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뇌전증 환자에서 과다주간졸음과 불면증상에 관계된 인자들

Factors associated with excessive daytime sleepiness and insomnia symptoms in patients with epilepsy

울산대학교 대학원

의학과

조성양

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이 논문을 의학석사 학위논문으로 제출함

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의학과

조성양

조성양의 의학석사학위 논문을 인준함

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Abstract

Background and Aims: Sleep disorders in patients with epilepsy have been increasingly recognized, because sleep disturbances increase the seizure frequency, and decrease quality of life. The aim of this study is to find factors associated with insomnia and excessive daytime sleepiness (EDS) in patients with epilepsy, in terms of psychologic distress-related, epilepsy-related and other sleep disorder-related factors.

Method: This study included 126 patients with epilepsy at Asan Medical Center**.** We used Insomnia Severity Index (ISI) and Epworth Sleepiness Scale (ESS) to measure the severity of insomnia and excessive daytime sleepiness. Possible factors associated with severity of insomnia and daytimes sleepiness were investigated. Psychologic distress-related factors include depressive symptoms and anxiety. Epilepsy-related factors include age at onset, duration of epilepsy, seizure severity containing frequency and type of seizure, nocturnal seizure, types of antiepileptic drugs (AEDs) prescribed, number and dosage of AEDs. Sleep apnea and RLS symptoms were assessed by questionnaires, which are accessible and applicable methods in clinical practice. Multivariate linear regression models to assess variables associated with insomnia and EDS.

Results: Mean scores of ISI were 7.75 (SD 6.42) and mean scores of ESS were 6.06 (SD 4.19). ESS score was associated with symptoms of sleep apnea, depressive symptoms, and antiepileptic drug load. Sleep apnea was present in 24.6% of patients, and showed the highest association with ESS scores (B=3.109, $p<0.001$). Only 2 patients with restless leg syndrome, which was too small to prove the effect of RLS. Presence of depressive mood was associated with ESS scores (B=1.942, P=0.01), but anxiety was not. Higher drug load, which is sum of number and dosage of AEDs, was associated with higher ESS score (B=.686,

P=0.013). ISI score was strongly associated with anxiety (B=6.236, p<0.001) and depressive symptoms (B=3.811, P=0.005), rather than epilepsy related factors or sleep disorders. The interaction between use of perampanel and anxiety had negative correlation with insomnia with marginal significance (B=-3.393, p=0.092).

Conclusion: EDS was associated with symptoms of sleep apnea, depressive symptoms, and antiepileptic drug load in patients with epilepsy. Insomnia symptoms were related to anxiety, depressive symptoms, and the use of perampanel has negative correlation with insomnia in association with anxiety.

Key words: Insomnia, Daytime sleepiness, Epilepsy

Contents

List of Figures and Tables

Introduction

Epilepsy is one of the most common and disabling public health problems, affecting approximately 50 million people around the world (1-3). The abnormal and excessive discharges of neurons in the brain damage neurobiological, cognitive, psychological and social performances in patients with epilepsy (4). Sleep disorders in patients with epilepsy (PWE) have been increasingly recognized, because sleep disturbances increase the seizure frequency, decrease quality of life, and as a consequence, increase health and economic burden (5, 6). Sleep problems often encountered in PWE are insomnia and daytime sleepiness (7, 8).

The prevalence of insomnia in PWE was reported higher than general population, being 28.9-51% based on the insomnia severity index and 36-74.7% based on DSM-IV-TR or ICSD-2 (4, 9). In an attempt to discover treatable factors associated with insomnia (4), psychiatric disorders, combined other sleep disorders, such as restless leg syndrome, obstructive sleep apnea, narcolepsy and parasomnias (9), and epilepsy related factors had been investigated. Three studies reported that depressive mood was associated with insomnia (2, 3, 10), however, it did not sustain after multivariate analysis in the two studies (3, 10). Moreover, one study reported no relationship between insomnia symptom and psychiatric symptomatology (11). Insomnia is a known risk factor for the development of anxiety in general population, and patients with epilepsy showed high prevalence of anxiety (4). However, relationship between anxiety and insomnia in patients with epilepsy has not been investigated. Sleep disorders, such as restless leg syndrome (RLS), sleep apnea, narcolepsy and parasomnia disturb sleep architectures. Whether the comorbid sleep disorders attribute to insomnia is unclear in patients with epilepsy. Epilepsy-related features that is associated with insomnia include poor seizure control (8, 12), shorter duration of epilepsy (10), nocturnal seizures (13), AED polytherapy (2), or types of AEDs used. Lamotrigine therapy was associated with insomnia in one study (14). None of the studies assessed epilepsy surgery or other modalities of epilepsy treatment, such as vagal stimulation or diet (4).

