Evaluation of Sleep Disorders in Patients with Epilepsy: A Case-control Study

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Abstract

Objective: There is a bidirectional relationship between sleep and epilepsy. In our study, we aimed to determine the prevalence of sleep disorders in patients diagnosed with epilepsy by evaluating sleep disorders using a questionnaire and to determine whether they are affected by epilepsy type, seizure frequency, and antiepileptic use.

Methods: In this study, 100 patients who were followed up in our epilepsy outpatient clinic and who did not have psychiatric or systemic diseases that may cause underlying sleep disturbance and 50 healthy control groups compatible with them were included. Epworth Sleepiness Scale, STOP-Bang obstructive sleep apnea screening (OSAS) questionnaire test, REM Behavior Disorder-Hong Kong Questionnaire, Swiss Narcolepsy Scale, restless legs syndrome (RLS) Diagnostic Form, Beck Depression Scale, and Beck Anxiety Scale were applied to the patients and controls.

Results: Increased daytime sleepiness was found in 30% of the patients, and up to 50% of these patients had seizures in the last 6 months. The risk of OSAS syndrome was significantly increased in patients with epilepsy, especially in patients with left temporal lobe epilepsy, males, and older patients (p=0.02).The prevalence of RLS was increased in patients with epilepsy, and the risk was higher in female epileptics(p=0.04). Insomnia was 33% in our patient group, and no correlation was found between insomnia and age, gender, and number of anti-seizure medications used. The rate of moderate and severe depression in patients with epilepsy in our study was 45%, which was significantly higher than that in the general population (p=0.03). Anxiety was present in 50% of the patients (p<0.01).

Conclusion: There is a complex relationship between sleep disorders, psychiatric comorbidities, and epilepsy, and the presence of these comorbidities may significantly impair the quality of life of patients. In order to understand this multifaceted relationship, comparative studies with more homogenous groups and patients are needed.

Keywords: Comorbidity, epilepsy, psychiatric disorders, sleep disorders

INTRODUCTION

Insomnia is common among individuals with epilepsy, with an estimated prevalence of up to 50%.[1] Sleep disturbances are approximately twice as common in people with epilepsy as in healthy controls, with approximately one-third of people with epilepsy reporting sleep disturbances.[2] Up to half of newly diagnosed children with epilepsy have sleep disorders upon diagnosis, suggesting a common underlying mechanism or link to the seizures themselves. In fact, sleep disorders are less common when seizures are well controlled.[3,4]

It is thought that cortical excitability increases in non-rapid eye movement (NREM) stage 2 sleep; therefore, seizures are mostly seen in this stage, and desynchronization in rapid eye movement (REM) sleep is antiepileptogenic.[5]

Even if seizures occur during the day or while awake, they may affect sleep and fragment the sleep structure. Fragmentation of sleep leads to decreased sleep quality, increased daytime sleepiness, and sleep deprivation, which may trigger epileptic seizures and increase seizure frequency.[6]

It is known that epileptic seizures may be triggered by sleep deprivation and may occur during sleep. Approximately 20% of epileptic seizures occur during sleep, and this rate increases to 60%, especially in epilepsies originating from the frontal lobe.[7,8]

The frequency and severity of seizures and side effects of antiepileptic drugs (AEDs) may change sleep patterns and decrease sleep quality.[9] This reciprocal relationship between epilepsy and sleep may lead to comorbid psychiatric problems, including depression and anxiety, which are more common in individuals with epilepsy.[10]

It is also important to recognize and treat sleep disorders, depression, and anxiety in patients with epilepsy. With appropriate treatment of these comorbidities, both quality of life and epileptic seizures can be significantly improved and controlled.

