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ORIGINAL ARTICLE

Mood disorders in patients with hypersomnia: comparison of sleep-related breathing disorders versus narcolepsy

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Abstract

BACKGROUND: Anxiety and depression are common comorbidities of excessive daytime sleepiness (EDS). Sleep-related breathing disorders (SBD) and central disorders of hypersomnolence (like narcolepsy [NA]) are the most frequent causes of EDS. This study aimed to evaluate mood disorders in NA patients compared to the subjects with EDS due to SBD (SBD-EDS).
METHODS: In a retrospective analysis, subjects with NA and SBD-EDS were compared. All subjects underwent overnight polysomnography. NA patients underwent also multiple sleep latency test. Epworth sleepiness scale (ESS), Pittsburgh Sleep Quality Index (PSQI), Becks questionnaire, and Zung depression scale were used to assess EDS, sleep quality, anxiety, and depression, respectively.
RESULTS: We enrolled 24 NA and 41 SBD-EDS subjects. Values of PSQI and Zung scale were significantly worse in the SBD-EDS group than in NA patients (8.34±3.84 vs. 6.83±2.25, p=0.04; 46.86±12.69 vs. 40.81±11.27, p=0.03, respectively). Anxiety was significantly more frequent in SBD-EDS subjects compared to NA (63.4% vs. 37.5%, p=0.04). Out of all observed sleep-related indices, PSQI was the only factor, that significantly correlated with the measures of anxiety in both groups (NA: r=0.65, p=0.001; SBD-EDS: r=0.45, p=0.003) and with the measures of depression in NA subjects (r=0.51, p=0.01). In SBD-EDS group, measures of depression significantly correlated with PSQI (r=0.46, p=0.002), oxygen desaturation index (r=0.35, p=0.03), and ESS (r=0.5, p=0.001).
CONCLUSION: Compared to NA, our results suggest significantly worse measures of depression and a significantly higher frequency of anxiety in the SBD-EDS population. Measures of anxiety and depression significantly correlated with quality of sleep in both groups.

Abbreviations:

AASM	- American Academy of Sleep Medicine
AHI	- apnea/hypopnea index
ArI	- arousal index
EDS	- excessive daytime sleepiness
ESS	- Epworth Sleepiness Scale
ICSD-3	- International classification of sleep disorders, 3rd edition, 2014.
IQR	- interquartile range
NA	- narcolepsy
NT1	- narcolepsy type 1
NT2	- narcolepsy type 2
PSG	- polysomnography
PSQI	- Pittsburgh Sleep Quality Index
SBD	- sleep-related breathing disorder
SBD-EDS	- excessive daytime sleepiness due to sleep-related breathing disorder
Zung SDS index	- Zung Self-Rating Depression Scale index

INTRODUCTION

Hypersomnolence or excessive daytime sleepiness (EDS) is defined as an inability to maintain sufficient vigility in the active part of the day. It may be manifested by problems with awakening, daytime sleepiness, reduced activity, or by more severe symptoms like imperative need to sleep, sleep attacks, and autonomic behavior in inadequate situations. EDS has a serious negative impact on the quality of life and is associated with an increased risk of accidents. The prevalence of mild EDS in the general population ranges between 15-20%, serious forms of EDS are present in 4-6% (Šonka 2007).

The most important causes of EDS are sleep disorders which lead to the fragmentation of sleep. They include sleep-related breathing disorders (SBD), restless legs syndrome, periodic limb movements, or chronic insomnia (Ferini-Strambi *et al.* 2017). EDS is considered a key symptom of obstructive sleep apnea syndrome. Repeated apneas, caused mainly by reversible obstruction of upper airways by tongue and tissue of the neck, lead to desaturation, increased breathing effort, and sympathetic nervous system activation. They are terminated by arousal and opening of the upper airways. SBD negatively influences the restorative function of sleep, cardiovascular system, mood, and cognition. Fragmentation of sleep has stronger relation to daytime sleepiness than nocturnal desaturations (Colt *et al.* 1991). Except for these reasons, the most frequent causes of EDS are diseases with hypersomnolence of central origin, including narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2), idiopathic hypersomnia, and recurrent hypersomnia (Overeem & Billiard 2006; American Academy of Sleep Medicine 2014).