Excessive daytime sleepiness (EDS) is frequently encountered sleep-related complaints in PWE, prevalence of which ranges from 10% to 48% (15). EDS is associated with high seizure frequency, and aggravates cognitive and behavioral symptoms, reducing social interaction and employment possibilities (15). The etiology of EDS in epilepsy has not been clarified, but it may be multifactorial, affected by epilepsy-related factors, psychological distress, or coexisting sleep disorders (15). In the aspect of epilepsy related factors, frequent seizures during sleep may directly disrupt sleep, and the sedative effects of antiepileptic drugs (AEDs) may affect EDS (15, 16). Psychological problems such as depression and anxiety might significantly affect sleep disturbance, resulting in daytime sleepiness in PWE. Nonetheless, a recent systematic review argued that EDS in epilepsy patients were more related to undiagnosed sleep disorders than epilepsy-related factors (15). For example, EDS, measured by Epworth sleepiness scale (ESS) > 10, in PWE was associated with obstructive sleep apnea (OSA) and restless leg syndrome (RLS) than epilepsy-related factors (16, 17).

Despite the fact that somnolence is a possible features of insomnia disorder, the presence of EDS was reported to be uncommon in insomnia (9). EDS and the severity of insomnia were positively related in univariate analysis, but not in multivariate analysis in two studies (3, 10).

Discrepancy between several studies that investigated risk factors for insomnia and EDS may come from methodological problem, because studies selected different risk factors, and used different definition and measurements. The aim of this study is to find factors associated with insomnia and EDS, in terms of psychologic distress-related, epilepsy-related and other sleep disorder-related factors. Especially, we tried to include risk factors that previous studies missed. For instance, dosage of the AEDs had not been investigated before. Therefore, we used drug load counting both number and dosage of AEDs. We investigated the impact of undergoing surgical resection for epilepsy on insomnia or daytime sleepiness, as it was known to reduce daytime sleepiness (18). We also included both depressive mood and anxiety symptoms, as these two factors coexist and affect each other. In addition, several AEDs were reported to be positively or negatively associated with insomnia as well as psychologic

distress related, other epilepsy related and sleep related factors. We investigated interactions between AEDs and other independent variables that were associated with insomnia.

Methods

Subjects

This is a cross-sectional study conducted in single university hospital in 2018. Individuals aged over 18 who had been diagnosed with epilepsy and had been treated for more than 1 year were included. A revised 2014 definition of epilepsy was used in this study: 1) two unprovoked seizures more than 24 h apart or 2) one unprovoked seizure and a risk of at least 60% for another in the next 10 years (19). Because calculating the recurrence risk after a single seizure in particular clinical circumstance is inapplicable to all cases, the diagnosis of epilepsy after a single seizure was made in this study when the findings of electroencephalography(EEG) or magnetic resonance imaging(MRI) supported the diagnosis of epilepsy (19). The new International League Against Epilepsy (ILAE) classification of seizures and epilepsy were applied in this study (20, 21). The participants were asked to fill out questionnaires on the day they visited their neurologist at the outpatient clinic. Patients were excluded if they had experienced a seizure in the 48 hours before the request to fill out the questionnaire, if type or dosage of prescribed anti-epileptic drugs (AEDs) were changed in a month, or if they were unable to read or understand the questionnaire.

Factors associated with insomnia and EDS were classified into psychologic distress-related, epilepsy-related and other sleep disorder-related factors. Psychologic distress-related factors include depressive symptoms and anxiety, based on questionnaires. Epilepsy-related factors include age at onset, duration of epilepsy, seizure severity containing frequency and type of seizure, nocturnal seizure, types of AEDs prescribed, number and dosage of AEDs. Sleep apnea and RLS symptoms were assessed by questionnaires, which are accessible and applicable methods in clinical practice. Demographic and clinical data including age, sex, comorbidities, current medication, body mass index, occupational status, age at onset of seizure, etiology of epilepsy and previous surgical resection for epilepsy were collected by interview and reviewing medical files. Written informed consent was obtained from all participants.

The study was reviewed and approved by the Institutional Review Board of Asan Medical Center.

Measurement of insomnia, excessive daytime sleepiness, anxiety and depression

Four questionnaires to measure insomnia, excessive daytime sleepiness, anxiety and depression were done; Insomnia Severity Index (ISI), Epworth Sleepiness Scale (ESS), General Anxiety Disorder-7 (GAD-7) and Patient Health Questionnaire-9 (PHQ-9).

