Daytime sleepiness and changes of sleep architecture in patients with epilepsy

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Abstract

OBJECTIVE: The relationship between epilepsy and sleep has been known for many years. Yet is still not well understood because of it's reciprocal and intrinsic influences. Epileptic manifestations during sleep may lead to fragmentation of sleep stages. On the other hand insomnia or other sleep disorders may cause sleep deprivation and increase number of epileptic seizures in patients with epilepsy. The study is designed to compare daytime sleepiness and architecture of sleep in patients with epilepsy and control subjects. We tried to evaluate factors that have influence on sleep architecture of patients with epilepsy.

METHODS: We evaluated the daytime sleepiness through a certain type of questionnaire called Epworth Scale of Sleepiness (ESS). The questionnaire was filled out by patients with epilepsy (83 patients) and a group of healthy controls (80 persons). Furthermore we evaluated the quatity of night sleep in both groups using polysomnograph (electroencephalography – EEG, electrooculography – EOG, electromyography – EMG). Sleep stages were scored according to Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects (Rechtschaffen, Kales, 9). Multiple sleep latency test (MSLT) was performed in the group of patients with epilepsy in order to objectivise daytime sleepiness.

RESULTS: Measuring by Epworth scale of sleepiness we found out that the patients with epilepsy suffered from a significantly higher daytime sleepiness than the healthy controls. Patients with epilepsy also experienced significant changes in sleep architecture, the reduction of NREM S3, S4 and REM stages and the increase of NREM S2 stage. These changes were not related to used antiepileptic medication.

ORIGINAL ARTICLE

1. INTRODUCTION

Many patients with epilepsy suffer from a daytime sleepiness or an insufficient sleep. Patients with epilepsy usually encounter with elevated occurence of sleep disorders, which have serious consequences (Bazil, 2003). Fragmentantion of sleep by nocturnal epileptic seizures or sleep disorders may induce sleep deprivation, whitch may elevate number of epileptic seizures. Yet disorders of daytime vigilance and sleep pathologies in patients with epilepsy are often overlooked.

The aim of this study was to evaluate daytime sleepiness and changes of sleep architecture in

patients with epilepsy and compare these changes with a group of healthy controls. We wanted to ascertain, if these changes corelate with parallel antiepileptic therapy.

2. METHODS

We examined 83 patients with the diagnose of epilepsy. They were followed up on the 1st Department of Neurology of Medical Faculty since January 2006 to January 2009 for diagnostic or therapeutic reasons. There were 40 men and 43 women with average age 34.3±11.1 years. The youngest patient was 9 years old and the oldest one was 61 years old. The average duration of epilepsy was 11.1 ± 10.0 years, in interval 0–47 years.

According to the International Classification of Epileptic Seizures (1989) patients were divided into two big gropus with focal and generalized epileptic seizures. First group of 65 patients had focal epileptic seizures (5 patients simplex partial epileptic seizures, 48 patients complex partial seizures and 12 patients partial epileptic seizures with secondary generalization). The next group of 18 patient sufferred of generalized epileptic seizures (2 patients with absences, 1 patient with myoclonic seizures and 15 patients with generalised tonic-clonic epileptic seizures).

According to the International Classification of Epilepsy and Epileptic Syndromes (1989) 65 patients were determined as focal epilepsy (41 patients with focal symptomatic epilepsy and 24 patients with focal cryptogenic epilepsy). The second group of 18 patients with generalised epilepsy consisted of 10 patients with idiopathic generalized epilepsy and 6 patients with symptomatic generalized epilepsy (Figure 1).

There were 80 persons in the control group, 35 men and 45 women. These healthy controls have never suffered from epilepsy or any other seizure disease. Average age was 38.8 ±14.3 years (range 17–78 years).

All patients were treated with antiepileptic drugs. Monotherapy had 47 patients (56.6%), 24 patients (28.9%) had two antiepileptic grugs and 12 patients (14.5%) were treated by combination of three or four antiepileptic drugs. We analysed monotherapy of antepileptic medication. The most frequently used monotherapy was carbamazepine in 24 patients (51% of patients on monotherapy). Valproate was used by 10 patients (21% of patients on monotherapy), also lamotrigine was used by 10 patients. One patient was treated by primidon (2.1% of patients on monotherapy), one by levetiracetam (2.1% of patients on monotherapy), and one by clonazepam (2.1% of patients on monotherapy).

