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Is nocturnal epilepsy cause of disturbed quality of sleep and elevated daytime sleepiness?

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Abstract

OBJECTIVES: Authors evaluated quality of sleep and daytime vigilance in patients with nocturnal epilepsy and compared it to those with daytime epilepsy.
BACKGROUND: Nocturnal seizures are an important type of epilepsy. They can result in morbidity due to disruption of sleep architecture. Daytime sleepiness, as a serious consequence of nocturnal seizures, has negative influence on quality of life in patients with epilepsy.
METHODS: Authors examined 100 patients with epilepsy. The occurrence of epileptic seizures in circadian rhythm, type of epilepsy and epileptic seizures, as well as aetiology of epilepsy were evaluated. Patients were divided in two groups, 17 patients with nocturnal epilepsy and 83 patients with epileptic seizures not related to sleep. All of them underwent overnight video-EEG-polysomnography and they filled in the Epworth Sleepiness Scale questionnaire (ESS) as well as The Pittsburgh Sleep Quality Index questionnaire (PSQI).
RESULTS: Overnight video-EEG-polysomnography detected significant changes in the sleep architecture in patients with nocturnal epilepsy. We detected significant decrease of N3 stage of NREM sleep (14.31%±8.07 in the group of nocturnal epilepsy vs. 20.12%±9.24 in the group of daytime epilepsy, p=0.01). Concurrently, significantly poorer sleep quality according to PSQI (18.52±7.51 in the group of nocturnal epilepsy vs. 6.21±3.62 in the group of daytime epilepsy, p=0.01) and tendency to increased daytime sleepiness according to ESS was revealed in these patients.
CONCLUSION: Remarkable changes in sleep architecture associated with poor quality of sleep and increased daytime sleepiness were detected in patients with nocturnal epilepsy. In conclusion, we emphasize the importance of sleep history taking in patients with epilepsy and their further evaluation in sleep laboratory.

INTRODUCTION

Relation between sleep and epilepsy has been noticed even in ancient times. Hippocrates described states of apprehension, ferocity and jumps from bed during sleep. Aristotle realized, that epilepsy is often associated with sleep (Passouant *et al.* 1984). Fere in 1890 reported, that 2/3 of all epileptic seizures in 1985 patients with epilepsy occurred between 8.00 pm and 8.00 am (Chokroverty *et al.* 1994; Kollár 2002). Frequency of epileptic seizures increases between midnight

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and early morning and another increase occurs in the evening (Griffiths & Fox 1938). According to these clinical observations, epilepsies are often divided into three types: nocturnal epilepsies, epilepsies connected to awakening and epilepsies without connection with circadian rhythm.

Benign epilepsy with rolandic spikes, benign epilepsy with centrotemporal spikes, acquired aphasia with epilepsy and electric status epilepticus during sleep (Landau-Kleffner syndrome) are typical focal epilepsies strongly associated to sleep. Autosomal dominant nocturnal frontal lobe epilepsy was described by Scheffer in 1994 (Zucconi 2007). It is characterised by clusters of brief frontal nocturnal motor seizures, negative finding on neuroimaging and absence of neurological and mental defects. (Engel & Pedley 1998). The association with chromosome 20q and defect of neuronal nicotine acetylcholine receptor alfa4subunit (CHRNA4) is suggested as a cause of this syndrome (Philips *et al.* 1995). Juvenile myoclonic epilepsy and epilepsy with grand mal on awakening are typical generalised epilepsies linked to sleep (Bazil 2004; Varsik *et al.* 2005). Probably every nocturnal epileptic seizure disrupts sleep architecture with microarousals, or longer wakefulness. Even simple epileptic seizures may result in prolonged alterations of sleep quality in postparoxysmal period. Generalised epileptic seizures have significantly more unfavourable effect on sleep. Some studies have shown improved quality of sleep, when nocturnal seizures were treated correctly (Tachibana *et al.* 1996).

