Seizure 34 (2016) 48–53

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Interictal fatigue and its predictors in epilepsy patients: A case-control study

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ARTICLE INFO

Article history:
Received 8 October 2015
Received in revised form 5 December 2015
Accepted 8 December 2015

Keywords:
Epilepsy
Fatigue
Sleep
Depression
Seizures

ABSTRACT

Purpose: Fatigue impairs the quality of life (QOL) of epilepsy patients, but few studies have investigated this issue and no systematic analysis of the predictors of fatigue in epilepsy patients has been performed. Thus, we investigated the degree and predictors of fatigue in epilepsy patients.
Methods: We enrolled 270 consecutive adult patients with epilepsy and categorized them into three subgroups: uncontrolled epilepsy (UCE), well-controlled epilepsy (WCE), and poorly controlled epilepsy (PCE). All subjects were asked to complete the Korean versions of the Fatigue Severity Scale (K-FSS), the Neurological Disorders Depression Inventory for Epilepsy (K-NDDI-E), the Generalized Anxiety Disorder-7 (K-GAD-7) scale, and the short forms of the Patient-Reported Outcomes Measurement Information System Sleep-Related Impairment (PROMIS-SRI) and Sleep Disturbance (PROMIS-SD) scales. Additionally, 200 normal control subjects who completed the K-FSS, K-NDDI-E, and K-GAD-7 measures were included. The K-FSS scores of the epilepsy subgroups and the control group were compared, and stepwise multiple regression analysis was performed to identify predictors of high scores on the K-FSS among epilepsy patients.
Results: The K-FSS, K-NDDI-E, and K-GAD-7 scores were higher in the epilepsy patients than in the controls. The K-FSS scores of the UCE subgroup, but not of the PCE and WCE subgroups, were higher than those of the control group. K-FSS scores of epilepsy patients were predicted by PROMIS-SRI and K-NDDI-E scores.
Conclusions: Fatigue was more severe in epilepsy patients than in healthy controls without epilepsy, especially when seizures were not controlled. Sleep-related impairments and depression aggravated fatigue in epilepsy patients.

1. Introduction

Fatigue has been defined as the experience of extreme and persistent tiredness, weakness, or exhaustion that can be mental, physical, or both [1]. Fatigue is associated with and may be aggravated by neurological disorders such as multiple sclerosis, Parkinson's disease, and stroke [2–6]; similarly, fatigue is also a common complaint of epilepsy patients [7–12]. The prevalence of fatigue ranges from 35.0% to 66.7% in epilepsy patients [9–12] but only occurs in 10–25% of the general population [7,8,13]. The fatigue experienced by epilepsy patients is more severe than that of healthy volunteers and the degree of fatigue in these patients is comparable to that of patients with multiple sclerosis [1]. Moreover, fatigue in epilepsy patients may precipitate their seizures [14,15] and, for this reason, a better understanding of fatigue in epilepsy patients is crucial to effectively manage the course of the disease and the treatment regimen. However, only a few studies have compared the degree of fatigue in epilepsy patients with that of the general population and, even studies that have assessed the propensity for fatigue in epilepsy patients, have used relatively small numbers of patients and controls [1].

Likewise, studies investigating the predictors of fatigue in epilepsy patients are also relatively rare. Although several studies have shown that fatigue in epilepsy patients is related to sleep quality, depression, and anxiety [1,12,16,17], the variables associated with epilepsy, including seizure types, seizure freedom, and factors related to antiepileptic drugs (AEDs), have not been correlated with fatigue [1,16–18]. Of these studies, one [1] observed a tendency for increased fatigue based on the number of AEDs or the number of seizures, but without statistical

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http://dx.doi.org/10.1016/j.seizure.2015.12.003
1059-1311/

significance. Nonetheless, the relationships between fatigue and a number of epilepsy-related factors remain unclear.

Thus, the present study aimed to determine the degree and predictors of fatigue in epilepsy patients by comparing their characteristics with those of healthy control subjects. To accomplish this, a wide variety of epilepsy-related variables, including socioeconomic factors, seizure-related features, and depression, anxiety, and sleep-related problems were assessed to determine the predictors of fatigue in epilepsy patients.

2. Methods

The present cross-sectional study was approved by the Institutional Review Board of Kyungpook National University Hospital. Upon enrollment, all subjects provided informed consent and were asked to complete a battery of reliable and validated self-report health questionnaires that included the Korean versions of the Fatigue Severity Scale (K-FSS), the Neurological Disorders Depression Inventory for Epilepsy (K-NDDI-E), the Generalized Anxiety Disorder-7 (K-GAD-7) scale, and the short forms of the Patient-Reported Outcomes Measurement Information System (PROMIS™) Sleep-Related Impairment (PROMIS-SRI) and Sleep Disturbance (PROMIS-SD) scales.