NT1 is a typical central disorder of hypersomnolence, which manifests with attacks of imperative sleep and signs of REM-sleep dissociation, like cataplexy, sleep paralysis, hypnagogic, or hypnopompic hallucinations, or episodes of autonomic behavior. It is caused by selective loss of the neurons of the lateral hypothalamus (probably due to the autoimmune process), which produces orexins (hypocretins) (Ollila 2020). Orexin peptides regulate the sleep-wake cycle, promote arousal and suppress REM sleep, and are supposed to play a role also in the pathophysiology of major depressive disorder (Shariq *et al.* 2019). They are involved in motivation, reward processing, feeding, and metabolism. Loss of orexin neurons results in daytime sleepiness and dysregulation of REM sleep even with possible signs of REM sleep behavior disorder (Mahoney *et al.* 2019; Knudsen *et al.* 2010). Multiple other psychiatric, emotional, cognitive, and autonomic symptoms are present in narcolepsy subjects (Bassetti *et al.* 2019).

NT 2 (narcolepsy without cataplexy) is more likely a heterogeneous disorder. The majority of these patients have normal levels of hypocretin-1 in cerebrospinal fluid, but approximately 24% of these patients have a low concentration and another 8% have intermediate levels of hypocretin-1 in cerebrospinal fluid. Partial hypocretin deficiency in these patients is supposed to cause daytime sleepiness, but not cataplexy (American Academy of Sleep Medicine 2014). Psychiatric and sleep disorders often co-occur and influence each other. Associations of EDS and depressive symptoms are complex and often bidirectional. Many patients with central hypersomnias report depressive symptoms (Lopez *et al.* 2017). EDS in patients with mood disorders is usually a subjective complaint with less obvious objective signs. To assess hypersomnia, not only self-reporting questionnaires, but also objective methods such as overnight polysomnography or multiple sleep latency test should be used (Dauvilliers *et al.* 2013). Hypersomnolence in patients with mood disorders commonly lacks objective signs (like short sleep latency in multiple sleep latency test), making the diagnostic process even more complicated (Barateau *et al.* 2017). Nevertheless, most psychiatric patients in a study of Benca *et al.* showed significantly reduced sleep efficiency and total sleep time (Benca *et al.* 1992). Evaluation and quantification of EDS in patients with psychiatric hypersomnolence, or central hypersomnia with comorbid psychiatric symptoms may be challenging even for the sleep specialists.

Patients with hypersomnolence of central origin as well as patients with EDS due to SBD (SBD-EDS) suffer not only EDS but their complaints also commonly include the changes of mood. The current retrospective study aimed to compare the occurrence and severity of anxiety and depression in patients with narcolepsy and patients with SBD-EDS.

MATERIAL AND METHODS

In a retrospective analysis, subjects were chosen from the pool of patients, who were hospitalized in the Sleep Laboratory of the 1st Department of Neurology, Medical Faculty, Comenius University in Bratislava due to hypersomnia, or suspected SBD with EDS. Two groups of patients were compared. The first one