Authors hypothesized that nocturnal epilepsy should have more unfavourable influence on quality of sleep and daytime vigility than epilepsy with no connection to sleep.

METHODS

In this prospective non-randomised cohort study 100 patients a with diagnosis of epilepsy were hospitalized and assessed at the 1st Department of Neurology, University Hospital in Bratislava, Slovakia, between January 2011 and January 2013. There were 38 men and 62 women with average age 34.68±13.55 years, range from 9 to 61 years old. Mean duration of epilepsy was 9.33±7.31 years. All patients underwent standard diagnostic algorithm focused on epilepsy (EEG, EEG after sleep deprivation, 24 hour monitoring of EEG, magnetic resonance of brain, psychological evaluation). Type of epileptic seizure was established according to the criteria of EEG phenomenology and semiology of epileptic seizures (Varsik & Černáček 1997; Brežný *et al.* 2002; Kollár 2013). Patients with nonepileptic or psychogenic seizures were excluded (Kollár & Mikeš 2004; Kollár *et al.* 2008). Only patients with fully compensated epilepsy were evaluated. Compensation of epilepsy was evaluated according to criteria of Epi-Stop 2010 (Brázdil *et al.* 2010). Full compensation according to these criteria is defined as seizure-free period for at least one year. All patients were on antiepileptic therapy. Monotherapy was used in 75 patients (45 patients were treated with carbamazepine, 20 patients with valproate and 10 patients with levetiracetam). Combination of two antiepileptic drugs was used in 21 patients. In this group of patients the most frequently used combination was carbamazepine + valproate (8 patients) and carbamazepine + lamotrigine (6 patients). Combinations of valproate + lamotrigine and carbamazepine + levetiracetam were both used in 3 patients. One patient was treated with combination of valproate + zonisamide. Combination of three antiepileptic drugs was used in 4 patients (there were combinations of carbamazepine, valproate, lamotrigine, levetiracetam, zonisamide and clonazepam).

After obtaining patient´s informed consent, the routine neurological examination was performed. In patient´s history, special attention was paid to the occurrence of epileptic seizures in relation to circadian rhythm. Afterwards, patients were divided into two groups. The first group consisted of 17 patients with only nocturnal epileptic seizures (occurrence of epileptic seizures exclusively between 10.00 pm and 6.00 am). Patients in the second group (83 persons) suffered epileptic seizures only when awake or randomly during whole sleep-wake cycle.

Daytime sleepiness was assessed by the Epworth Sleepiness Scale questionnaire (ESS) (Johns 1991). Value in range 0–8 was considered as normal, score 9–16 indicated increased daytime sleepiness and value >16 was rated as excessive daytime sleepiness (Watanabe *et al.* 2003). The quality of sleep was self-rated by The Pittsburgh Sleep Quality Index (PSQI) questionnaire (Buysse *et al.* 1988).

Sleep pattern was objectively evaluated by whole night video-polysomnography using Alice 5 device (Philips-Respironics, Netherlands). Monitoring of sleep was done during one night in a sleep laboratory between 10.00 pm and 6.00 am.

Video-EEG-polysomnography included eight EEG channels (electrodes F3, F4, C3, C4, T3, T5, O1, O2) placed on patient's head according to international 10–20 system. Next channels registered electrooculogram (EOG) (left and right eye), EMG activity of chin muscles (two electrodes placed on *musculus mentalis*) and both legs (*musculus tibialis anterior*). Synchronously the video of patient´s bed was recorded.

Scoring of sleep stages was done according to The AAMS Manual for the scoring of Sleep and Associated Events (AASM 2007). We evaluated sleep stages of NREM sleep – N1, N2, N3, REM sleep, movement time and number of microarousals, total sleep time (TST in minutes), time in bed (TIB) (in minutes), efficiency of sleep (ratio of TIB and TST in %), proportional representation of sleep stages N1, N2, N3 and REM sleep in %, latency of the first N1 sleep and latency of the first REM sleep stage in minutes.

