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Sleep-disordered breathing and excessive daytime sleepiness in patients with epilepsy – a polysomnographic study

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Abstract

OBJECTIVES: Epilepsy and sleep-disordered breathing (SDB) are relatively common disorders. SDB induces repetitive arousals and sleep fragmentation and may cause symptomatic epileptic seizures or hypoxic encephalopathy. Epileptic seizures change sleep architecture with increase of light sleep and reduction of REM sleep, which may lead to central apneas. The aim of this study was to evaluate the relationship between SDB and daytime sleepiness in patients with epilepsy, who underwent polysomnography (PSG) due to problems with breathing during sleep or due to excessive daytime sleepiness.

METHODS: We enrolled 40 patients with epilepsy. Type, etiology of epilepsy and actual antiepileptic therapy was recorded. All of them underwent overnight PSG. Excessive daytime sleepiness (EDS) was assessed by Epworth Sleepiness Scale (ESS).

RESULTS: SDB (apnea-hypopnea index [AHI]<5) was present in 25 patients, 15 patients had no SDB (AHI≥5). EDS was present in 16 patients (40%). ESS significantly correlated with presence of symptomatic epilepsy (r=0.385, p=0.014), presence of SDB (r=0.524, p=0.001), AHI (r=0.416, p=0.003) and duration of REM sleep (r=–0.476, p=0.002). The presence of SDB (beta=0.447, p=0.002) and duration of REM sleep (beta=–0.308, p=0.029) were the only independent variables significantly associated with ESS in regression analysis.

CONCLUSION: SDB has negative influence on quality of sleep and daytime vigility in patients with epilepsy. Sleep fragmentation with the reduction of the REM sleep seems to be the most important mechanism leading to EDS. We suppose that PSG could be beneficial in all patients with epilepsy and EDS.

Abbreviations:

AHI	- apnea-hypopnea index
AI	- arousal index
BiPAP	- bilevel positive airway pressure
BMI	- body mass index
CPAP	- continuous positive airway pressure
EDS	- excessive daytime sleepiness
ESS	- Epworth Sleepiness Scale
NREM	- non-rapid eye movement
ODI	- desaturation index
OSA	- obstructive sleep apnea
PSG	- polysomnography
REM	- rapid eye movement
SDB	- sleep-disordered breathing
TST	- total sleep time

ORIGINAL ARTICLE

INTRODUCTION

Both, epilepsy and sleep-disordered breathing (SDB) are relatively common disorders. Their comorbidity has negative influence on both conditions and is more frequent than expected (Teran-Santos *et al.* 1999; Höllinger *et al.* 2006). SDB is present in 24% of men and in 9% of women (Young *et al.* 1993). Epilepsy is also a common condition with prevalence 0.5–1% of general population (Wallace *et al.* 1998). About 5% of patients with SDB have also epilepsy (Höllinger *et al.* 2006). SDB with repetitive episodes of hypoxia and hypercapnia may induce frequent microarousals and lead to fragmentation of sleep, chronic sleep deprivation, excessive daytime sleepiness (EDS) and increase of epileptic seizures in patients with epilepsy (Bateman *et al.* 2008). SDB has negative influence on epilepsy and may lead to cumulation of epileptic seizures. According to literature, one third of patients with refractory epilepsy has mild sleep apnea syndrome with five and more apneas/hypopneas per hour. Repetitive apneas with oxygen desaturation during sleep can also lead to encephalopathy with symptomatic epilepsy (Malow *et al.* 2000).

On the other hand, epileptic seizures may change the sleep architecture, lead to increase of light sleep and reduction of REM sleep, and negatively influence regulation of breathing during sleep as well (Bazil *et al.* 2000). Patients with epilepsy often complain of bad quality of sleep and daytime sleepiness. Daytime sleepiness leads to napping, that also rises the risk of epileptic seizures. SDB in patients with epilepsy can be aggravated by antiepileptic therapy (benzodiazepines can lead to relaxation of upper airways, valproate can worsen SDB by weight gain) (Ebben *et al.* 2008; Joutsa *et al.* 2015). The aim of this study was to evaluate the relationship between daytime sleepiness and SDB in patients with epilepsy, who underwent polysomnography (PSG) due to problems with breathing during sleep or due to EDS.