Tab. 1. Statistical comparison of parameters in patients with NA and SBD-EDS

	NA	SBD-EDS	*p*
N	24	41	
Men	10	34	**0.001****
Women	14	7	
Age (years)	40.5 ± 12.1	56.14 ± 13.07	<**0.001** ***
ESS	17.2 ± 2.85	13.29 ± 4.12	<**0.001** ***
Sleep N1 (%)	26.99 ± 14.69	40.29 ± 15.11	<**0.001** ***
Sleep N2 (%)	30 ± 9.43	25.79 ± 9,77	0.094
Sleep N3 (%)	28.2 ± 10.45	25.01 ± 11,55	**0.025***
REM (%)	6.61 ± 8.16	8.63 ± 7.35	**0.003****
Sleep efficiency (%)	96.16 ± 3.28	97.05 ± 4.4	0.39
AHI	4.56 ± 3.08	48.66 ± 25.1	<**0.001** ***
BMI (kg/m^2)	25.78 ± 5.69	33.59 ± 6.73	<**0.001** ***
ArI	12.18 ±6.59	28.52 ± 16.11	<**0.001** ***
PSQI	6.83±2.25	8.34 ± 3.84	**0.04***
SDS index	40.81 ± 11.27	46.86 ± 12.69	**0.03***
Patients with depression (SDS index > 50) (n), (%)	5 / 20.8%	14 / 34.2%	0.26
Patients with moderate-to-severe depression (SDS index > 60) (n), (%)	2 / 8.3%	7 / 17%	0.33
Beck score of anxiety	7.71±5	10.97±8.38	0.12
Patients with anxiety (Beck score>5) (n), (%)	9 / 37.5%	26 / 63.4%	**0.04***

AHI – apnea/hypopnea index, ArI - arousal index, BMI – Body Mass Index, ESS – Epworth Sleepiness Scale, NA - narcolepsy, PSQI - Pittsburgh Sleep Quality Index, REM – rapid eye movement sleep, SBD-EDS - excessive daytime sleepiness due to sleep-related breathing disorders, SDS index - Self-Rating Depression Scale index., * – *p* below 0.05, ** – *p* below 0.01, *** – *p* below 0.001.

included subjects with the diagnosis of NT1 and NT2. Subjects with EDS due to moderate-to-severe sleep apnea were enrolled into the second group (SBD-EDS).

Patients in our study filled in the Epworth Sleepiness Scale questionnaire (ESS) (Johns 1991) to prove EDS and only patients with the ESS score >9 were selected. They were neurologically evaluated, their body mass index (BMI) was recorded and blood samples at fasting condition were obtained to exclude other medical reasons for EDS. All of the selected subjects underwent overnight polysomnography (PSG) using Alice 6 device (Philips-Respironics, Netherlands) according to the standardized criteria of the American Academy of Sleep Medicine (AASM) (Berry *et al.* 2020). Proportions of particular sleep stages (N1, N2, N3, and REM sleep) in % of total sleep time were recorded and sleep effectivity was counted as (total sleep time / total recording time) x 100 in %. Arousal index (ArI) was evaluated as a count of arousals per hour of sleep. Arousals are defined as abrupt shifts of electroencephalographic activity including alfa, theta, or frequencies greater than 16 Hz (but not spindles), that lasts at least 3 seconds, which are preceded with at least 10 seconds of stable sleep. Respiratory parameters were scored as apnea/hypopnea index (AHI). It was counted from the number of apnea and hypopnea episodes per hour of sleep. Apnea episode was scored if a drop of the amplitude of airflow registered by oronasal thermistor exceeded 90% of the previous value and lasted ≥10 seconds. Hypopnea was scored, if all of these three rules were present: a drop of airflow amplitude ≥30% of the previous amplitude of oronasal flow measured by a nasal pressure sensor, duration of the event exceeded ≥ 10 seconds and desaturation was ≥3% compared to the previous value, or associated arousal was present. Apneas were scored as obstructive, central, or mixed (Berry *et al.* 2020).

The next day, a multiple sleep latency test (MSLT) was performed in cases, where NA was suspected according to the current complaints and the results of previous evaluations excluded other possible reasons for EDS (no SBD proved by PSG). MSLT consisted

Tab. 2. Correlations in the group of patients with narcolepsy

	Zung SDS Index		Beck Index		ESS	
	r	*p*	r	*p*	r	*p*
PSQI	**0.51**	**0.01***	**0.65**	**0.001****	0.09	0.65
Age	0.24	0.26	0.41	0.85	-0.24	0.26
BMI	0.02	0.94	-0.14	0.52	-0,25	0,23
N1%	-0.08	0.68	0.06	0.79	0.39	0.06
N2%	-0.07	0.73	0.28	0.18	0.06	0.78
N3%	0.34	0.1	-0.11	0.59	**-0.44**	**0.03***
REM%	-0.79	0.71	-0.43	0.84	-0.2	0.34
AHI	-0.15	0.95	0.004	0.98	0.14	0.5
ODI	0.07	0.76	-0.11	0.59	-0.12	0.57
ArI	-0.12	0.55	-0.08	0.68	0.25	0.24
ESS	-0.17	0.41	0.15	0.5	-	-