Results obtained from the group of 17 patients with nocturnal epilepsy were compared with the group

of 83 patients with daytime or random epileptic seizures. The distribution of the data was tested by Lilliefors test (Connover 1999). All values in the paper are given as mean±standard deviation. Student's t-test was used for further statistical analysis of measured parameters (Kirkwood & Sterne 2003). Moreover, non-parametrical statistical tests Kruskal-Wallis and Kolmogorov-Smirnov tests were used (Dušek *et al.* 2009). For graphical presentation of the results box-and-whisker plots graphs were used (Tukey 1977).

RESULTS

Mean score of ESS was 9.18±5.84 in the group of patients with nocturnal epilepsy. This represented increased daytime sleepiness in this group of patients (Table 1). Patients in the second group with daytime or random epileptic seizures had score of ESS 6.69±4.14 (Table 2), which is within physiological range. Although the statistical comparison between the both groups was not statistically significant (p=0.13) (Table 3 and Figure 1), increased daytime sleepiness in the group of patients

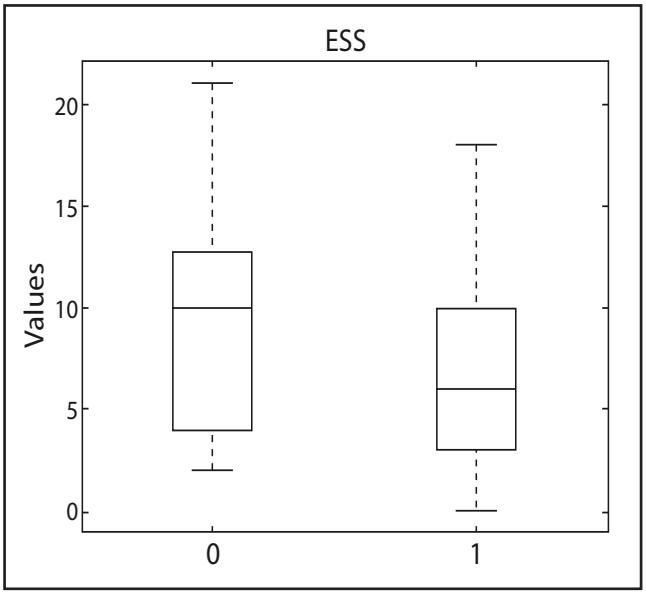

Fig. 1. Score of Epworth sleepiness scale in the group with nocturnal epileptic seizures (0) and daytime or random epileptic seizures (1). The difference is not statistically significant (p=0.13).

Tab. 1. Measured values in the group of patients with nocturnal epileptic seizures.

	patients	mean	SD	Min value	Max value	median	Lilliefors test (p-value)
ESS	17	9.18	5.84	2	21	10	0.16
PSQI	17	18.52	7.51	5	31	17,2	0.19
Eff. of sleep (%)	17	74.76	16.70	38	95	82	0.04
N1 (%)	17	26.91	8.95	15.1	44.7	25.2	0.50
N2 (%)	17	38.98	11.15	15.9	52.5	43.3	0.14
N3 (%)	17	14.31	8.07	0.23	32.7	13.2	0.50
REM (%)	17	19.15	11.80	5.5	54.3	15.7	0.13
Lat. to N1 (min)	17	46.5	45.14	3.5	130.5	18.5	0.003
Lat. to REM (min)	17	155.10	78.01	39	378	154.5	0.18

SD - standard deviation; ESS - The Epworth Sleepiness Scalel PSQI - The Pittsbourgh Sleep Quality Index; Eff. of sleep - efficiency of sleep

Tab. 2. Measured values in the group of patients with daytime or random epileptic seizures.

