Sleep Quality and Daytime Sleepiness in Patients with Epilepsy

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Abstract-

Purpose: Poor sleep quality and excessive daytime sleepiness (EDS) are common complaints of patients with epilepsy (PWE). This study aimed to evaluate possible predisposing factors for EDS and subjective sleep quality in PWE.

Methods: One hundred and seventeen PWE were enrolled and 30 healthy volunteers were recruited as controls. EDS was evaluated by the Epworth Sleepiness Scale (ESS) while the Pittsburg Sleep Quality Index (PSQI) was designed to evaluate overall sleep quality. Clinical baseline data and possible risk factors for sleep disturbances were included in the statistical analysis.

Results: Twenty percent of PWE (23/117) and 7% of healthy controls (2/30) had excessive daytime sleepiness (p = 0.007). PWE had significantly higher PSQI total scores (6.5 ± 3.8 vs. 3.7 ± 2.9), sleep latency (1.2 ± 0.8 vs. 0.6 ± 0.7) and sleep efficiency (0.8 ± 1.0 vs. 0.0 ± 0.2) scores than the controls (all $p < 0.001$). A significantly higher prevalence of poor sleep quality was found in the partial seizure, non-seizure-free, and polytherapy groups (all $p < 0.05$). Multivariate analysis showed that poor seizure control was the strongest independent risk factor for poor sleep quality (OR = 2.43, 95% CI = 1.15-5.15, p = 0.02).

Conclusion: EDS and poor sleep quality are common in PWE and are closely related to partial epilepsy, poor seizure control, and polytherapy. These relationships must be addressed in order to provide the best management of sleep disturbance in such patients.

Key Words: epilepsy, sleep quality, excessive daytime sleepiness, Epworth Sleepiness Scale, Pittsburg sleep quality index

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INTRODUCTION

Sleep disorder is a common clinical complaint of patients with epilepsy (PWE), regardless of age. It can have a major impact on quality of life[1,2], and several studies have confirmed that both daytime sleepiness and poor sleep quality are common complaints[1,2]. The prevalence of excessive daytime sleepiness (EDS) in PWE is as high as 16.9%, whereas that of insomnia is 24.6%[2]. Some studies indicate that predisposing factors

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to EDS in such patients include frequency of seizures, use of antiepileptic drugs (AEDs), and seizure types[3-7]. However, there is still no consensus regarding the relationship between sleep quality, EDS, and epilepsy[3,8,9].

The Epworth Sleepiness Scale (ESS) and Pittsburg sleep quality index (PSQI) are two questionnaires commonly used in the clinical measurement of EDS and sleep quality[10]. ESS[11] is a standardized scale for measuring sleepiness that is frequently used to evaluate EDS in PWE[12,13]. PSQI is a questionnaire designed to evaluate overall sleep quality, including sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, medication use, and daytime dysfunction[10,14]. The present study uses both ESS and PSQI to investigate predisposing factors for EDS and subjective sleep quality in PWE.

METHODS

Subjects

This single-center, case-control study enrolled 117 PWE aged 16-63 years, who were seen at the Epilepsy Outpatient Clinic of Chang Gung Memorial Hospital-Kaohsiung, a medical center and main referral hospital serving an area of 3 million inhabitants in southern Taiwan. Thirty healthy volunteers aged 18-59 years who received an annual physical check-up were recruited as controls.

The exclusion criteria included known mental retardation (IQ < 60), psychiatric comorbidities, pre-existing medical diseases (including hypertension, diabetes mellitus, stroke, heart diseases, chronic obstructive pulmonary disease, and sleep disorders), night work, and shift work. Patients who received medication that could affect sleep, like stimulants, antidepressants, antipsychotic drugs, phenobarbital, and benzodiazepines, were also excluded. The hospital's Institutional Review Committee on Human Research approved the study.

Clinical assessment and sleep questionnaires

The clinical records of the epilepsy patients were reviewed, and the age of onset, type of seizure, duration of epilepsy, seizure control, etiology of seizure, associated medical diseases, and current antiepileptic drugs (AEDs) were recorded. Seizure-free status was defined as no seizure attacks for at least 12 months under current AED therapy[15].