The ISI consists of seven items that assess difficulty falling asleep and staying asleep, problems waking up too early, satisfaction with current sleep patterns, noticeability of impairment attributed to sleep problems, distress caused by the sleep problem, and interference with daily functions (22). Each item is rated on a 5-point Likert scale ranging from 0 to 4; the total score ranges from 0 to 28, with a higher score indicating greater insomnia severity. The validated Korean version of the ISI used in this study demonstrated excellent internal consistency, good test-retest reliability, and adequate convergent and divergent validities (23). A cutoff score of 15.5 on the Korean versions of ISI was optimal for discriminating patients with insomnia (23). Therefore, we defined patients with insomnia when the patients scored ISI score $\geq$ 16.

EDS was assessed using the validated Korean version of Epworth Sleepiness Scale (ESS) (24), consisting of eight questions about how often a person dozed during daily activities. The answers were on a 4-point scale ranging from 0 (never dozed) to 3 (high chance of dozing), with total scores ranging from 0 to 24. Higher scores indicate greater sleep propensity during the day. We defined EDS if ESS scores $\geq$ 11 (25).

The Generalized Anxiety Disorder-7 (GAD-7) is a 7-item self-report scale used for the rapid detection of generalized anxiety disorder (26). Subjects are asked to respond to questions about how much they have been bothered by anxiety-related problems over the past two weeks. Each item is rated on a 4-point Likert scale ranging from 0 to 3. The total score of GAD-7 ranges from 0 to 21;

higher scores indicate more intense anxiety. Korean version of the GAD-7 were validated in patients with epilepsy (27). A GAD-7 score ≥ 7 is considered indicative of anxiety disorder.

The Patient Health Questionnaire-9 (PHQ-9) is a 9-item questionnaire used to assess and grade the severity of depression. The PHQ-9 exclusively covers the 9 diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), in which clinical diagnosis of depressive disorder is based (28). Subjects are asked to respond to questions regarding experiences bothering them in the last 2 weeks such as: anhedonia, feeling sad or depressed, trouble falling asleep or sleeping too much, feeling tired or having little energy, eating problems, feelings of worthlessness or guilt, concentration problems, psychomotor retardation or agitation, and suicidal thoughts. Each item is rated on a 4-point Likert scale ranging from 0 (absence of symptom) to 3 (presence of symptom nearly every day). The total score of PHQ-9 ranges from 0 to 27; The higher scores indicate greater risk of depression. The Korean version of the PHQ-9 was validated (28). A PHQ-9 score ≥ 10 is considered indicative of depression (28).

Measuring epilepsy severity and type of seizure

A composite epilepsy severity score was determined based on type and frequency of seizures, and number of antiepileptic drugs (29). Seizure type was scored 3 for generalized tonic–clonic seizures, 2 for complex partial seizures, 1 for simple partial seizures, and 0 for absence of seizures for at least 1 year. When patients had more than 1 type of seizure, the most severe seizure type was used for scoring. Seizure frequency during past 1 year was scored; 3 for weekly or daily seizures, 2 for monthly seizures, 1 for 1–11 seizures a year, and 0 for absence of seizures for at least 1 year. The type of AED regimen was scored 3 for a regimen with 3 or more AEDs, 2 for 2 AEDs, 1 for monotherapy, and 0 for no medication. The composite epilepsy severity score ranges from 0 to 9, with higher scores reflecting higher epilepsy severity. We defined nocturnal seizure as '>90% of seizures occurring during sleep' (30).

Measuring antiepileptic drug load

Drug loads for each individual patient were calculated as the sum of the prescribed daily dose (PDD)/ defined daily dose (DDD) ratios for each AED included in the treatment regimen (31), where DDD corresponds to the assumed average maintenance daily dose of a drug used for its main indication (32).

Measuring symptoms of sleep apnea and restless leg syndrome

The snoring, tiredness, observed apnea, high BP-body mass index (BMI), age, neck circumference and gender (STOP-Bang) questionnaire were developed for obstructive sleep apnea (OSA) screening tool in preoperative clinics (33). The STOP-Bang questionnaire shows a moderately high level of sensitivity (74%) and specificity (53%) for detecting moderate to severe OSA (apnea-hypopnea index > 15) (33). It includes eight questions, each of them scored 0 (no) or 1(yes). The total score ranges from 0 to 8. Patients with STOP-Bang score ≥ 3 were considered to have moderate to severe OSA (34). Physicians interviewed the patients and determined whether the patients had restless leg syndrome. When the patients had an urge to move the legs that is accompanied by or occurs in response to uncomfortable and unpleasant sensations in the legs, that occurs primarily with rest/inactivity, is partially or totally relieved by movements and that occurs primarily in the evening or night, the physician scored 1(yes) (35).