METHODS

Our study was conducted between September 2019 and February 2020 by applying questionnaire forms to patients diagnosed with epilepsy over the age of 18 years who had been followed up in the epilepsy outpatient clinic for at least 2 years and who regularly attended the controls. The study protocol was approved by the Ethics Committee of Eskişehir Osmangazi University (decision no: 19, date: 22.01.2019). Patients who presented with single or provoked seizures, those with incomplete differentiation of epileptic seizures, such as syncope or psychogenic seizures, those with severe mental retardation, and those with primary neurological diseases such as tumors, ischemia, demyelinating lesions, previous intracranial operations, or other neurodegenerative diseases causing seizures were not included in the study. Patients with known psychiatric disorders and anti-depressant use who were being followed up by the psychiatry department were also excluded.

A total of 100 patients were included in the study. Questionnaire forms were read and completed by the patients. In cases of incomprehensible questions, the patient was explained while filling out or handing over the questionnaire and was expected to answer. In addition, age, gender, seizure type, seizure frequency in the last 6 months, anti-seizure drugs (ASMs), use of multiple ASMs, and epilepsy syndromes that could be identified based on neuroimaging or video-EEG monitoring information were recorded.

Epworth Sleepiness Scale (ESS), STOP-Bang questionnaire obstructive sleep apnea screening test, REM Behavioral Disorder-Hong Kong Questionnaire (RBDQ-HK), SWISS Narcolepsy Scale, restless legs syndrome (RLS) Diagnostic Form, Beck Depression Scale, and Beck Anxiety Scale were applied.

Questionnaire Forms Used

Epworth Sleepiness Scale: ESS is a scale that evaluates daytime sleepiness.[11,12]

STOP-Bang Questionnaire: This questionnaire is used as a screening test for obstructive sleep apnea.[13]

MAIN POINTS

- Patients with epilepsy have a higher risk of psychiatric and sleep disorders.
- Because seizure frequency and antiepileptic drug use may change sleep structure and efficiency, sleep habits should be routinely evaluated.
- The risk of obstructive sleep apnea screening is higher in males and older adults, especially in patients with left temporal lobe epilepsy.
- Comorbid sleep and psychiatric disorders should be considered and treated.

The Diagnostic and Statistical Manual of Mental Disorders criteria were adapted to define insomnia based on a "yes" response to any of the following.[14]

Restless Legs Syndrome Diagnosis Form: The RLS Diagnosis Form, developed by the International Restless Legs Syndrome Study Group, was first created in 1995 and revised in 2012 in light of new data.[15]

REM Behavior Disorder Questionnaire-Hong Kong: The RBDQ-HK, which can be used as a screening test in REM behavior disorder to evaluate the severity of symptoms, has been shown to be an easily applicable, valid, and reliable test.[16]

SWISS Narcolepsy Scale: Narcolepsy or narcolepsy with cataplexy can be detected in some patients with daytime sleepiness. The Swiss narcolepsy scale has been proven to have high sensitivity and specificity in a study conducted in 2004.[17]

Beck Depression Scale: Beck Depression Scale was revised in 1996. Turkish validity and reliability study of the revised second version was conducted by Aktürk et al.[18]

Beck Anxiety Scale: Beck Anxiety Scale is a scale developed in 1988 that consists of 21 questions probing anxiety symptoms. The reliability and validity of this method have been proven, and its effectiveness in differentiating depression and anxiety has been demonstrated.

Statistical Analysis

The statistical analyses were performed using IBM Statistical Package for the Social Sciences version 23 software.

Descriptive analyses for parametric data are presented as mean and standard deviation. All data were re-recorded as dichotomous data, such as high-low, present-absent, above-below a specified score. The risk and scale results were analyzed using cross-tabulations according to the clinical characteristics and demographic data of the patients. The differences between the groups in terms of frequencies were compared using chi-square tests or Fisher's exact tests when the values observed in the cells did not fulfill the assumptions of the chi-square test. P values below 0.05 were considered as statistically significant results.

Multiple logistic regression analysis including relevant and potential confounding factors, such as age, gender, and type of antiepileptic used, was performed to analyze the association between epilepsy and sleep disorders, anxiety, and depression.

RESULTS

Demographic Characteristics

In our study, questionnaire forms filled out by 100 patients who were followed up in the neurology epilepsy outpatient clinic and came to regular controls were evaluated. Of the patients included in the study, 38 were male and 62 were female. The mean age of the patients was 30.48±10.0 years (18-58 years).