The subjects were asked to complete the Chinese versions of ESS and PSQI[16,17]. The Chinese versions of PSQI and ESS used in this study were authorized by the original authors. The ESS was designed to evaluate the general level of daytime sleepiness[11]. In this questionnaire, subjects are instructed to rate, on a scale of 0-3 (never = 0, slight = 1, moderate = 2, high = 3), the likelihood of dozing off or falling asleep in eight different situations. An ESS score ≥10 was considered to be EDS[2,11]. The PSQI is a 19-item self-rated questionnaire for evaluating subjective sleep quality over the previous month[14]. The 19 questions are combined into seven clinically derived component scores: subjective sleep quality (C1), sleep latency (C2), sleep duration (C3), habitual sleep efficiency (C4), sleep disturbances (C5), use of sleeping medication (C6), and daytime dysfunction (C7). Each item is weighted equally, and is rated from 0 to 3 (0 = no difficulty, 3 = severe difficulty). The component scores are added to obtain a global score of 0-21, with higher scores indicating worse sleep quality. A global sum of "5" or greater was considered poor overall sleep quality[10,14].

Seven components of sleep disturbance within PSQI were also recorded, including (1) inability to get to sleep within 30 minutes, (2) waking up in the middle of the night or early morning, (3) getting up to use bathroom, (4) coughing or snoring loudly, (5) feeling too cold or warm, (6) bad dreams, and (7) pain.

Statistical analysis

Three separate statistical analyses were performed. First, the risk factors for EDS were determined. Baseline clinical data, including gender and clinical manifestations, between two groups of PWE (ESS ≥ 10 vs. ESS < 10, PSQI > 5 vs. PSQI ≤ 5), were analyzed by chi-square or Fisher's exact test. Continuous variables between these two patient groups were logarithmically transformed to improve normality, and comparisons were made using Student's *t*-test. Second, multiple logistic

regression was used to evaluate relationships between baseline clinical factors and overall sleep quality during the study period, with adjustments for potential confounding factors. Third, because both the scores of the questionnaires and the risk factors of poor sleep quality were not normally distributed, a Mann-Whitney U test was used to explore the relationship between the two groups of PWE.

Because ESS scores were not normally distributed, Spearman's correlation was used to explore the correlation between ESS and PSQI. Correlation analysis with partial correlation was used to check for correlations between variables after controlling for the possible confounding effects of seizure control. All statistical analysis was conducted using the Statistical Package for Social Sciences software package (version 13 for Windows?, SPSS Inc., Chicago, IL).

RESULTS

Characteristics and demographic data of the subjects

Age and gender between patients and controls was not significantly different (p = 0.222 and 0.475, respectively; Table 1). In PWE, the age at onset ranged from one month to 57 years (mean, 19.0 ± 11.0 years) and the duration of epilepsy ranged from 0.42 to 47 years (mean, 15.8 ± 11.3 years). In terms of etiology, 55 patients (47%) had idiopathic/cryptogenic epilepsy and 62 patients (53%) had symptomatic epilepsy. Twenty-one patients (18%) had generalized epilepsy and 96 patients (82%) had focal epilepsy, while 66 patients (56%) were considered seizure-free. Forty-nine patients (42%) received monotherapy and 68 (58%) were treated with polytherapy. Forty-nine patients received AED monotherapy that included enzyme-inducing (phenytoin, n = 11; carbamazepine, n = 13; and oxcarbazepine, n = 2), enzyme-inhibiting (valproic acid, n = 13), and non-inducing (lamotrigine, n = 9 and levetiracetam, n = 1) AEDs. However, there was no significant difference between these monotherapy groups.

ESS and PSQI measurement

The ESS and PSQI scores of patients and normal controls were compared (Table 2). The number of PWE with ESS scores ≥ 10 was significantly higher than in the control group (p = 0.007). The PSQI total score, sleep quality, sleep latency, sleep duration, and sleep efficiency were also significantly poorer in the patient group (all $p < 0.05$). However, sleep disturbance, medication

Table 1. Demographic data of patients with epilepsy and controls

	Controls (n = 30)	Patients (n = 117)	
		Seizure-free (n = 66)	Non seizure-free (n = 51)
Sex(M/F)	15/15	34/32	33/18
Age, years	34.4 ± 8.48	33.4 ± 10.8	37.0 ± 10.7
Etiology, n (%)			
Symptomatic		33 (28%)	29 (24%)
Cryptogenic/Idiopathic		33 (28%)	22 (19%)
Seizure type, n (%)			
Partial		47 (40%)	49 (42%)
Generalized		19 (16%)	2 (2%)
Age at onset, years		19.7 ± 10.9	18.1 ± 11.3
Duration of epilepsy, years		13.7 ± 10.2	18.6 ± 12.0
Mode of therapy, n (%)			
Monotherapy		43 (37%)	6 (5%)
Polytherapy		23 (20%)	45 (38%)

Values are expressed in mean ± SD.