Statistical analysis

Data are presented as means and standard deviations (SD) for numeric variables and numbers and percentages for nominal variables. The potential factors independently associated with insomnia

and EDS in patients with epilepsy were assessed with multivariate linear regression analyses (MLR). The dependent variables were ESS scores and ISI scores. The independent variables included sex, BMI, sleep apnea, as defined by the STOP-Bang scores ≥ 3, occupational status, particular occupations that might disrupt circadian rhythm, such as shift work or night work, epilepsy-related variables and psychological variable. Epilepsy-related variables were age at onset of seizure, etiology of epilepsy, duration of epilepsy, type and frequency of seizures in the last year, presence of nocturnal seizure, composite epilepsy severity score, surgical resection for epilepsy, and antiepileptic drug loads. Psychological variables including PHQ-9 scores and GAD scores were not normally distributed, and scores were classified into the presence of depressive symptoms (PHQ-9 scores ≥ 10) and anxiety symptoms (GAD scores ≥ 7). The frequency of seizure was categorized into 3; one or more per month, 1-11 per year and seizure-free. Univariate analyses were conducted using an unpaired *t*-test or a chi-squared test depending on types of independent variables. Variables with $p < 0.1$ on univariate analysis were then entered into MLR models to assess variables associated with insomnia and EDS. The stepwise regression method for variable selection was used.

AEDs have an influence on anxiety or depressive symptoms(36). Thus, we investigated interaction between AEDs and anxiety or depressive symptoms by developing general linear model (GLM). If significant interaction factors were identified, MLR was conducted to include two variables and its interaction to determine the interaction effect. Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 21.0 (International Business Machines Corp., Armonk, NY, USA).

Results

Subject characteristics

Study population were composed of 126 patients with epilepsy, of whom 64 (50.8%) were male. The mean age was 41.7 (SD 12.8), mean age at onset of seizure was 22.1 (SD 12.0) and mean duration of epilepsy was 19.6 (SD 12.2) years (Table 1). Twenty-eight (22.2%) patients had 1 or more seizure per month, and 53 (42.1%) patients were seizure-free in the last year. 20 (15.9%) patients had nocturnal seizures. 92 (73.0 %) patients took more than two types of AEDs, and 57 (45.2%) patients took more than three types of AEDs. Levetiracetam was most frequently prescribed AEDs, followed by valproic acid and oxcarbazepine. Mean scores of ISI were 7.75 (SD 6.42) and mean scores of ESS were 6.06 (SD 4.19). 15.1% of study population had insomnia, based on ISI scores ≥ 16, 17.5% had EDS, based on ESS scores ≥ 11 (Table 2). The presence of anxiety (GAD-7 score ≥ 7), depression (PHQ-9 score ≥ 10) were identified in 36 (28.6%) and 38 (30.2%), respectively, although only 14 (11.1%) patients reported previous history of depression. 31 (24.6%) patients had symptoms of sleep apnea and 2 (1.59%) patients had symptoms of restless leg syndrome.

Factors associated with excessive daytime sleepiness

Univariate analysis showed that ESS score was in linear association with BMI (p=0.005), antiepileptic drug load(p=0.005), composite epilepsy severity score(p=0.0012), ISI scores(p=0.014), presence of anxiety and depressive symptoms (p<0.001), sleep apnea measured by STOP-Bang sleep apnea questionnaire (p<0.001), unemployed status (p=0.056), use of valproic acid (p=0.062) and perampanel (p=0.067) (Table 3). There were no significant association between nocturnal seizure or surgical resection for epilepsy. On multiple linear regression analysis, symptoms of sleep apnea showed strong association with EDS (B=3.109, p<0.001), followed by depressive symptoms

(B=1.942, P=0.01), and antiepileptic drug load (B=0.686, P=0.013) (Table 4). Coefficient of determinant was 0.239.

Factors associated with insomnia

Univariate analyses showed that ISI score was significantly associated with ESS scores (p=0.014), composite epilepsy severity score (p=0.046), seizure frequency (p=0.026), anxiety and depressive symptoms (p<0.001), and the use of valproic acid (p= 0.017) (Table 5). There were no significant associations of insomnia with nocturnal seizure, sleep apnea symptoms, age at onset of seizure or disease duration. Multivariate linear regression analysis demonstrated that only anxiety (B=6.236, p<0.001) and depressive symptoms (B=3.811, P=0.005) were in linear correlation with insomnia (Table 6). Coefficient of determinant was 0.441.