AHI – apnea/hypopnea index, ArI - arousal index, BMI – Body Mass Index, ESS – Epworth Sleepiness Scale, N1 – NonREM sleep 1, N2 – NonREM sleep 2, N3 – NonREM sleep 3, ODI – oxygen desaturation index, PSQI - Pittsburgh Sleep Quality Index, REM – rapid eye movement sleep, SDS index - Self-Rating Depression Scale index, * – *p* below 0.05, ** – *p* below 0.01

of five short polysomnographic recordings, which started at 8:00 A.M., 10:00 A.M., 12:00 A.M., 2:00 P.M., and 4:00 P.M. and lasted maximally 20 minutes, or were terminated 15 minutes after sleep onset. Average latency of sleep onset, as well as presentation of sleep onset REM phase (SOREMP), were analyzed using Alice 6 device (Philips-Respironics, Netherlands) according to the AASM criteria (Berry *et al.* 2020). The level of hypocretin in cerebrospinal fluid was not assessed. One of the patients was genetically evaluated with a positive HLA DQB1*0602 haplotype. Only patients with proved EDS according to ESS>9, with a mean latency of sleep by MSLT < 8 minutes and absent or just mild SBD (according to the PSG with AHI <15) were included in the NA group. The diagnosis of NA was newly established in all of these subjects and these subjects were treatment-naive for NA. The second group (SBD-EDS) included patients with EDS (ESS score >9) and moderate-to-severe sleep apnea with AHI≥15/hour. The diagnosis of SBD was newly established in all of these subjects and these subjects were treatment-naive for SBD.

Anxiety was evaluated in all subjects by the Beck questionnaire with a score >5 indicating anxiety (Beck *et al.* 1988). The self-rating depression scale (SDS) of the Zung questionnaire was used to assess the depressive features. SDS index >50 was considered as reflecting depression (Zung 1965). Quality of sleep was measured by the Pittsburgh Sleep Quality Index (PSQI), where a score >5 indicates "poor" quality of sleep (Buysse *et al.* 1989).

Patients without EDS (ESS score ≤9) and patients with other diagnoses considered as a possible reason for EDS (like hypothyreosis, anemia, chronic heart failure, chronic fatigue syndrome, abuse of medications or alcohol) were not included in the study. The study was approved by the institutional ethics committee and all patients at the beginning of the diagnostic procedure signed the informed consent.

Statistical analysis was performed using SPSS, version 18 (SPSS Inc., Chicago, USA). Continuous variables were presented as mean ± standard deviation or median and interquartile range (IQR). Categorical variables were presented as numbers and proportion in %. For comparison of two groups, Student t-test, Mann–Whitney test, and Chi-squared tests were used for particular variables. Pearson or Spearman correlation coefficients were used for evaluation of the association between particular continuous variables, when appropriate. Values of $p < 0.05$ were considered statistically significant.

RESULTS

In our study, 24 patients (10 men and 14 women with average age 40.5 ± 12.1 years) fulfilled the criteria for NA. All of them had imperative sleep attacks (100%), 58% of them had active dreams, 33% had hypnagogic or hypnopompic hallucinations, 32% reported automatic behavior and 27% had sleep paralysis. Twenty of them (83%) reported cataplexy and 4 of them (17%) did not. The mean latency of sleep by MSLT was 4.18 ±0.8 minutes with at least 2 SOREMPs in each test. The average AHI was 4.56 ± 3.08 / hour of sleep. According to these results, 20 patients were diagnosed as NT1 and 4 patients as NT2 (see Table 1).