	patients	Mean	SD	Min value	Max value	median	Lilliefors test (p-value)
ESS	83	6.69	4.14	0	18	6	0.03
PSQI	83	6.21	3.62	1	11	5	0.15
Eff. of sleep (%)	83	77.57	14.77	30	98	80	0.001
N1 (%)	82	21.89	11.58	1.3	48.5	20.25	0.18
N2 (%)	83	38.73	13.21	12.8	68.9	36.4	0.11
N3 (%)	83	20.12	9.24	1.1	43	18.7	0.01
REM (%)	83	18.76	8.48	1.9	42.8	18.6	0.14
Lat. to N1 (min)	83	40.54	63.06	1.5	386.5	21.5	0.001
Lat. to REM (min)	81	164.98	98.24	33	454.5	130.5	0.001

SD - standard deviation; ESS - The Epworth Sleepiness Scalel PSQI - The Pittsbourgh Sleep Quality Index; Eff. of sleep - efficiency of sleep

with nocturnal epilepsy seem to reflect some disturbances of sleep pattern in this group. This anticipated poor quality of sleep was further evaluated by PSQI test. Total score >5 indicates "poor sleepers" and total score <5 indicates "good sleepers" in this test. Patients with nocturnal epilepsy had significantly higher PSQI score (18.52±7.51) than patients with random occurrence of epileptic seizures (6.21±3.62) (see Tables 1 and 2). Statistical comparison showed significant difference in Students t-test (p=0.01) (Table 3).

Consequently, sleep architecture was evaluated in both groups. Efficiency of sleep as well as proportion of N1, N2 and REM sleep were similar in the both groups. However, significant difference in the proportions of delta sleep (N3 NREM sleep) was observed. Patients with nocturnal epilepsy had significantly less delta sleep (14.31%±8.07%) (Table 1) than patients with daytime or random epileptic seizures (20.14%±9.24%) (Table 2), (p=0.01) (Table 3, Figure 2).

Tab. 3. Statistical comparison of evaluated parameters in the group of patients with nocturnal epileptic seizures and in the group of patients with daytime or random epileptic seizures (p-values).

	***p*-value**
ESS	0.13
PSQI	0.01*
Eff. of sleep (%)	0.53
N1 (%)	0.06
N2 (%)	0.94
N3 (%)	0.01*
REM (%)	0.90
Lat. to N1 (min)	0.51
Lat. to REM (min)	0.91

ESS - Epworth Sleepiness Scale
PSQI - The Pittsbourgh Sleep Quality Index
Eff. of sleep - efficiency of sleep

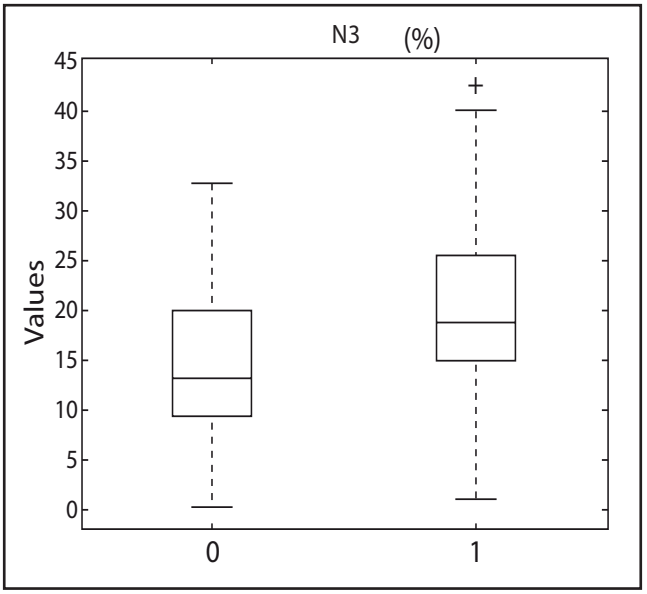

Fig. 2. Portion of N3 NREM sleep in % in the group with nocturnal epileptic seizures (0) and daytime or random epileptic seizures (1). The difference is statistically significant (p=0.01).