Interactions between independent variables on insomnia severity index

The interaction analysis between AEDs and anxiety or depressive symptoms revealed that anxiety symptoms were associated with the use of perampanel (p=0.025). Among patients who had anxiety symptoms, use of perampanel was associated with less insomnia (Figure 1). Multivariate linear regression analysis considering interaction between use of perampanel and anxiety symptom showed that this interaction has negative correlation with insomnia with marginal significance (B=-3.393, p=0.092) (Table 7). Coefficient of determinant was 0.489.

Discussion

We found that in patients with epilepsy, ESS score was associated with symptoms of sleep apnea, depressive symptoms, and antiepileptic drug load. ISS score was strongly associated with anxiety, depressive symptoms, and the use of perampanel in association with anxiety, rather than other epilepsy related factors or sleep disorders. In this study, the prevalence of EDS and insomnia in PWE were 17.5%, and 15.1% respectively, which were consistent with previously reported prevalence of 10-48% (15) and 14.5-51.0% (4).

Daytime sleepiness is one of the most frequently encountered complaints of epilepsy patients. The prevalence of EDS in PWE is comparable with the prevalence of EDS in general population (37), although the impact of EDS on quality of life is larger in PWE. ESS scores in newly diagnosed, drug-free epilepsy and ESS scores in healthy controls were not significantly different, suggesting that treatment or acquired factors like psychologic distress, and sleep disorders could attribute to EDS (38). Therefore, it may benefit patients to find and correct modifiable factors associated with EDS.

In a systematic review, EDS was associated with undiagnosed sleep disorder rather than epilepsy related factors. In this study, sleep apnea was present in 24.6% of PWE, and showed the highest association with ESS scores. EDS and fatigue are the most common complaints of sleep apnea. In one study of PWE, obstructive sleep apnea (OSA) confirmed by polysomnography, was not associated with EDS (39), and patients with OSA had more EDS in the other study (17). Continuous positive airway pressure (CPAP) treatment for sleep apnea in PWE improved seizure control, as well as EDS (40). Therefore, we need to evaluate and treat sleep apnea, if patients with epilepsy complaint of EDS. We found only 2 patients with restless leg syndrome, which was too small to prove the effect of RLS. Low frequency of RLS can be explained by use of AEDs, because many AEDs, including carbamazepine, gabapentin, pregabalin, and clonazepam were effective for treating RLS in double-blind, placebo-controlled trials (41).

We found that presence of depressive mood was associated with ESS scores, but anxiety was not. A Brazilian study of 99 PWE found that anxiety, using Beck Anxiety Inventory (BAI) was associated with EDS (42). A Chinese study of 147 PWE using Hospital Anxiety Depression Scale-Anxiety subscale (HADS-A) found no association between daytime sleepiness and anxiety[46]. Inconsistent results can be explained by comorbid depressive mood in patients with anxiety, making the anxiety a significant factor in univariate analysis, but not in multivariate analysis. Furthermore, anxiety might provoke insomnia, resulting in daytime sleepiness.

Being unemployed was associated with high ESS score in univariate analysis, but employed status was not associated with ESS score in multivariate analysis. Previous study reported that being employed was associated with high EDS, explaining long work-hour might have contributed to daytime sleepiness (37). This is a cross-sectional study, and we cannot distinguish causality between employed status and EDS from correlation. Excessive and overtime work might contribute to decreased total sleep time and increased daytime sleepiness. On the contrary, daytime sleepiness might reduce the chance of being employed.

AEDs including phenobarbital, valproic acid and levetiracetam affect sleep architecture, provoking daytime sleepiness (43). Pregabalin was reported to improve wake after sleep onset (WASO) (44). Not only the type of the AEDs, but also dosage could have affected daytime sleepiness. Therefore, we calculated drug load that includes drug dose, and found that higher drug load was associated with higher ESS score. But we did not find any association of single AED with daytime sleepiness. Epilepsy surgery was known to reduce PSQI scores, but none of the case was pathologic daytime sleepiness (18). In this study, epilepsy surgery was not related to ESS score in both univariate and multivariate analysis.

We found that epilepsy related factors other than drug load show no relationship with EDS. Many studies argued that epilepsy related factors were not associated with EDS (15, 16, 45). One study found that seizure frequency was related to daytime sleepiness (17). Although refractory epilepsy,

nocturnal seizure, type of epilepsy and type of AEDs can affect sleep architecture (17, 42, 46), it may be unrelated to pathologic daytime sleepiness.

Recently, insomnia attracts medical attention because it reduces quality of life, and increases risk for hypertension, diabetes and cardiovascular disease (9, 47-49). In this study, depressive and anxiety symptoms were related to high insomnia score. Insomnia is one of the common signs of depression, and also a risk factor for the development of depression and anxiety (9). In clinical point of view, clinicians should evaluate and manage depression and anxiety in patients with insomnia.