The second group included 41 SBD-EDS subjects. There were 34 men and 7 women with an average age of 56.14 ± 13.07 years. Moderate SBD (15≤AHI<30) was present in 14 of them (34.1%) and 27 patients (65.9%)

Tab. 3. Correlations in the group of patients with SBD-EDS

	Zung SDS Index		Beck Index		ESS	
	r	p	r	p	r	p
PSQI	**0.46**	**0.002****	**0.45**	**0.003****	**0.44**	**0.004****
Age	**-0.36**	**0.02***	-0.18	0.24	-0.13	0.41
BMI	0.22	0.17	0.08	0.63	0.26	0.1
N1%	-0.12	0.46	-0.14	0.37	-0.12	0.94
N2%	0.09	0.56	0.06	0.7	0.16	0.32
N3%	0.12	0.46	0.14	0.37	0.02	0.89
REM%	-0.12	0.46	-0.5	0.77	-0.22	0.16
AHI	0.3	0.05	0.07	0.67	**0.45**	**0.003****
ODI	**0.35**	**0.03****	0.2	0.89	**0.42**	**0.006****
ArI	0.26	0.12	0.07	0.64	**0.43**	**0.005****
ESS	**0.5**	**0.001****	0.29	0.07	-	-

AHI – apnea/hypopnea index, ArI - arousal index, BMI – Body Mass Index, ESS – Epworth Sleepiness Scale, N1 – NonREM sleep 1, N2 – NonREM sleep 2, N3 – NonREm sleep 3, ODI – oxgen desaturation index, PSQI - Pittsburgh Sleep Quality Index, REM – rapid eye movement sleep, SBD-EDS - excessive daytime sleepiness due to sleep-related breathing disorders SDS index - Self-Rating Depression Scale index, * – *p* below 0.05, ** – *p* below 0.01

had severe SBD with AHI over 30. The average AHI was 48.66 ± 25.1 (see Table 1).

According to the ESS, patients with NA had a significantly higher score of ESS than patients with SBD-EDS (17.2 ± 2.85 vs. 13.29 ± 4.12; $p<0.001$). The overnight PSG revealed significant differences in sleep architecture. Patients with SBD-EDS had a significantly higher proportion of N1 sleep (40.29 ± 15.11% vs. 26.99 ± 14.69%; $p<0.001$), significantly higher proportion of REM sleep (8.63 ± 7.35% vs. 6.61 ± 8.16%; $p = 0.003$) and significantly lower proportion of deep N3 sleep (25.01 ± 11.55% vs. 28.2 ± 10.45%; $p = 0.025$) than patients with NA. Sleep efficiency was similar in both groups, but the fragmentation of sleep measured by ArI was significantly higher in patients with SBD-EDS than in patients with NA (28.52 ± 16.11 vs. 12.18 ± 6.59; $p<0.001$). This was probably caused by apparently big differences in AHI between both groups (patients with SBD-EDS had AHI 48.66 ± 25.1 and patients with NA only 4.56 ± 3.08, $p<0.001$). Patients with SBD-EDS were significantly more obese and were also significantly older than patients with narcolepsy (BMI: 33.59 ± 6.73 kg/m^2 vs. 25.78 ± 5.6 kg/m^2, $p<0.001$; age: 33.59 ± 6.73 years vs. 25.78 ± 5.69 years, $p<0.001$).

The quality of sleep evaluated by PSQI was "poor" in both groups (the average score was higher than 5 in each of them). It was significantly worse in patients with SBD-EDS than in patients with NA (8.34 ± 3.84 vs. 6.83 ± 2.25; $p=0.04$) (see Figure 1).

Anxiety according to the Beck questionnaire (Beck score >5) and depression according to Zung scale (SDS index >50) were more frequent in the group of patients with SBD-EDS than in patients with NA (63.4% vs. 37.5%, $p=0.04$; 34.2% vs. 20.8%, $p=0.26$; respectively). The difference in average Beck score of anxiety was not statistically significant, but the SDS index was significantly higher in the group of patients with SBD-EDS than in patients with NA (46.86 ± 12.69 vs. 40.81 ± 11.27; $p=0.03$) (see Figure 2).