Abbreviations: M, male; F, female

Table 2. Comparison of ESS and PSQI between patients and controls

	Patients	Controls	*p* value
ESS	5.9 ± 4.2	4.8 ± 2.4	0.326
ESS ≥ 10, n (%)	23 (20%)	2 (7%)	0.007
PSQI			
Total scores	6.5 ± 3.8	3.7 ± 2.9	< 0.001
Sleep quality (C1)	1.2 ± 0.8	0.6 ± 0.7	< 0.001
Sleep latency (C2)	1.2 ± 1.1	0.6 ± 0.8	0.006
Sleep duration (C3)	1.1 ± 1.1	0.6 ± 0.6	0.024
Sleep efficiency (C4)	0.8 ± 1.0	0.0 ± 0.2	< 0.001
Sleep disturbance (C5)	1.2 ± 0.5	1.0 ± 0.5	0.102
Medication use (C6)	0.2 ± 0.7	0.1 ± 0.6	0.409
Daytime dysfunction (C7)	0.9 ± 1.0	0.8 ± 0.8	0.953

Values are expressed as mean ± SD.

Abbreviations: ESS, Epworth Sleepiness Scale; PSQI, Pittsburg sleep quality index

Comparison of ESS scores was performed using the chi-square test.

PSQI and its component were compared using Student's *t*-test and the Mann-Whitney U test

Table 3. The percentage of sleep disturbance items among patients with epilepsy and normal controls

	Patients	Controls	*p* value
Cannot get to sleep within 30 minutes, n (%)	20 (17%)	2 (7%)	0.03
Wake up in the middle of the night or early morning, n (%)	67 (57%)	6 (20%)	<0.001
Get up to use bathroom, n (%)	59 (50%)	6 (20%)	<0.001
Cough or snore loudly, n (%)	50 (43%)	5 (17%)	<0.001
Feel too cold/warm, n (%)	16 (14%)	3(10%)	0.38
Bad dreams, n (%)	36 (31%)	2(7%)	<0.001
Pain, n (%)	7 (6%)	2(7%)	0.78

Chi-square tests were performed to compare the patients with epilepsy and normal controls

usage, and daytime dysfunction were not significantly different between the two groups.

The percentage of positive responses to items on PSQI that indicate sleep disturbances are presented in Table 3. We found a higher percentage of PWE responded positively to the following items than did normal controls (all $p < 0.05$): "cannot get to sleep within 30 minutes" (17%), "easily to wake up in the midnight or early morning" (57%), "get up to use bathroom" (50%), "cough or snore loudly" (43%), and "bad dreams" (31%). PWE and controls did not respond differently to the "too cold or warm" or "pain" items.

Risk factors for poor sleep quality in patients with epilepsy

The PWE were divided into two groups according to their ESS scores. Statistical analysis of the clinical manifestations between these two groups did not reveal significant risk factors. They were also divided into two groups according to PSQI scores. Between these two groups, statistical analysis revealed that seizure sub-type ($\chi^2 = 4.891$, $p = 0.027$), seizure control ($\chi^2 = 5.487$, $p = 0.019$), mode of AED therapy ($\chi^2 = 4.579$, $p = 0.032$), and EDS ($\chi^2 = 3.85$, p = 0.008) were significantly related to sleep quality (Table 4). Of these variables, only seizure control ($p = 0.02$, OR = 2.43, 95% CI

Table 4. Risk factors of poor sleep quality in patients with epilepsy

	PSQI ≤ 5 (*n* = 58)	PSQI > 5 (*n* = 59)	*p* value	OR	95%CI
Age, years	35.5 ± 11.8	33.8 ± 10.0	0.731		
Sex (M/F)	32/26	35/24	0.650	0.844	0.405-1.757
Etiology, n (%)			0.311	0.686	0.331-1.423
Cryptogenic/idiopathic	30 (26%)	25 (21%)			
Symptomatic	28 (24%)	34 (29%)			
Seizure type, n (%)			0.027	0.325	0.116-0.908
Partial	43 (37%)	53 (45%)			
Generalized	15 (13%)	6 (5%)			
Seizure control, n (%)			0.019	2.433	1.149-5.152
Non seizure-free	39 (33%)	27 (23%)			
Seizure-free	19 (16%)	32 (27%)			
Age at onset, years	19.2 ± 10.7	19.4 ± 11.4	0.532		
Duration, years	15.9 ± 11.4	15.7 ± 11.2	0.937		
Mode of therapy, n (%)			0.032	2.256	1.065-4.778
Monotherapy	30 (26%)	19 (16%)			
Polytherapy	28 (24%)	40 (34%)			
ESS	5.0 ± 3.4	6.7 ± 4.3	0.010		
ESS ≥ 10, n (%)	8 (14%)	15 (25%)	0.008	1.855	1.044-3.295

Values expressed as mean ± SD.