METHODS

The study population consisted of 40 patients with epilepsy, who were examined in Sleep laboratory of the 1st Department of Neurology, Bratislava, Slovakia for suspected SDB, or EDS. Type, etiology of epilepsy, as well as actual antiepileptic therapy was recorded on admission. Only the patients without a history of epileptic seizure during the month prior to enrollment were included. Excessive daytime sleepiness (EDS) was assessed by Epworth Sleepiness Scale (ESS) (Johns 1991). ESS ≥10 was considered as EDS. All patients underwent standard overnight video-polysomnography (PSG) using Alice 5 device (Philips Respironics, Netherland). Sleep parameters and respiratory events were recorded and scored according to The American Association of Sleep Medicine Manual for the Scoring of Sleep and Associated Events (Iber *et al.* 2007). Parameters of sleep architecture and respiration during sleep were assessed. Apnea-hypopnea index (AHI), arousal index (AI), desaturation index (ODI) as well as duration of N1,N2,N3 NREM and REM sleep (as proportion of total sleep time [TST]) were recorded. Apnea was defined as the cessation of the reduction of airflow of ≥90% for >10 seconds and hypopnea as a reduction of airflow ≥50% for 10 seconds with oxygen desaturation of >3%. The statistical analyses were performed using SPSS version 18 (SPSS Inc., USA). Categorical variables were expressed as numbers and proportions (%), continuous variables as means ± standard deviation or median, interquartile range, minimal and maximal values. Chi-squared test, Student t test and Mann–Whitney test were used for group comparison. Pearson or Spearman correlation coefficients were used to determine the relationships between particular study characteristics. Stepwise multiple linear regression analysis was used to identify factors that contributed to ESS. A p-values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of two groups (epileptic patients with SDB and without SBD) are shown in Table 1. Sleep disordered breathing (AHI≥5) was diagnosed in 25 patients (62.5%). In this group, 7 patients (28%) had central sleep apnea, 4 patients (16%) had mild obstructive sleep apnea (OSA) with AHI 5–15, 8 patients (32%) had moderate OSA (AHI 15–30) and 6 patients (24%) had severe OSA (AHI over 30). The group without SDB (AHI<5) consisted of 15 patients (37.5%). Patients with SDB, compared to patients without SDB, were significantly older (52.5±12.8 years vs. 36±8.8 years, p=0.006), had significantly higher body mass index (BMI) (31±18.6 kg/m^2 vs. 25.7±15.8 kg/m^2, p=0.03), significantly higher proportion of symptomatic epilepsy (60% vs. 20%, p=0.015), significantly higher ESS (9.8±4.3 vs. 5.6±2.5, p<0.001, see Figure 1) and had significantly higher proportion of EDS (52% vs. 20%, p=0.046). Sleep fragmentation measured by AI was significantly higher in the group of epileptic patients with SDB than in the group without SDB (18.9±7.9/h vs. 5.9±3.6/h, p=0.001). Significant differences were found also in sleep architecture. Patients with SDB had significantly higher proportion of N1 NREM sleep (35.2±18.5% vs. 20.4±17.1%, p=0.009) and significantly lower proportion of N3 NREM sleep (27.1±14.6% vs. 38.8±22.3%, p=0.02). Patients with SDB had also lower proportion of REM sleep, but this difference was not statistically significant.

We found, that ESS significantly correlated with the presence of idiopathic epilepsy (r=–0.385, p=0.014), presence of symptomatic epilepsy (r=0.385, p=0.014), presence of SDB (r=0.524, p=0.001), AHI (r=0.416, p=0.003) and duration of REM sleep (r=–0.476, p=0.002) (see Table 2). Presence of SDB (beta=0.447, p=0.002) and duration of REM sleep (beta=–0.308, p=0.029) were the only independent variables signifi-