Evaluation of the association between anxiety, depression and sleep parameters revealed, that both, measures of depression as well as measures of anxiety significantly correlated with sleep quality measured by PSQI in both groups of patients (see Table 2 and Table 3). Out of all observed sleep-related indices, PSQI was the only factor, that significantly correlated with the measures of anxiety in both groups (NA: r=0.65, $p=0.001$; SBD-EDS: r=0.45; $p=0.003$) and with the measures of depression in NA subjects (r=0.51, $p=0.01$). In SBD-EDS group, measures of depression significantly correlated with PSQI (r=0.46, $p=0.002$), oxygen desaturation index (ODI) (r=0.35, $p=0.03$), and ESS (r=0.5, $p=0.001$). Other correlations in the group of patients with SBD-EDS showed a significant negative correlation with age (r=-0.36, $p=0.02$) (see Table 3).

Sleepiness measured by ESS significantly negatively correlated only with the amount of REM sleep (r=-0.44; $p=0.03$) in patients with NA (see Table 2). Different situation was in the group of patients with SBD-EDS, where ESS correlated with PSQI and Zung SDS index (r=0.44, $p=0.004$; r=0.5, $p=0.001$; respectively). There was also significant correlation of ESS with sleep parameters like AHI (r=0.45, $p=0.003$), ODI (r=0.42, $p=0.006$) and ArI (r=0.43, $p=0.005$) in this group of SBD-EDS patients (see Table 3).

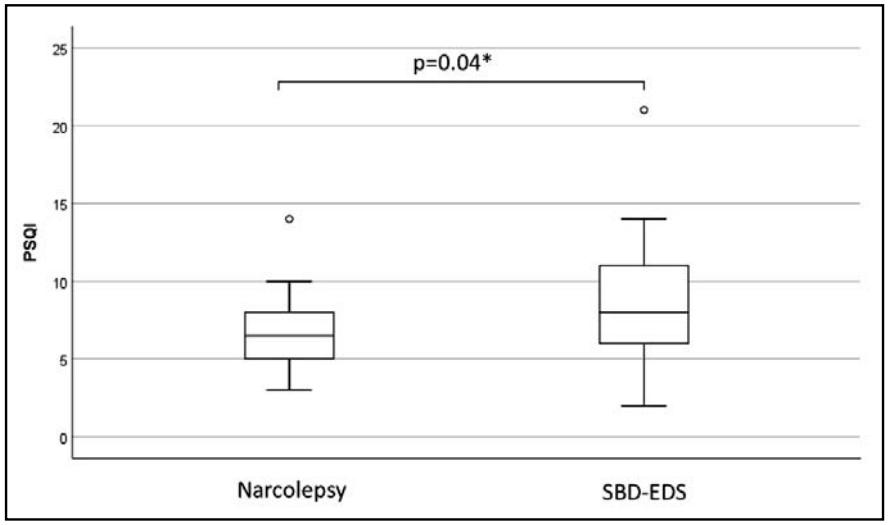

Fig. 1. Statistical comparison of PSQI in the group of patients with narcolepsy and patients with SBD-EDS (median, IQR).
Legends: PSQI – Pittsburgh Sleep Quality Index, SBD-EDS – excessive daytime sleepiness due to sleep-related breathing disorder

