

Several mechanisms might explain the transient decrease of CSF hypocretin-1 levels in the acute phase after TBI, with subsequent 'recovery' of levels at retesting 6 months later. Autopsy studies have shown necrosis, haemorrhage or structural abnormalities in the hypothalamus in up to 2/3 of patients with TBI (Crompton, 1971; Benvenga *et al.*, 2000). Thus, TBI may damage hypocretin neurons or their axons. If so, then recovery of hypocretin levels after TBI would reflect adaptation by other hypocretin-producing cells. In patients with increased sleep propensity after TBI, hypocretin production of the remaining neurons may be inadequate, resulting in residual low levels (Gerashchenko *et al.*, 2003; Scammell, in press). Thus, it is conceivable that critical/insufficient adaptation by surviving hypocretin cells might be involved in post-traumatic EDS/hypersomnia.

Another explanation of transient CSF hypocretin-1 deficiency in acute TBI would be a reduction in hypocretin neuron activity without injury of the cells or their axons, e.g. mediated by increased inhibition, decreased excitation, or in relation to altered vigilance (sleep, coma) or to impaired circadian waking drive. Hypocretin is wake-promoting and there is evidence that sleep enhances plasticity effects after brain damage (Stickgold *et al.*, 2001; Carmichael *et al.*, 2002). It is therefore reasonable to assume that downregulation of hypocretinergic activity may have beneficial effects regarding functional outcome. In our study, however, there were no associations between hypocretin levels in the acute phase after TBI and outcome parameters.

Other factors

We found an association between severe TBI (as assessed by the Glasgow Coma Scale) and post-traumatic hypersomnia. Otherwise, we could not identify predisposing factors ('risk factors') for the development of post-traumatic SWD. There were no associations between gender, localization of TBI, residual neurological symptoms, overall clinical outcome (as assessed by the Glasgow Outcome Scale), HLA typing, specific sleep study findings and the development or severity of post-traumatic SWD. In general, therefore, our findings are in line with reports of previous studies that also could not identify correlations between characteristics of TBI and post-traumatic SWD (Lankford *et al.*, 1994; Guilleminault *et al.*, 2000; Masel *et al.*, 2001). Besides the small number of patients, a major limitation of our study, however, is that patients only received CT examinations. High-resolution neuroimaging (such as magnetic resonance imaging), allowing for a better localization and characterization of cerebral lesions, was not available.

Post-traumatic sleep–wake disturbances and depression

We could not find associations between Beck Depression Inventory scores and the presence or severity of post-traumatic SWD. In contrast, significantly more SWD were reported by patients with mild TBI compared to patients with severe TBI in a recent study with the Pittsburgh Sleep Quality Index (Mahmood *et al.*, 2004). This might give rise to the assumption that—especially in mild TBI patients—neuropsychiatric factors may trigger the development of post-traumatic SWD. Our findings, however, suggest that the development of post-traumatic sleep–wake disorders in TBI patients cannot be explained only on the

basis of underlying psychiatric disorders or other 'functional' factors. We have not performed extensive psychiatric evaluations in our patients so we cannot rule out a preponderance of psychiatric disturbances in patients with post-traumatic SWD.

Post-traumatic sleep–wake disturbances and quality of life

Quality of life was affected most by a loss of vitality complaints (SF-36) whereas bodily pain, physical or psychological problems were rated less limiting. Emanuelson and colleagues (2003) also examined the quality of life after TBI with the SF-36 questionnaire in a Scandinavian population, and also found vitality given the lowest rating. Our findings indicate that complaints about sleep–wake disorders (and particularly EDS) significantly affect quality of life and social functioning, and must be taken seriously.

Conclusion

In this prospective study, we found a high frequency of SWD following TBI, in particular post-traumatic EDS, fatigue and hypersomnia. In at least 43% of patients, post-traumatic SWD appeared to be directly related to the injury itself. An involvement of the hypocretin system in the pathophysiology of post-traumatic SWD appears possible. However, we could not identify risk factors predisposing towards the development of post-traumatic SWD.

Post-traumatic SWD significantly harm quality of life and social functioning. Further studies are needed to identify the underlying pathophysiology of post-traumatic sleep–wake disorders (perhaps using functional imaging and histopathological techniques). A better understanding of the neuropathophysiology of TBI and post-traumatic SWD should lead to better therapeutic strategies for these patients.

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