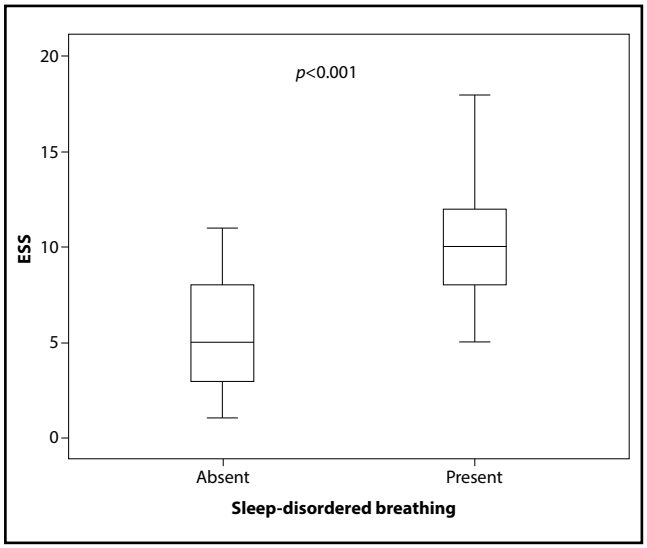

Fig. 1. Daytime sleepiness according to Epworth Sleepiness Scale (ESS) in patients with epilepsy with presence and absence of sleep-disordered breathing.

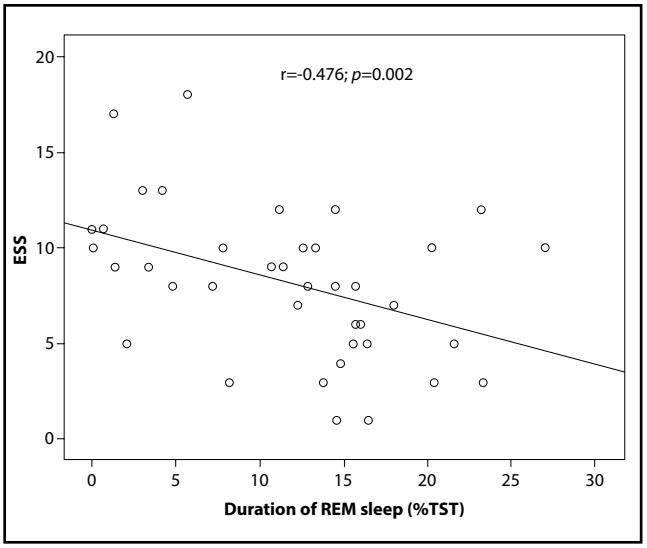

Fig. 2. Association of Epworth Sleepiness Scale (ESS) with the duration of REM sleep.

Tab. 1. Baseline characteristics of study population.

	SDB (AHI≥5)	No SDB (AHI<5)	*p*-value
Number of patients	25	15	
Males/females	15/10	5/10	0.102
Age (year)	52.5±12.8	36±8.8	0.006**
Epworth sleepiness scale	9.8±4.3	5.6±2.5	<0.001***
Excessive daytime sleepiness	13	3	0.046*
Body mass index (kg/m^2)	31±18.6	25.7±15.8	0.03*
Type of epilepsy (focal/generalized)	12/13	10/5	0.251
Type of epilepsy (idiopathic/symptomatic)	10/15	12/3	0.015*
Type of epilepsy (nighttime/daytime)	14/11	8/7	0.870
Number of antiepileptic drugs	3	1	0.586
Monotherapy	12	9	0.462
Two antiepileptic drugs	7	3	0.572
Three antiepileptic drugs	3	2	0.902
Carbazepine	7	3	0.572
Valproate	9	3	0.285
Levetiracetam	10	5	0.673
Pregabaline	2	2	0.586
Zonisamide	0	1	NA
Oxcarbazepine	2	0	NA
Lacosamide	1	0	NA
Gabapentine	1	0	NA
Arousal index	18.9±7.9	5.9±3.6	0.001**
N1sleep (% of TST)	35.2±18.5	20.4±17.1	0.009**
N2 sleep (% of TST)	27.5±16.3	26.7±16.6	0.798
N3 sleep (% of TST)	27.1±14.6	38.8±22.3	0.021*
REM sleep (% of TST)	10.1±5.3	14.1±9.6	0.09

SDB: sleep-disordered breathing, TST: total sleep time, *p<0.05, **p<0.01, ***p<0.001, NA: not available

cantly associated with ESS in stepwise multiple linear regression analysis (see Figure 2).