Combination of two antiepileptic drugs used 24 patients with epilepsy. The most frequent combination was carbamazepine/valproate used by 6 patients. Another combination valproate/lamotrigine was used by 5 patients. Next combinations are in Table 1.

Combination of three antiepileptic drugs was used by 11 patients. Only one patient was treated by four antiepileptic drugs. The most often was used the combination of carbamazepine, valproate and lamotrigone in 7 patients. Next combinations are in Table 2.

2.1. Methods used to examine daytime sleepiness

In both groups (patients with epilepsy and healthy controls) we used a questionnaire known as Epworth Scale of Sleepiness (ESS) (Johns, 1991). It is widely used selfevaluating method. By answering certain questions about probability of falling asleep in standard situations we come to the result, i.e. score of daytime sleepiness ranging from 0 to 24. Rate 0–9 is considered as normal value, above 9 as elevated daytime sleepiness and value above 16 is considered as remarkably elevated daytime sleepiness.

In order to objectivise the daytime sleepiness we also used another method called Multiple Sleep Latency Test (MSLT) (Carscadon and Dement, 1982). The latency of sleep was measured in five 20 minute polysomnographic registrations in this test. Between the registrations the patient should be awake (Usui *et al.* 2008). Mean latency of sleep shorter than 6 minutes was considered as indicative of elevated sleepiness (American sleep disorders association, 1992). This method was used only in the group of patients with epilepsy.

2.2. Methods used to register sleep architecture

Nocturnal polysomnografy was used in the both groups to evaluate quality of sleep. We used program Brain Quick System 98 for polysomnography. Scoring

Tab. 1. Combinations of two antiepileptic drugs used in the group of patients with epilepsy.

Carbamazepine	+	+	+	+	+	+	+	+	+	+	+	+	+										
Valproate	+	+	+	+	+	+								+	+	+	+	+	+	+	+		
Lamotrigine							+	+						+	+	+	+	+				+	+	
Topiramate									+	+									+	+		+	+	+
Levetiracetam											+										+			
Zonisamid																								+
Gabapentin												+												
Pregabalin													+											

Tab. 2. Combinations of three or four antiepileptic drugs used in the group of patients with epilepsy.

Carbamazepine	+	+	+	+	+	+	+	+	+	+	+	+
Valproate	+	+	+	+	+	+	+	+	+	+	+	
Lamotrigine	+	+	+	+	+	+	+					+
Topiramate										+		+
Levetiracetam											+	
Clonazepam								+	+			
Benzodiaz.												+

of sleep stages was done with Sleep View Rembrandt Sleep Analysis Program.

Registration and scoring of sleep stages was done according to criteria of Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects (Usui *et al.* 2008). We used four electrodes (T3,C3,T4,C4) in EEG registration. When topographical localization of epileptiform discharges was needed, we used 19 EEG electrodes located according to international system 10–20.

The result of sleep analysis was hypnogram, amount of sleep stages (NREM S1, NREM S2, NREM S3–S4, REM) in %, total sleep time in minutes and efficiency of sleep in %.

For purpose of registration of different abnormal movement manifestations (epilepsy, REM behavior diseases etc.), a video was recorded simultaneously with polysomnography.

3. Statistical analysis

The normality of distribution of data was analyzed by Lilliefors test. The results were compared with Student´s t-test for normally distributed data. Significance of differences between the groups was set at the level of $p<0.05$ (Kirkwood and Sterne, 2003).

4. RESULTS

4.1. Changes in daytime sleepiness

Mean value of Epworth Scale of Sleepiness (ESS) in patients with epilepsy was 7.1 ± 4.4 which is in physiological range. We divided this group into three categories according to score of ESS. The value of ESS below 9 (physiological value) was registered in 52 patients (62.7% of all patients). Moderate daytime sleepiness (ESS 9–16) occurred in 29 patients, (34.9%). Seriously elevated daytime sleepiness, ESS above 16, had 3 patients, i.e. 2.4% of all patients. These results show, that 37.3% of patients with epilepsy have a mild or serious daytime sleepiness (ESS above 9).