DISCUSSION

The aim of this study was to evaluate the relationship between epilepsy and sleep. Previous studies have shown, that patients with epilepsy have significantly lower efficiency of sleep, have more N2 NREM sleep and less REM sleep with prolonged latency to REM sleep in comparison to healthy population (Bazil 2003; Niedermeyer 2002; Sammaritano *et al.* 1991; Touchon *et al.* 1991). These changes might be caused by several factors. The type of epilepsy (focal, generalised), lateralisation of partial epilepsies, the effect of epileptic ictal or interictal activity are known to modulate sleep. Localization of epileptic focal activity may play a role in timing of awakening mechanisms during nocturnal partial seizures (Yildiz *et al.* 2012). Antiepileptic therapy has influence on quality of sleep too. Some authors reported strong effect of medication on daytime vigility and sleep (Bazil *et al.* 2002; Kollár *et al.* 2002). However some authors did not prove any influence of antiepileptic medication on sleep (Klobučníková *et al.* 2009). According to literature, sudden withdrawal of antiepileptic treatment is a risk factor of the occurrence of awake-state epileptic seizures in previously pure sleep epilepsy (Benavente & Javier 2007). Actual compensation of epilepsy has also influence on sleep. Patients with medically refractory epilepsy have markedly disturbed sleep (Zanzmera *et al.* 2012). Coincidence of epilepsy and sleep disorders, like sleep apnea syndrome, may cause excessive daytime sleepiness or induce epileptic seizures (Devinsky *et al.* 1994; Bialasiewicz & Nowak 2009). The type of epilepsy is another factor with strong influence on sleep (Varsik *et al.* 2005). Partial epileptic seizures during sleep have minimal influence on sleep architecture as they do not lead to arousals and fragmentation of sleep. In case of accumulation of partial epileptic seizures or secondary generalization of epileptic seizures, the decomposition of sleep architecture is more relevant (Dasheiff & Kofke 2003). Bazil *et al.* reported, that even daytime epileptic seizures lead to changes of sleep architecture in the period after seizure represented by reduction of REM sleep (Bazil *et al.* 2000).

Only minimal literature sources describe nocturnal epilepsy and it´s effect on the changes of sleep. We have focused our attention on quality of daytime vigility and quality of sleep in these patients. We observed more significant influence of nocturnal epilepsy on sleep structure in comparison with daytime epilepsy. A statistically significant worse self-reported quality of sleep by PSQI and significant reduction of slow-wave N3 NREM sleep in patients with nocturnal epilepsy is very interest-

ing result. We concluded, that these changes were not caused by nocturnal epileptic seizures, as all patients were well compensated on antiepileptic therapy and no epileptic seizure was detected on video during night video-polysomnography. However, the epileptic interictal discharges during sleep or the undetected nocturnal seizures during nights previous to monitored night might be the factors that lead to alteration of sleep pattern in patients with nocturnal epilepsy. This disruption of sleep architecture may have negative impact on restorative functions of sleep followed by daytime drowsiness. Excessive daytime sleepiness was also detected in the group of patients with nocturnal epilepsy. This is in accordance with published case report of patient with nocturnal frontal lobe epilepsy presenting as excessive daytime sleepiness (Cheng *et al.* 2013).

CONCLUSION

As epilepsy is heterogenous disease, the patients with epilepsy require individual and consistent medical management. Special attention should be paid to quality of their life, including quality of sleep. We documented, that patients with nocturnal epilepsy are endangered by insufficient sleep. Potential reason of sleep alteration could be undetected night seizures.

We recommend to focus on quality of sleep during the management of patients with epilepsy. Detailed history taking and application of correct questionnaires are the first steps. In case of daytime sleepiness and sleep problems the correct diagnosis should be established in sleep laboratory with video-EEG-polysomnography. Adequate antiepileptic therapy (changes in antiepileptic therapy in case of nocturnal epileptic seizures or interictal discharges) or management of other sleep disorder, for example sleep apnea syndrome, should lead to the improvement of general conditions of these patients.

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