DISCUSSION

EDS and sleep disorders are frequently reported by patients with epilepsy. Prevalence of subjective sleep disturbances is two times higher in patients with partial epilepsy than in controls and is associated with impaired quality of life (De Haas *et al.* 2002; Del-Rosso *et al.* 2016). There are several possible reasons for EDS and disrupted sleep in patients with epilepsy. They include insufficient sleep due to inadequate sleep hygiene, coincidence of sleep disorders, effect of epileptic seizures, antiepileptic medication or pathology underlying epilepsy (symptomatic epilepsy).

In patients with epilepsy, coincidence of primary sleep disorders is quite common (Im *et al.* 2016). Several studies used PSG to diagnose sleep disorders in patients with epilepsy. Sleep apnea was found in 44% to 71% of patients, who underwent PSG (Malow *et al.* 1997b; Beran *et al.* 1999) We diagnosed SDB in 62.5% of 40 patients with epilepsy, but our patients were referred due to some problems with breathing while sleeping or due to EDS, so the prevalence in common population of patients with epilepsy could be lower.

Although ESS in our study significantly correlated with the presence of symptomatic epilepsy (r=0.385,

Tab. 2. Correlations of Epworth Sleepiness Scale with the baseline characteristics of the population.

	R	*p*-value
Age	0.173	0.286
Female sex	–0.133	0.414
Body mass index	0.244	0.130
Focal epilepsy	–0.011	0.947
Generalized epilepsy	0.011	0.947
Symptomatic epilepsy	0.385	0.014*
Idiopathic epilepsy	–0.385	0.014*
Nighttime epilepsy	–0.304	0.056
Daytime epilepsy	0.304	0.056
Number of antiepileptic drugs	0.017	0.916
Carbazepine	–0.07	0.965
Valproate	0.007	0.965
Levetiracetam	0.031	0.847
Pregabaline	–0.16	0.325
Zonisamide	0.167	0.302
Oxcarbazepine	–0.005	0.976
Lacosamide	0.105	0.521
Gabapentine	0.258	0.108
Presence of SDB	0.524	0.001**
Apnea-hypopnea index	0.416	0.003**
Desaturation index	0.309	0.052
Arousal index	0.1	0.538
N1sleep (% of TST)	0.290	0.07
N2 sleep (% of TST)	–0.110	0.5
N3 sleep (% of TST)	–0.126	0.437
REM sleep (% of TST)	–0.476	0.002**

SDB: sleep-disordered breathing, TST: total sleep time, *p<0.05, **p<0.01

p=0.014), presence of SDB (r=0.524, p=0.001), AHI (r=0.416, p=0.003) and the duration of REM sleep (r=0.–476, p=0.002), presence of SDB (beta=0.447, p=0.002) and duration of REM sleep (beta=–0.308, p=0.029) were the only independent variables significantly associated with ESS in regression analysis. We failed to find any association of EDS with antiepileptic drugs.

It is known that EDS is common in both, epilepsy and SDB. Our results are consistent with previous studies and association of EDS with SDB is well known (Malow *et al.* 1997a). We suppose SDB could be one of the most important predictors of EDS in patients with epilepsy. Physiological architecture of sleep is important for restorative function of sleep and disruption of sleep has negative consequences on daytime vigility. We found significantly higher proportion of N1 sleep and significantly lower proportion of N3 sleep in patients with SDB and epilepsy. These results are similar to findings of our previous studies, where changes of sleep architecture (decrease of N3 sleep and REM sleep) were associated with poor quality of sleep and EDS (Klobucnikova *et al.* 2014; Klobucnikova *et al.* 2009). Sleep fragmentation in patients with epilepsy could be caused not only by SDB, but also by nighttime seizures. No seizure was recorded during PSG in our population. Impact of epileptic seizures could be bigger in patients with decompensation of epilepsy. Our study included only patients without a history of epileptic seizure during the month prior to PSG. On the other hand, it is known, that SDB in patients with epilepsy should be adequately treated to improve seizure frequency in patients with epilepsy (Carreno & Fernandez 2016; Pornsriniyom *et al.* 2014). All patients in our study with AHI over 15 were indicated for noninvasive continuous positive airway pressure (CPAP) or bilevel positive airway pressure therapy (BiPAP). Influence of this therapy on daytime sleepiness and compensation of epilepsy should be evaluated in our next study. In our study, we also found positive correlation between ESS and the presence symptomatic epilepsy. Exact underlying conditions causing symptomatic epilepsy and their association with EDS and SDB should be investigated in future studies.