In general population, female gender was associated with insomnia (9). However, we did not find sex differences in patients with insomnia. Previous studies of patients with epilepsy, age, sex and BMI showed no relationship with insomnia (3, 10, 11, 50, 51).

High occurrence of nocturnal seizure might disturb sleep and cause insomnia (13), but we did not find any relationship. Nocturnal seizure was present in 20 (15%) patients, but the frequency of the seizure was low in those patients. 50% of patients with nocturnal seizure were seizure-free in the last year, and rest of them had less than 1 seizure per month. Low frequency of nocturnal seizure might have little effect on sleep or insomnia. Seizure severity, a sum of seizure frequency and seizure type, showed linear correlation with insomnia in univariate analysis, but this relationship did not persist after multivariate analysis. However, two studies found that higher odds of insomnia were found in refractory PWE (8, 12). The reason for different result can be from exclusion criteria, as we excluded patients who had seizure within 48 hours at the time of study enroll, which excluded patients with refractory epilepsy.

AED polytherapy is reported to be associated with insomnia severity (2, 3). For example, lamotrigine provokes insomnia (14). Despite sedative effects of many AEDs (52), the reasons for high occurrence of insomnia in AED polytherapy are explained as follows; We use polytherapy in pharmaco-resistant seizures, and insomnia comes from frequent seizure, rather than AEDs. We found no association between insomnia and drug load or single specific AED in multivariate analysis. Medical treatment could affect sleep disorder though depressive mood and anxiety, which are risk factors for

insomnia we found in this study. We discovered interaction between anxiety and use of perampanel on multivariate analysis for insomnia. In PWE with anxiety, ISI score was lower in patients who used premapanel, than patients who did not use perampanel with marginal significance. Perampanel is an α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) antagonist typically taken at night. It has been reported to improve sleep quality and daytime sleepiness (43). We cannot infer causality in this cross-sectional study, but possible explanations are that the effect of perampanel to reduce ISI score was more prominent in patients with anxiety, whose ISI score were high. Longitudinal study to evaluate effect of perampanel on insomnia in association with anxiety is required in the future study.

Other epilepsy-related factors including type of epilepsy or surgical treatment for epilepsy were investigated in this study, which had rarely been explored in the previous study. Type of epilepsy or surgical treatment for epilepsy were not related to insomnia.

There was no association between insomnia and EDS in PWE, which was consistent with previous reports (4).

We have several limitations. First, we did not use objective measurement for the detection of insomnia, daytime sleepiness and sleep apnea. Gold standard objective measurement are multiple sleep latency test (MSLT) for daytime sleepiness, and polysomnography for insomnia and sleep apnea. ESS score was correlated with total sleep time and psychological factors, rather than mean sleep latency (53). Thus, only subjective daytime sleepiness was counted in this study. To outcome this shortcoming, we used questionnaire that were validated in previous study to show high correlation with objective measurements. ISI scores have correlations with sleep parameters of PSG (24). The STOP-Bang scores more than 3 showed high correlation with obstructive sleep apnea (33, 34). Second, this is a cross-sectional study, showing association, not causality. Third, study population was from single university hospital, so that severity of patients was higher than patients at primary care clinic. Also, patients who cannot cooperate for questionnaires, and who had recent seizure within 48 hours were excluded in this

study. Therefore, the results in this study might not represent whole population of PWE. However, the prevalence of insomnia, daytime sleepiness was comparable with previous studies.

In conclusion, EDS was associated with symptoms of sleep apnea, depressive symptoms, and antiepileptic drug load in patients with epilepsy. Insomnia symptoms were related to anxiety, depressive symptoms, and the use of perampanel has negative correlation with insomnia in association with anxiety.

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국문 요약

제목: 뇌전증 환자에서 과다주간졸음과 불면증상에 관계된 인자들

연구 배경 및 목적: 뇌전증 환자에서 수면장애는 경련의 빈도를 늘리고, 삶의 질을 감소시킬 수 있기 때문에, 최근에 주목을 받고 있다. 이 연구의 목적은 뇌전증 환자에서 과다주간졸음과 불면증상에 관련된 인자들을 심리, 뇌전증, 수면관련 측면에서 찾아보고자 한다.