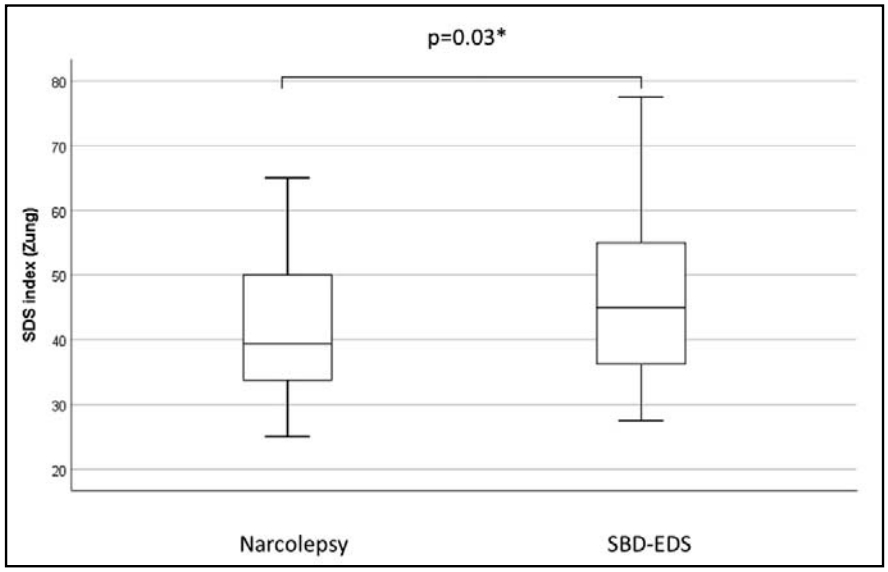

Fig. 2. Statistical comparison of SDS index in the group of patients with narcolepsy and patients with EDS due to SBD (median, IQR).
Legends: SBD-EDS – excessive daytime sleepiness due to sleep-related breathing disorder, SDS index – Self-Rating Depression Scale.

DISCUSSION

There is growing interest in mood disorders and EDS in the past years. However, less attention is paid to the etiology of EDS and its influence on anxiety or depression.

EDS is typically more severe in patients with NA than in subjects with sleep apnea syndrome (Morrison & Riha 2012). Our results suggest the same fact. Patients with NA had significantly higher measures of EDS than patients with SBD (ESS score: 17.2 ± 2.85 vs. 13.29 ± 4.12; $p<0.001$). When evaluating factors influencing EDS in our patients, we found, that in patients with NA, ESS only correlated with the amount of REM sleep. This was expected, as NA belongs to central disorders of hypersomnolence with disturbed REM phase of sleep. A different situation was found in the group of patients with SBD-EDS, where ESS correlated with PSQI, Zung SDS index, and also with parameters connected with disturbed breathing (like AHI, ODI, and ArI). It suggests that sleepiness in patients with NA is a relatively independent feature linked probably only to the pathology of REM sleep. On the other hand, EDS in patients with SBD is a result of more complex reasons like "poor" quality of sleep with apneas, desaturations, arousals, and probably also the presence of depression. We have to admit, that the study was not designed to prove any causality in these relationships.

According to the literature, there is an increased prevalence of depressive symptoms in patients with NA, as well as a high level of anxiety, panic attacks, or social phobias in about 20% of them (American Academy of Sleep Medicine 2014). Underactivity of reward pathways in NT1 could probably be manifested as depression, which is twice as prevalent among individuals with NT1 than in the general population (Cohen *et al.* 2018). Whether this increased rate of depression is a direct consequence of the loss of orexin neurons, or if it reflects many everyday challenges associated with narcolepsy, is currently unknown (Lee *et al.* 2017). In NT2, patients have daily periods of irresistible need to sleep, but cataplexy is absent and there is no deficiency in hypocretin-1 metabolism (American Academy of Sleep Medicine 2014). There were 37.5% patients with anxiety and 20.8% patients with depression in our group of patients with NA. Fortuyn *et al.* found a higher frequency of anxiety (53%) and less depression (13%) in their patients with NA (Fortuyn *et al.* 2010). According to our observations, anxiety was present in 63.4% and depression in 34.2% of the patients with SBD-EDS. Rezaeitalab *et al.* reported similar results, 53.9% of patients with sleep apnea had anxiety and 46.1% had depression (Rezaeitalab *et al.* 2014). When comparing both groups in our study, we found a significantly higher