CONCLUSION

Sleep disorders are common in patients with epilepsy. Despite SDB has negative influence on quality of life, it is often under-diagnosed in patients with epilepsy. Our results suggest, that SDB could be one of the most important predictors of EDS in patients with epilepsy. Sleep fragmentation with the reduction of the REM sleep seems to be the most important mechanism leading to EDS. Screening for sleep apnea could be beneficial in every patient reporting problems with nocturnal breathing or EDS.

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REFERENCES

1 Bateman LM, Li CS, Seyal M (2008). Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. Brain **131**: 3239–3245.
2 Bazil CW, Castro LH, Walczak TS (2000). Reduction of rapid eye movement sleep by diurnal and nocturnal seizures in temporal lobe epilepsy. Arch Neurol **57**: 363–368.
3 Beran RG, Plunkett MJ, Holland GJ (1999). Interface of epilepsy and sleep disorders. Seizure **8**: 97–102.
4 Carreno M, Fernandez S (2016). Sleep-Related Epilepsy. Curr Treat Options Neurol **18**: 23.

5 De Haas S, De Weerd A, Otte A (2002). Epidemiology of sleep disturbance in patients with partial seizures. 5th European congress on epileptology (ECE), p. 6–10.
6 Delrosso LM, Hoque R, Contreras M, Ly NP (2016). A 16-Year-Old Boy with Refractory Epilepsy and Sleep-Disordered Breathing. J Clin Sleep Med **12**: 00109–00116.
7 Ebben MR, Sethi NK, Conte M, Pollak CP, Labar D (2008). Vagus nerve stimulation, sleep apnea, and CPAP titration. J Clin Sleep Med **4**: 471–473.
8 Höllinger P, Khatami R, Gugger M, Hess CW, Bassetti CL (2006). Epilepsy and obstructive sleep apnea. Eur Neurol **55**: 74–79.
9 Iber CAIS, Chesson A, Quan SF. The AASM Manual for the scoring of sleep and associated events: Rules, terminology and technical specification. Westchester, IL: American Academy of Sleep Medicine. 2007.
10 Im HJ, Park SH, Baek SH, Chu MK, Yang KI, Kim WJ, Yun CH (2016). Associations of impaired sleep quality, insomnia, and sleepiness with epilepsy: A questionnaire-based case-control study. Epilepsy Behav **57**: 55–59.
11 Johns MW (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep **14**: 540–545.
12 Joutsa J, Suomela M, Jutila L, Erkinjuntti M, Soilu-Hanninen M, Muller M (2015). [Respiratory disturbance during sleep induced by vagus nerve stimulator]. Duodecim **131**: 1811–1815.
13 Klobucnikova K, Carnicka Z, Wagnerova H, Siarnik P (2014). Is nocturnal epilepsy cause of disturbed quality of sleep and elevated daytime sleepiness? Neuro Endocrinol Lett **35**: 405–410.
14 Klobucnikova K, Kollar B, Martiniskova Z (2009). Daytime sleepiness and changes of sleep architecture in patients with epilepsy. Neuro Endocrinol Lett **30**: 599–603.
15 Malow BA, Bowes RJ, Lin X (1997a). Predictors of sleepiness in epilepsy patients. Sleep **20**: 1105–1110.
16 Malow BA, Fromes GA, Aldrich MS (1997b). Usefulness of polysomnography in epilepsy patients. Neurology **48**: 1389–1394.
17 Malow BA, Levy K, Maturen K, Bowes R (2000). Obstructive sleep apnea is common in medically refractory epilepsy patients. Neurology **55**: 1002–1007.
18 Pornsriniyom D, Kim H, Bena J, Andrews ND, Moul D, Foldvary-Schaefer N (2014). Effect of positive airway pressure therapy on seizure control in patients with epilepsy and obstructive sleep apnea. Epilepsy Behav **37**: 270–5.
19 Teran-Santos J, Jimenez-Gomez A, Cordero-Guevara J (1999). The association between sleep apnea and the risk of traffic accidents. Cooperative Group Burgos-Santander. N Engl J Med **340**: 847–851.
20 Wallace H, Shorvon S, Tallis R (1998). Age-specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy. Lancet **352**: 1970–1973.
21 Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S (1993). The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med **328**: 1230–1235.