연구 방법: 뇌전증으로 1년 이상 치료를 받은 18세 이상 환자를 대상으로 연구를 진행하였다. 과다주간졸음을 측정하기 위해 Epworth Sleepiness Scale (ESS)을 사용하였고, 불면증상은 Insomnia Severity Index (ISI)을 사용하였다. 수면에 영향을 끼칠 수 있는 심리적인 요인으로 우울 증상, 불안 증상을 확인하였고, 뇌전증 관련 인자들로는 발병나이, 유병기간, 경련의 빈도와 종류를 고려한 경련의 중증도, 야간발작, 항경련제의 종류, 개수, 용량을 측정하였다. 수면 무호흡과 하지불안증후군을 확인하였다. 다변량 선형 회귀분석을 통해 과다주간졸음과 불면증상에 관련된 인자들을 찾아보았다.

결과: 총 126명의 뇌전증 환자가 연구에 참여하였고, ESS 평균값은 6.06 (표준편차 4.19), ISI 평균값은 7.75 (표준편차 6.42) 였다. ESS점수는 수면 무호흡, 우울 증상, 항경련제 용량과 관련이 있었다. 수면 무호흡은 24.6%의 환자에서 존재하였고, ESS와 가장 높은 연관성을 보였다 (비표준화 계수=3.109, p<0.001). 하지불안증후군은 2명의 환자에서만 보였기 때문에 통계적인 유의성을 알아보기 어려웠다. 우울증상이 ESS 점수와 연관성을 보였고 (비표준화 계수=1.942, p=0.01), 불안증상은 관련이 없었다. 항경련제의 개수와 용량이 높을 수록 높은 ESS점수를 보였다(비표준화 계수=3.811, p=0.005). ISI 점수는 불안증상 (비표준화 계수=6.236, p<0.001), 우울증상(비표준화 계수=3.811, p=0.005) 과 연관성을 보였으나, 뇌전증 관련인자나 다른 수면장애와는 연관성이 없었다. 항경련제 중 perampanel의 사용과 불안증상의 상호작용은 불면증상과 음의 상관관계를 보였다.

고찰: 과다주간졸음증상은 뇌전증 환자에서 수면무호흡, 우울증상, 항경련제 용량과 연관성이 있었다. 불면증상은 불안, 우울증상과 연관이 있었고, 항경련제 중 perampanel의 사용과 불안증상의 상호작용은 불면증상과 음의 상관관계를 보였다.

중심단어: 불면증, 과다주간졸음, 뇌전증

Table 1. Subject characteristics (n=126)

Age, years, mean (SD)	41.7 (12.8)
Men, n (%)	64 (50.8)
Body mass index, kg/m2, mean (SD)	24.3 (3.8)
Unemployed n (%)	32 (25.4)
Age at onset of seizure, years, mean (SD)	22.1 (12.0)
Duration of epilepsy, years, mean (SD)	19.6 (12.2)
Epilepsy and etiology, n (%)	
Genetic	17 (13.5)
Hippocampal sclerosis	11 (8.7)
CNS infection	10 (7.9)
Traumatic	8 (6.3)
Vascular	7 (5.6)
MCD	5 (4.0)
Tumor	1 (0.8)
Unknown etiology	67 (53.2)
Composite seizure severity score, mean (SD)	4.6 (2.4)
Seizure frequency in the last year, n (%)	
Seizure-free	53 (42.1)
1-11 per year	45 (35.7)
1 or more per month	28 (22.2)
Nocturnal seizure, n (%)	20 (15.9)
Surgical resection for epilepsy, n (%)	8 (6.3)
Antiepileptic drug load	2.09 (1.27)
AEDs polytherapy, n (%)	57 (45.2)
Individual AEDs prescribed, n (%)	
Levetiracetam	68 (54.0)
Valproic acid	50 (39.7)
Carbamazepine	29 (23.0)
Topiramate	31 (24.6)
Oxcarbazepine	46 (36.5)
Lamotrigine	26 (20.6)
Perampanel	31 (24.6)
Others*	23 (18.3)

AEDs, antiepileptic drugs; CNS, central nervous system; MCD, malformation of cortical development; n, number; SD, standard deviation

*Zonisamide, clobazam, clonazepam, phenobarbital, pregabalin, phenytoin, vigabatrin, gabapentin, and lacosamide were prescribed individually less than 10%.