portion of patients with anxiety and a significantly higher Zung SDS index of depression in patients with SBD-EDS than in the group with NA. This connection of SBD and mood disorders may be linked to obesity, hypertension, and decreased quality of life in patients with sleep apnea (Hobzova *et al.* 2017). It is known, that sleep apnea has serious comorbidities, especially metabolic syndrome with diabetes mellitus type 2, hypercholesterolemia, hypertension, and obesity, which is also a risk factor for sleep apnea (Jehan *et al.* 2017). According to the previous studies, also the patients with NA have changes in basal metabolism with a risk of diabetes mellitus type 2 and higher BMI than the healthy population. It may be caused by altered eating behavior linked to a deficiency of hypocretins, or it may arise from the disease-related reduced physical activity (Schuld *et al.* 2000). In our study, patients with NA had a BMI of 25.78 ± 5.69 kg/m^2, which was significantly lower compared to the patients with SBD-EDS, where BMI was 33.59 ± 6.73 kg/m^2 (p <0.001). Balcan *et al.* in the multivariate analysis showed, that depressive mood was significantly associated with female sex, BMI, and ESS (Balcan *et al.* 2019). These facts support a possible connection between obesity and depression in patients with sleep apnea. However, we failed to find any correlation between BMI and mood disorders.

The quality of sleep measured by PSQI indicated "poor" sleep in both groups of patients and it was the only factor, that significantly correlated with the measures of anxiety and depression in patients with NA. In patients with SBD-EDS, also significant correlations of depression measures with age, ODI, and sleepiness were found. According to our results, quality of sleep is probably the most important factor influencing the mood in patients with hypersomnolence of different etiology.

Evaluation of hypersomnolence and comorbid mood disorders may be challenging. EDS is a frequent symptom in patients with anxiety or depression. EDS may be induced by medication or sleep apnea. There is a higher prevalence of obstructive sleep apnea in patients with depression or posttraumatic stress disorder. Less attention is focused on anxiety, schizophrenia, or psychotic disorders (Fortuyn *et al.* 2010). Evaluation of depression in patients with central hypersomnia may be difficult because of the overlap of symptoms of both disorders (Nanthakumar *et al.* 2016; Lopez *et al.* 2017). Symptoms of depression may interfere with clinical signs of central hypersomnia (like narcolepsy), as well as secondary hypersomnia due to SBD. Correct diagnosis and differentiation of signs of hypersomnolence due to depression or as a part of hypersomnia is challenging and requires a whole diagnostic procedure (medical history, questionnaires, revision of medication, psychiatrical and neurological evaluation, overnight polysomnography, multiple sleep latency test) (Barateau *et al.* 2017).

Our study has several limitations. Both patients with NT1 and NT2 are presented together in the group of patients with NA as central hypersomnia. However, there is probably different pathophysiology of hypersomnolence in these patients. Deficiency of orexin metabolism, which is probably linked to depression in patients with NT1, cannot be the only reason for mood disorders in this group of patients. The main limitations of our study are significant differences of NA and SBD-EDS subjects in some general baseline characteristics (including age, sex, BMI, and ESS), which limits the interpretation of our findings. On the other hand, it is necessary to highlight, that subjects in our study represent the "real-life" patients with NA and SBD-EDS at the time when the diagnosis was newly established. It is also necessary to mention that none of these parameters correlated with measures of anxiety in both groups and with the measures of depression in the NA group. Measures of depression in SBD-EDS significantly negatively correlated with age though it is known, that depression is a common disorder in later life with negative health outcomes over time (Almeida 2014).

CONCLUSIONS

According to our results, there is a high frequency of mood disorders in patients with central hypersomnias, but it is even higher in patients with EDS due to sleep apnea. Quality of sleep measured by PSQI was the common factor associated with the measures of both anxiety and depression in patients with EDS independently of the etiology of EDS. Patients with EDS should not be overlooked and a whole diagnostic procedure should be done to evaluate not only the etiology of hypersomnolence but also the presence of mood disorders. Consecutive proper management of reasons of hypersomnolence, including sleep-disordered breathing, could improve the quality of life of these patients.

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COMPLIANCE WITH ETHICAL STANDARDS

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Conflict of Interest

All authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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