Mean value of ESS in the control group was 5.5 ± 2.1. In the category ESS <9 with not elevated daytime sleepiness were 71 persons (88.8% of controls). Moderate daytime sleepiness with ESS in range 9–16 had 9 per-

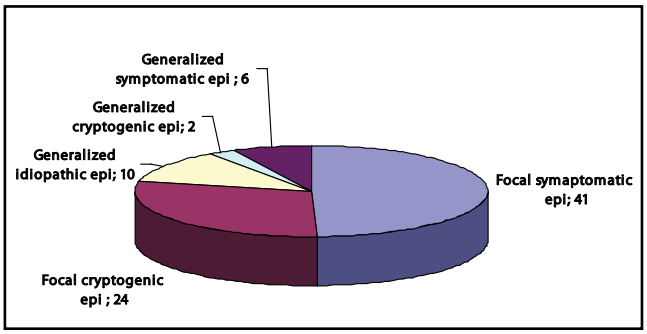

Fig. 1. Amount of patients according to the type of epilepsy.

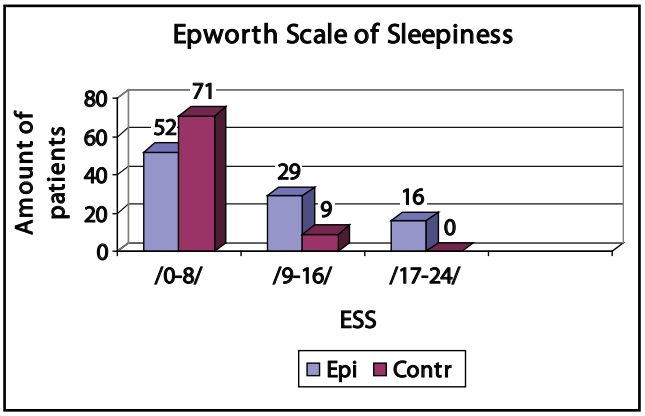

Fig. 2. Number of patients and controls in three divisions according to value of Epworth Scale of Sleepiness (ESS).

Tab. 3. Distribution of epiletic patients and controls in % according to the Epworth Scale of Sleepiness (ESS) score (<9 /9–16/ >16) and mean score of ESS in both groups.

	ESS <**9 / 9–16 /** >**16** (%)	**ESS** (mean value ± SD)
Epileptic patients	62.7% / 34.9% / 2.4%	7.1± 4.4
Control group	88.8% / 11.2% / 0%	5.5± 2.1
		p=0.005

sons (11.2%). There were no persons with ESS >16. (See Figure 2, Table 3.)

Our results show, that both patients with epilepsy and controls had mean score of ESS in physiological range with higher value in the group of patients with epilepsy. This difference was statistically significant on significance level of p=0.005. (See Table 3).

4.2. Changes in night sleep

Architecture of night sleep was different between patients with epilepsy and control group. Patients with epilepsy have had significantly more NREM S2 stage, less NREM S3 and S4 stages and less REM sleep than controls. All these changes were statistically significant. There was no significant difference according to parts of NREM S1 sleep stage between both groups. Patients with epilepsy have had significantly decreased efficiency of sleep in comparison with control group . This difference was statistically significant (p<0.001). (See Table 4).

Tab. 4. Sleep architecture in the group of patients with epilepsy and in the control group.

	Pacients with epilepsy	Control group	*p*
ESS (score ± SD)	7.1 ± 4.4	5.5 ± 2.1	0.005
S1 NREM (% ± SD)	28.8 ± 17.9	26.4 ± 12.6	0.3
S2 NREM (% ± SD)	37.8 ± 14.1	29.4 ± 10.1	<0.001
S3 + S4 NREM (% ± SD)	17.5 ± 10.4	21.0 ± 9.3	<0.001
REM (% ± SD)	15.4 ± 10.5	23.0 ± 9.9	<0.001
Efficiency of sleep (% ± SD)	76.6 ± 15.5	87.4 ± 9.9	<0.001

ESS – Epworth Scale of Sleepiness, S1 NREM – 1st stage of NREM sleep, S2 NREM – 2nd stage of NREM sleep, S3 + S4 NREM – 3rd and 4th stage of NREM sleep.