In total, 50 healthy adults (25 males and 25 females) were included as the control group. The mean age of the control group was

31.6±6.4 years (20-56 years). No significant differences were found between the groups in terms of age and gender (Table 1).

Among the patients, 64% had no seizures in the last 6 months, whereas 36% had at least 1 seizure. The mean number of seizures within 6 months was 12.53±13.12.

A total of 59 (59%) patients received single AED treatment. Of the 41 patients using more than one AED, 29 were dual, 11 were triple, and 1 was quadruple.

Regarding the antiepileptics used, 57 patients used levetiracetam, 29 used valproic acid, 33 used carbamazepine/oxcarbazepine, 16 used lacosamide/zonisamide, 10 used lamotrigine, 3 used topiramate, and 2 used clobazam.

The epilepsy syndromes of the patients were determined according to the International League Against Epilepsy 2017 epilepsy classification by evaluating clinics, electroencephalography (EEG), and neuroimaging findings during seizures. Of all patients, 47 and 53 had generalized and focal onset epilepsy. In patients with focal onset, imaging and EEG findings were compatible with frontal lobe-induced seizures in 18 patients and temporal lobe-induced seizures in 25 patients.

The rates of sleep disorders in the epilepsy and control groups are presented in Table 2.

Epworth Sleepiness Questionnaire

The mean ESS score was 6.83±6.74 in the epilepsy group and 5.94±4.49 in the control group. There were a total of 30 patients (30%), 20 females and 10 males, in the epilepsy group and 7 patients (14%), 5 females and 2 males, in the control group, with excessive daytime sleepiness ESS scores greater than 10 and increased daytime sleepiness.

When the epilepsy and control groups were compared, increased daytime sleepiness was significantly increased in the epilepsy group (p=0.3). No relationship was found between gender and AGU score (p=0.3).

Table 1. Demographic characteristics of the patient and control groups

	Epilepsy patients (n=100)	Control (n=50)	p value
Female/male	62/38	25/25	0.06
Age (mean±SD)	30.48±10.0	31.6±6.4	0.61
Duration of epilepsy (mean±SD)	12.10±8.03	-	-
Treatment of NPI		-	-
Monotherapy	59		
Polytherapy	41		
Epilepsy type		-	-
Generalized	47		
Focal	53		
Temporal	25		
Frontal	18		

NPI: Neuropsychiatric inventory, SD: Standard deviation

Table 2. Sleep disorders in the epilepsy and control groups

	Epilepsy patients (n=100)	Control (n=50)	p value
ESS	30	7	p<0.01
Insomnia	33	15	p=0.7
STOP-Bang Survey			
High risk	15	4	p<0.01
Medium risk	4	4	p>0.01
Low risk	81	44	p<0.01
Restless Leg Diagnosis Form	20	5	p<0.01
RBDQ-HK	12	1	p=0.01
Swiss Narcolepsy Scale	15	1	p=0.01
Beck Depression Scale			
Minimal	29	19	p>0.01
Mild	31	8	p<0.01
Moderate	14	-	p<0.01
Beck Anxiety Scale			
Minimal	20	15	p>0.01
Mild	21	5	p<0.01
Moderate	29	3	p<0.01

ESS: Epworth Sleepiness Scale, RBDQ-HK: REM Behavioral Disorder-Hong Kong Questionnaire, REM Sleep Behavior Disorder Questionnaire

When analyzed according to epilepsy groups, 13 (27.7%) patients with generalized epilepsy and 17 (32.1%) with focal epilepsy. No significant difference was observed between the two groups (p=0.6). However, when the focal epilepsy group was analyzed within itself, the AGI score of patients with frontal lobe epilepsy (10.22±8.40) was significantly higher than that of patients with temporal lobe epilepsy (5.66±4.83) (p=0.01) (Graphic 1). Unlike the other neuropsychiatric inventories, the AGU score increased in the carbamazepine/oxcarbazepine group, and daytime sleepiness was observed in almost half of the patients (45.5%) (p=0.01).