Abbreviations: M, male; F, female; PSQI, Pittsburg sleep quality index; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness

Sex, etiology, seizure type, seizure control, mode of therapy, and ESS scores were compared using the Chi-square test.

Age, age at onset, and duration were compared using Student's t-test.

Table 5. Comparison between ESS and PSQI by seizure sub-type, mode of therapy, and seizure control

	Seizure type		Mode of therapy		Seizure control	
	Generalized (n = 21)	Partial (n = 96)	Monotherapy (n = 49)	Polytherapy (n = 68)	Non-seizure-free (n = 51)	Seizure-free (n = 66)
ESS	5.3 ± 4.1	6.0 ± 4.2	5.8 ± 3.9	6.0 ± 4.3	6.1 ± 4.7	5.7 ± 3.8
PSQI						
Total scores	5.3 ± 3.0	6.7 ± 3.9	5.5 ± 3.0	7.2 ± 4.1 α	7.2 ± 4.2	5.9 ± 3.3
Sleep quality (C1)	1.1 ± 0.7	1.2 ± 0.8	1.0 ± 0.7	1.3 ± 0.8	1.3 ± 0.8	1.0 ± 0.7
Sleep latency (C2)	1.1 ± 1.0	1.2 ± 1.1	1.0 ± 0.9	1.4 ± 1.2	1.3 ± 1.1	1.2 ± 1.0
Sleep duration (C3)	0.7 ± 1.0	1.2 ± 1.1	1.0 ± 1.0	1.2 ± 1.1	1.1 ± 1.1	1.1 ± 1.0
Sleep efficiency (C4)	0.6 ± 0.7	0.8 ± 1.1	0.7 ± 0.8	0.9 ± 1.1	0.7 ± 1.0	0.9 ± 1.1
Sleep disturbance (C5)	1.2 ± 0.5	1.2 ± 0.5	1.1 ± 0.4	1.2 ± 0.6	1.3 ± 0.6	1.1 ± 0.4
Medication use (C6)	0.0 ± 0.0	0.2 ± 0.8	0.1 ± 0.6	0.2 ± 0.8	0.2 ± 0.7	0.2 ± 0.7
Daytime dysfunction (C7)	0.7 ± 0.8	0.9 ± 1.0	0.7 ± 0.8	1.0 ± 1.1	0.6 ± 0.8	1.1 ± 1.1 β

Values are expressed as the mean ± SD. Comparison were performed using the Mann-Whitney U test. α = p < 0.05 vs. monotherapy; β = p < 0.05 vs. non seizure-free.

Abbreviations: ESS, Epworth Sleepiness Scale; PSQI, Pittsburg sleep quality index

= 1.15-5.15) was independently associated with overall sleep quality. Spearman rank correlation analysis showed a high correlation between mode of therapy and seizure control (rho = 0.537, p = 0.000) and mild correlation between ESS and PSQI (rho = 0.270, p = 0.001). Partial correlation analysis revealed a mild correlation between sleep latency and mode of therapy (r = 0.189, p = 0.022) after adjusting the factor of seizure control.

The comparison of seizure subtype, seizure control, and mode of AED therapy with ESS and PSQI parameters is shown in Table 5. Patients receiving polytherapy had higher overall PSQI scores (p = 0.041) than patients receiving monotherapy. Daytime dysfunction was more severe in patients who were not seizure-free than in those who were seizure-free (p = 0.021).

DISCUSSION

The present study confirms that patients with chronic epilepsy frequently have sleep problems. They have a significantly higher chance of disturbance in sleep, including problems with sleep quality, sleep latency, sleep duration, and sleep efficiency, than do healthy controls. Furthermore, this study suggests that EDS in PWE may be due to poor sleep quality. Polytherapy, partial seizure, and poor seizure control are important factors that contribute to poor sleep quality and lead to EDS in PWE.