Tab. 5. Influence of antiepileptic therapy on daytime sleepiness and sleep architecture.

	Monotherapy	Two and more antiepileptic drugs	*p*
ESS (score ± SD)	6.7 ± 4.2	7.6 ± 4.7	0.35
MSLT (minutes ± SD)	13.3 ± 4.7	13.7 ± 5.0	0.78
S1 NREM (% ± SD)	31.1 ± 21.3	26.0 ± 12.5	0.17
S2 NREM (% ± SD)	35.7 ± 15.0	40.3 ± 12.2	0.14
S3 + S4 NREM (% ± SD)	16.4 ± 10.3	18.9 ± 10.4	0.27
REM (% ± SD)	16.4 ± 12.0	14.1 ± 8.4	0.32
Efficiency of sleep (% ± SD)	75.4 ± 15.8	78.0 ± 15.2	0.45

4.3. Influence of antiepileptic therapy on daytime sleepiness and architecture of sleep

All patients in the group of epileptic patients had undergone an antiepileptic therapy. We divided this group in two divisions according to number of antiepileptic drugs. In the first group were 47 patients with the monotherapy. In the second group were 36 patients with the combination of two or more antiepileptic drugs. We observed that the both groups revaled normal mean value of ESS, though patients with higher amount of antiepileptics had mildly elevated daytime sleepiness (ESS 7.6 ± 4.7 against ESS 6.7 ± 4.2). This difference was not statistically significant (p=0.35). Mean latency of sleep (measured in minutes) in Multiple Sleep Latency Test (MSLT) was identical in the groups. There were also no significant differences in sleep stages of NREM and REM sleep and efficiency of sleep between these two groups. (See Table 5)

5. DISCUSSION

Sleep is an active stage of brain. This is essential for restorative functions of brain. It is known that epilepsy causes alteration of sleep organization of NREM and REM stages (Moráň, 2005; Nešpor, 2007). Our results of a statistically significant changes in sleep architecture together with decreased sleep efficiency in patients with epilepsy are in agreement with these informations. Watanabe *et al*. published that both the epileptic patients and the healthy controls have physiological value of Epworth Scale of Sleepiness (Watanabe *et al.* 2003). Our results are concodrant with this analysis, although our patients with epilepsy have significantly higher value of ESS still in interval of normal daytime vigility. We suppose that changes in daytime vigility are tightly coupled with quality of night sleep.

Antiepileptic drugs can have both beneficial or negative influence on sleep. By seizure suppression or reduction of interictal epileptiform discharges during sleep antiepileptic drugs can stabilize night sleep. On the other side antiepileptic drugs can have negative effects on sleep, which are independent to those involved in seizure control (Bazil, 2003). Carbamazepine, for example, elongates NREM S3 and S4 sleep (Placidi *et al.* 2000) while valproate extends awakening (Moráň, 2005). It might be expected that application of higher amount of antiepileptic drugs would elevate their negative effect on daytime sleepiness and quality of sleep. Suprisingly, this hypothesis has not been proved in the present study.

6. CONCLUSION

We have proved significant changes in the architecture of night sleep in patients with epilepsy. Reduction of sleep stages NREM 3, NREM 4 and REM sleep and increase of NREM 2 stage in the evaluated group of patients with epilepsy may negatively influence the restorative functions of sleep. This may be connected

with elevated daytime sleepiness of patients with epilepsy seen in our group of patients.

There are probably complex reasons of these changes, like nocturnal epileptic seizures, interictal epileptiform discharges or epilepsy by itself. We did not prove the influence of antiepileptic drugs on quality of night sleep and daytime sleepiness. The further evaluation of factors influencing quality of sleep of patients with epilepsy should be done.

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