Insomnia

In our study, we did not apply a different questionnaire for insomnia, but 33 patients (33%) in the epilepsy group answered the question of not sleeping frequently and almost always. In the control group, 15 patients (30 per cent), 6 males and 9 females (30 per cent) who answered frequently and almost always to the question about insomnia. There were no significant differences between the control and epilepsy groups (p=0.7).

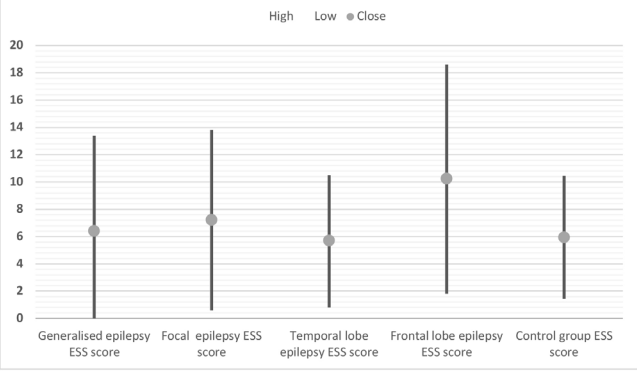
In 45.5% of the patients who complained of insomnia, seizures were present in the last 6 months; however, the result did not reach statistical significance (p=0.1).

STOP-Bang Survey

In our study, the number of patients who were evaluated using the STOP-Bang questionnaire and found to be at medium and high risk for obstructive sleep apnea syndrome (OSAS) was 19 (19%). Moreover, 28.9% of males and 12.9% of females were found to be at risk for OSAS. When the risk of OSAS was compared with the epilepsy type, the risk of OSAS was found to be higher in focal epilepsies, especially in focal epilepsies with left temporal lobe onset, than in generalized epilepsies (22.7% vs. 14.9%). However, this difference did not reach statistical significance (p=0.3).

Diagnosis Form for Restless Legs Syndrome

In 20 (20%) of 100 patients in the epilepsy group, answers compatible with RLS were provided in the RLS questionnaire. In the control group, RLS was found in 5 patients (10%), 3 females and 2 males. This rate was 2 times higher than that of the control group. Of the 20 patients, 17 (85%) were female and 3 (15%) were male, and a significant correlation was found between the risk of RLS and being female (p=0.01).



Graphic 1. Epilepsy types and mean Epworth Sleepiness Scale (ESS) scores

REM Behavior Disorder-Hong Kong Questionnaire

The mean score of patients on the RBDQ-HK was 16.33±12.27. There was no significant difference between genders in the mean score (mean score of males 15.53±12.69; mean score of females 16.82±12.09) (p=0.6).

The mean RBDQ-HK score of the control group was 11.72±8.33. The mean score of healthy women was 14.0±9.25, the mean score of healthy men was 9.25±6.52 and the mean RBDQ-HK score was found to be higher in the female gender (p=0.04).

Compared with the control group, the mean scores of the epilepsy group were significantly higher (11.7 vs. 16.3) (p=0.01).

SWISS Narcolepsy Scale

According to the Swiss Narcolepsy Scale, 15 patients (15%), 10 females and 5 males, had narcolepsy risk in the epilepsy group. In the control group, 1 patient (2%) was at risk of narcolepsy. The risk of narcolepsy was significantly increased in epileptics (p=0.01). There was no significant difference in the risk of narcolepsy in terms of gender (p=0.6).

The mean age of patients with and without narcolepsy risk was 32.07±7.66 years, while the mean age of the patients without narcolepsy risk was 30.14±10.33 years. No significant difference was found (p=0.4).

Approximately half (46.7-7%) of the patients with high risk of narcolepsy had a history of seizure in the last month. This rate increased to 75% (6 patients) in focal epilepsy. However, no statistically significant relationship between seizure in the last 6 months and narcolepsy was not found in any epilepsy group (p=0.2).

Beck Depression Scale

The mean Beck Depression Scale score of the control group was 11.06±7.34 and 16.77±10.26 in the epilepsy group.