In this study, two tools were used to explore the sleep problems in PWE, including ESS, a widely accepted tool for EDS evaluation[2,18], and PSQI[10], for overall sleep quality evaluation. Results indicate that PWE suffer from more EDS (20%), insomnia (17%) and overall poor sleep quality (50%) than normal controls. These results are consistent with the reported prevalence rate of EDS (16.9%-28%)[2,13] and other sleep problems, including obstructive sleep apnea (10.2%-28.2%)[2,19,20], insomnia (24.6-34%)[2,21], and sleep disturbance (38.6%)[3] in PWE. In our study, patient with epilepsy suffered from more coughing or snoring loudly and woke up in the middle of the night or early morning. These factors may be related to the symptoms of a sleep-related breathing disorder. However, the exact diagnosis of sleep-related breathing disorders require further examination, using tools like polysomnography or the multiple sleep latency test[22].

Poor sleep quality at night may lead to EDS and daytime dysfunction, which is reported in many neurologic disorders, such as epilepsy, Parkinson's disease, dementia, migraine, restless leg syndrome, and myotonic dystrophy type 1[1,2,4,23-26]. Poor sleep hygiene also leads to sleep fragmentation, which can exacerbate seizures and EDS in PWE[5]. In this study, the ESS in PWE significantly correlated with PSQI, indicating that EDS in such patients is related to poor nighttime sleep quality.

This study reveals a high percentage of PWE with poor sleep quality (50%), including problems with sleep quality, sleep latency, sleep duration, and sleep efficiency. However, there was no difference between PWE and controls on the PSQI subscales of sleep disturbance, medication use, and daytime dysfunction. We excluded those patients who need medication to sleep, and that may have resulted in the lack of significance seen in these comparisons. Alternatively, the lack of difference in sleep disturbance between groups may be related to the limitation of the PSQI questionnaire in detecting primary sleep disorder, as sleep disturbance is occasionally related to primary sleep disorder. There was no significant difference in daytime dysfunction between PWE and normal controls. However, in the correlation analysis, frequent seizure attacks were associated with increased daytime dysfunction.

Patients with partial epilepsy are more vulnerable to poor sleep quality. Patients with different types of seizures have varying degrees of sleep problems[1,3,4,18]. For instance, temporal lobe epilepsy has been documented to be associated with a high rate of sleep disruption[6], whereas nocturnal frontal lobe epilepsy is reportedly associated with problems of sleep fragmentation and increased daytime sleepiness[27]. Thus, partial seizure may be a factor contributing to poor sleep quality in PWE.

Sleep is a potent activator of seizures. It may activate interictal epileptiform discharges or ictal seizures[24]. Compared to wakefulness, the spike rate is increased during non-rapid eye movement sleep and is reduced

during rapid eye movement sleep[28]. Benign focal epilepsy of childhood with centrotemporal spikes, supplementary sensorimotor area epilepsy, and Lennox-Gastaut syndrome are some of the common epilepsy syndromes characterized by nocturnal seizures[5,24]. Furthermore, frequent seizure attacks may influence sleep quality[24]. Increased epilepsy severity, including increased interictal epileptiform activity, may be associated with aggravated sleep disturbances in PWE[29]. The present study demonstrates that patients with poor seizure control have poorer sleep quality than those with fewer seizure attacks, indicating that seizure severity may also play a crucial role in sleep problems.

Among the PWE enrolled in this study, more patients who received polytherapy had PSQI scores above the cut-off (59%) than did patients who received monotherapy (39%). The prevalence of EDS is likewise significantly higher in patients with polytherapy than in those with monotherapy. Daytime sleepiness in PWE significantly improves after reducing the number of AEDs[30,31]. As such, it is reasonable to conclude that the use of multiple AEDs may increase adverse effects and drug interactions, resulting in EDS and poor sleep quality. The correlation between mode of therapy and sleep latency remains even after adjusting for the confounding factor of seizure control. Thus, mode of therapy may be a risk factor for poor sleep quality in PWE.

It is notable that different AEDs have different effects on sleep. Phenobarbital and benzodiazepines have been shown to alter normal sleep architecture[32]. Phenytoin and valproic acid disrupt sleep while gabapentin improves sleep quality[33]. The effect of carbamazepine on sleep is controversial[33], whereas topiramate, lamotrigine, and levetiracetam reportedly have no effect on sleepiness[29]. The influence of specific drugs cannot be determined from the present study, due to insufficient case numbers. Further studies are needed to clarify this issue.

In conclusion, sleep problems, including EDS and poor sleep quality, appear to be common in PWE. In these patients, poor sleep quality is closely related to partial epilepsy, poor seizure control, and polytherapy. Poor nighttime sleep quality may also lead to EDS and daytime dysfunction. Improving seizure control, avoiding polytherapy, and selecting the proper AEDs are important for providing the best benefit in managing sleep disturbance in PWE.

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