Table 2. Questionnaire for anxiety, depression, sleep apnea and restless leg syndrome (n=126)

ISI scores, mean (SD)	7.75 (6.42)
ISI ≥ 16 , n(%)	19 (15.1)
ESS scores, mean (SD)	6.06 (4.19)
ESS ≥ 11 , n (%)	22 (17.5)
GAD-7 scores, mean (SD)	5.1 (5.1)
GAD-7 scores ≥7, n(%)	36 (28.6)
PHQ-9 scores, mean (SD)	6.8 (6.9)
PHQ-9 scores ≥ 10, n(%)	38 (30.2)
STOP-BANG, mean (SD)	1.79 (1.29)
STOP-BANG ≥ 3, n(%)	31 (24.6)
Restless leg syndrome, n(%)	2 (1.59)

ESS, Epworth sleepiness scale; GAD-7, General Anxiety Disorder-7; ISI, Insomnia Severity Index; PHQ-9 Patient Health Questionnaire-9; STOP-BANG, Sleep Apnea Questionnaire; n, number; SD, standard deviation

Table 3. Variables showing $p < 0.1$ in association with excessive daytime sleepiness in patients with epilepsy (n=126)

	Total scores of ESS, *r* or mean (SD)
Body mass index, kg/m^2	0.251
Antiepileptic drug load	0.247
Composite seizure severity score	0.224
ISI scores	0.218
Age at onset of seizure, years	0.139
Anxiety (GAD-7 ≥ 7)	
No	5.20 (3.76)
Yes	8.22 (4.47)
Depression (PHQ-9 scores ≥ 10)	
No	5.13 (3.61)
Yes	8.24 (4.65)
Sleep apnea, (STOP-BANG score ≥ 3)	
No	5.21 (3.86)
Yes	8.68 (4.11)
Occupation	
Unemployed	7.28 (5.18)
Employed	5.65 (3.73)
Valproic acid	
No	5.50 (3.91)
Yes	6.92 (4.48)
Perampanel	
No	5.67 (4.11)
Yes	7.26 (4.25)

r, correlation coefficient; SD, standard deviation; ESS, Epworth sleepiness scale; GAD-7, General Anxiety Disorder-7; ISI, Insomnia Severity Index; SD, *PHQ-9, Patient Health Questionnaire-9; STOP-BANG, STOP-BANG Sleep Apnea Questionnaire;*

Table 4. Multivariate linear regression analysis for EDS in patients with epilepsy (n=126)

	ESS scores			
	B	SE	beta	*p* value
Sleep apnea (STOP-Bang score ≥ 3)	3.109	0.791	0.321	<0.001
Depressive symptoms (PHQ-9 scores ≥ 10)	1.942	0.77	0.214	0.01
Antiepileptic drug load	0.686	0.273	0.207	0.013

B, Non-standardized coefficient; beta, standardized coefficient; SE, Standard Error; ESS, Epworth sleepiness scale; PHQ-9, Patient Health Questionnaire-9; STOP-Bang, STOP-Bang Sleep Apnea Questionnaire;

Table 5. Variables showing p < 0.1 in association with insomnia in patients with epilepsy (n=126)

	Total scores of ISI, *r* or mean (SD)	*p*-value
ESS scores	0.218	0.014
Composite seizure severity score	0.18	0.046
Seizure frequency in the last year		
Seizure-free	6.79 (5.43)	0.026
1-11 per year	7.40 (6.42)	
1 or more per month	10.11 (7.68)	
Anxiety (GAD-7 ≥ 7)		
No	5.40 (4.66)	<0.001
Yes	13.6 (6.51)	
Depressive symptoms (PHQ-9 scores ≥ 10)		<0.001
No	5.08 (4.44)	
Yes	13.9 (6.06)	
Use of valproic acid		0.017
No	6.64 (6.06)	
Yes	9.42 (6.64)	
Use of perampanel		0.46
No	7.99 (6.61)	
Yes	7.00 (5.84)	
Interaction between anxiety symptoms and user of perampanel		0.025

r, correlation coefficient; SD, standard deviation; ESS, Epworth sleepiness scale; GAD-7, General Anxiety Disorder-7; ISI, Insomnia Severity Index; SD, *PHQ-9, Patient Health Questionnaire-9;*

Table 6. Multivariate linear regression analysis for insomnia in patients with epilepsy

	ISI scores			
	B	SE	beta	p value
Depressive symptoms (PHQ-9 scores ≥ 10)	6.236	1.305	0.448	<0.001
Anxiety symptoms (GAD-7 ≥ 7)	3.811	1.326	0.269	0.005

B, Non-standardized coefficient; beta, standardized coefficient; SE, Standard Error; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7;

Table 7. Multivariate linear regression analysis for insomnia in patients with epilepsy, considering interaction between use of perampanel and anxiety

	ISI scores			
	B	SE	beta	p value
Depressive symptoms (PHQ-9 scores ≥ 10)	5.923	1.272	.425	<0.001
Anxiety symptoms (GAD-7 ≥ 7)	5.678	1.508	.401	<0.001
Use of perampanel	-1.632	1.261	-.110	.190
Interaction between anxiety symptoms and user of perampanel	-3.393	2.052	-.167	0.092

Figure 1. Interaction of anxiety symptoms and use of perampanel on ISI