When categorized as no depression, mild, moderate, and severe depression according to the scores, 26 patients with no depression, 29 patients with mild depression, 31 patients with moderate depression, and 14 patients with severe depression were found in the epilepsy group. In the control group, 23 patients did not have depression, 19 patients had mild depression, 8 patients had moderate depression, and no patient had severe depression.

The rates of moderate and severe depression were significantly higher in the epileptic group than in the non-epileptic group (45% vs. 8%) (p<0.01).

Moderate to severe depression was found in 69.4% of patients who had a seizure in the last 6 months. Having a seizure significantly increased the risk of depression (p<0.01).

Beck Anxiety Scale

When categorized according to Beck's anxiety scale scores, 30 of 100 patients in the epilepsy group had no anxiety, 20 mild anxiety, 21 moderate anxiety, and 29 severe anxiety. In the control group, 27 of 50 patients had no anxiety, 15 mild anxiety, 5 moderate anxiety, and 3 severe anxiety.

When the control and epilepsy groups were compared, the rates of moderate and severe anxiety were 50% and 16% in the epilepsy and control groups, respectively. The rate of anxiety was significantly increased in epileptics (p<0.01).

In the epilepsy group, 56.5% of women and 39.5% of men, and in the control group, 4.2% of men and 26.9% of women had moderate or severe anxiety, but no statistical relationship was found between gender and anxiety in the groups (p=0.09 and p=0.06).

DISCUSSION

In our study, we used questionnaire forms from 100 patients with epilepsy and 50 healthy controls who were followed up in our epilepsy outpatient clinic.

In patients with epilepsy, the complaint of increased daytime sleepiness is frequently encountered, and this is especially a subjective complaint. The rate of increased daytime sleepiness in patients with epilepsy has been reported to range between 10 and 47.5.[19] In our study, the proportion of patients with an ESS score >10 was 30%. In our study, we found no significant correlation between ESS score and other AEDs, except for increased daytime sleepiness (p=0.01) observed in carbamazepine/oxcarbazepine users. Although there are conflicting results in the literature, it has been reported that carbamazepine increases arousal, increases daytime sleepiness, increases slow-wave sleep (especially NREM stage 2), and increases REM latency.[19,20]

In patients with epilepsy, REM sleep behavior disorder (RBD) may be a comorbid condition and should be considered in the differential diagnosis of epilepsy. In the literature, it has been reported that RBD is more commonly observed in elderly, male, and cryptogenic epilepsy patients with sleep-related seizures.[21] In our study, we found that Rosai-Dorfman disease was significantly higher in patients than in control patients (p=0.01). We did not find any significant difference in terms of gender (p=0.6) and age (p=0.3). This may be attributed to the fact that patients older than 60 years were included in the study, and the mean age was 30.4 years in our study.

In our study, the rate of patients complaining of insomnia was found to be 33%, and rates of 24.6% and 43% are available in the literature.[22,23] We found no correlation between insomnia and age, gender, epilepsy type, and number of AEDs used by the patients, and our findings are consistent with the study of Im et al.[24] Other studies have also shown that NPI polytherapy is associated with increased insomnia scores.[23]

Of the 100 patients who were administered the Swiss Narcolepsy Questionnaire, 15 (15%) were evaluated as having a risk of narcolepsy with a negative score. Moreover, 10 of these patients responded positively to the cataplexy, emotional, triggering questions. The reported prevalence of narcolepsy in the normal population is 0.03-0.16%, and the rates in our study are considerably higher than those in the normal population. In a study evaluating the risk of narcolepsy in patients with epilepsy using a questionnaire, the risk of narcolepsy was found in 3 out of 100 patients; however, narcolepsy was not detected in any of them after the necessary evaluations.[25] In our study, there was 1 patient who was evaluated because of these complaints and then diagnosed with narcolepsy.

We believe that the diagnosis of narcolepsy may be overlooked; therefore, further evaluation with polysomnography and the multiple sleep latency test is important in patients with epilepsy who have a suspicious history or who are found to be at risk in screening tests.

The incidence of RLS in the Turkish population was 3.2%.[26] Öztürk et al.[27] analyzed the frequency of RLS in patients with epilepsy and found that it was 5.8%. However, they stated that this percentage may be lower than the actual rate because they did not include patients using drugs that may cause RLS or patients using gabapentin and pregabalin used in the treatment of RLS. RLS has been reported up to 28% in the literature.[28] In our study, we found the prevalence of RLS in patients with epilepsy to be 20%, which is quite high, and although none of the patients used gabapentin-pregabalin, this high prevalence suggests that the diagnosis of RLS may be overlooked in patients with epilepsy.

In our study, the anxiety scores of epilepsy patients with high OSAS risk were also significantly higher (p=0.02). This finding is consistent with the literature, and in one study, anxiety about seizure was found to be higher in patients with epilepsy and OSAS, which may increase Beck Anxiety Scale scores.[29]

When the risk of OSAS was compared with the epilepsy type, the risk was found to be higher in focal epilepsies, especially in focal epilepsies with left temporal lobe onset, than in generalized epilepsies (22.7% vs. 14.9%). However, this difference did not reach statistical significance (p=0.3). Consistent with our study, 7 studies were examined in a meta-analysis in the literature, and the rate of OSAS in focal epilepsies (32.2%) was found to be higher in all studies compared to generalized epilepsies (28.2%), but none of the studies reached statistical significance.[30]

Although the relationship between resistant and controlled epilepsy and OSAS has been investigated; however, no relationship between seizure frequency and OSAS has been found. It has been shown in many studies that OSAS treatment reduces seizure frequency and provides significant benefits to epilepsy control; however, there is no evidence that seizure frequency is associated with OSAS.[31]

It is known that the prevalence of depression is higher in patients with epilepsy, which significantly affects the quality of life of these patients. One study has even shown that the risk of suicide increases up to 3 times in patients with epilepsy. In studies examining the prevalence of depression in epilepsy patients, rates of up to 32.6% have been reported.[32] In our study, 45 patients (45%) had moderate to severe depression according to the Beck Depression Questionnaire scores. Of the 45 patients, 12 were male and 33 were female, and there was a significant difference between genders (p=0.03). Consistent with the literature, the rate of depression was significantly higher in women with epilepsy than in men.[33,34]

As shown in many studies, seizure frequency was found to be associated with depression in our study.[35,36] In our study, 69.4% of the patients with depression had a seizure in the last 6 months, and the variable most associated with depression was the presence of a seizure in the last 6 months, as shown by the regression analysis.

In the literature, it has been reported that epilepsy patients with depression experience more side effects of the ASMs they use.[37]

In the relationship between ASM use and depression, particularly in patients with a higher risk of depression, care should be taken in this respect.

Study Limitations

The distribution of men and women in our patient group should be more homogeneous, and the number of patients should be increased. The patient group included in the study comprised mostly young adults, and patients with advanced age and poor educational status were not included in the study; therefore, the low number of resistant epilepsy cases is one of the limitations of the study. In addition, although sleep and sleep disorders were evaluated in detail with a long questionnaire used in this study, patients were often distracted while giving answers.

CONCLUSION

In conclusion, there is a complex relationship between sleep disorders, psychiatric comorbidities, and epilepsy. In order to understand this multifaceted relationship, comparative studies with more homogenous groups and patients are needed. Nevertheless, the necessity of questioning epilepsy patients in terms of sleep disorders, depression, and anxiety in clinical conditions in line with the information we have presented has been observed once again in this study. Effective questionnaire forms suitable for clinical conditions to be developed on these subjects may be used in this respect in the future.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Eskisehir Osmangazi University (decision no: 19, date: 22.01.2019).

Informed Consent: Consent form was filled out by all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.B., D.İ.A., Concept: S.B., D.İ.A., Design: S.B., D.İ.A., Data Collection or Processing: S.B., D.İ.A., Analysis or Interpretation: S.B., D.İ.A., Literature Search: S.B., D.İ.A., Writing: S.B., D.İ.A.

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