2.1. Subjects

Epilepsy patients who had been treated with AEDs for at least 1 year and who had attended the epilepsy clinic at Kyungpook National University Hospital between July 1, 2014 and January 31, 2015 were consecutively enrolled in the present study. Epilepsy was diagnosed according to the criteria of the International League Against Epilepsy (ILAE) for seizures and epileptic syndromes [19]. Subjects younger than 19 years of age and older than 70 years of age and subjects with severe neurological, psychiatric, or other disorders that prevented them from understanding the questionnaires and fully cooperating with the study were excluded from the final analyses. The present study initially included 320 epilepsy patients, but 50 were excluded for the following reasons: refusal to complete the questionnaires ($n = 24$), severe neurological or other disorders ($n = 19$), psychosis ($n = 1$), being older than 70 years of age ($n = 4$), less than 1 year of AED treatment ($n = 1$), and lack of education ($n = 1$). Thus, 270 epilepsy patients were included in the final analyses of the present study.

The demographic, socioeconomic, and clinical characteristics of the study subjects are summarized in Table 1. The epilepsy patients were classified into three subgroups based on the state of their seizure control: uncontrolled epilepsy (UCE), well-controlled epilepsy (WCE), and poorly controlled epilepsy (PCE). UCE was defined as an average of more than one seizure per month for 18 months and no seizure-free periods longer than 3 months, which were the criteria used to determine drug-refractory epilepsy as a failure in previous adequate trials of two AEDs [20]. WCE was defined as freedom from seizures during the preceding year, and PCE was defined as an intermediate degree of seizure control that did not meet the criteria for UCE or WCE. Of the 270 epilepsy patients, 49 were classified with UCE, 78 with PCE, and 143 with WCE. The seizure-control classification for each epilepsy patient was determined based on information about seizure frequency obtained from their medical records. Additionally, 200 age- and sex-matched healthy adult volunteers were enrolled in the study

Table 1
Characteristics and questionnaire scores of eligible study subjects.

Characteristics	Mean ± SD (range) or percentage (%)		*p* value[a]
	Epilepsy patients ($n = 270$)	Controls ($n = 200$)	
Age, years	39.8 ± 12.4 (19–70)	40.3 ± 12.3 (19–70)	0.677
Gender, male	168 (62.2%)	125 (62.5%)	1.000
Education, years	12.9 ± 2.8 (6–20)	14.8 ± 2.4 (6–20)	<0.001
Job, yes	130 (48.1%)	137 (68.5%)	<0.001
Household income, ≥1 (million KRW per month)	209 (77.4%)	192 (96.0%)	<0.001
Drivers' license, yes	162 (60.0%)	178 (89.0%)	<0.001
Married but no divorce or bereavement	123 (45.6%)	125 (62.5%)	<0.001
Concurrent medical disease	80 (29.6%)	28 (14.0%)	<0.001
Age at onset, years	25.1 ± 13.1 (1–63)		
Duration of epilepsy, years	14.7 ± 11.0 (1–57)		
Type of seizure, partial	212 (78.5%)		
Epilepsy syndrome			
Temporal lobe epilepsy	131 (48.5%)		
Extra-temporal lobe epilepsy	81 (30.0%)		
Generalized epilepsy	50 (18.5%)		
Unknown	8 (3.0%)		
MRI, abnormal	122 (45.2%)		
Family history of epilepsy	21 (7.8%)		
History of febrile convulsions	60 (22.2%)		
Duration of AED intake, years	11.6 ± 10.0 (1–54)		
AED regimen, monotherapy	125 (46.3%)		
AED load	1.3 ± 0.9 (0.2–4.6)		
Seizure control			
Well-controlled epilepsy	143 (53.0%)		
Partially controlled epilepsy	78 (28.9%)		
Uncontrolled epilepsy	49 (18.1%)		
Co-administration of psychiatric drug	38 (14.1%)		
PROMIS-SD	48.6 ± 10.4 (28.9–76.5)		
PROMIS-SRI	48.3 ± 9.9 (30.0–80)		
K-QOLIE-10 overall score	75.5 ± 20.0 (7.5–100)		

[a] Independent *t*-test or Chi-square test used for analysis.

KRW: Korean won, MRI: magnetic resonance imaging, AED: antiepileptic drug, PROMIS-SD: short form of Patient-Reported Outcomes Measurement Information System-Sleep Disturbance, PROMIS-SRI: short form of Patient-Reported Outcomes Measurement Information System-Sleep-Related Impairment, K-QOLIE-10: Korean version of Quality of Life in Epilepsy Inventory-10, SD: standard deviation, MRI: magnetic resonance imaging

as control subjects. The comparisons of the characteristics of the epilepsy patients and the controls subjects are summarized in Table 1.

2.2. Study design

The electronic medical records of the enrolled patients were reviewed to obtain information regarding patient-related variables such as age, gender, concurrent medical diseases, and the co-administration of psychiatric drugs; epilepsy-related variables such as family history of epilepsy, age at onset, duration of epilepsy, duration of AED medication use, AED regimens, drug load of AEDs, etiology of epilepsy, seizure type, seizure freedom over the preceding year, and febrile convulsions; and psychosocial variables such as education, job, income, marriage, and possession of a drivers' license. Drug load of AED was estimated as the sum of the ratios of 'prescribed daily dose' over 'defined daily dose' for each AED in the regimen of individual patients [21]. The 'defined daily dose' means the assumed average daily maintenance dose of the AED when used for its main indication [22]. The K-NDDI-E, K-GAD-7, K-FSS, PROMIS-SRI, PROMIS-SD, and the Quality of Life (QOL) in Epilepsy Inventory-10 (K-QOLIE-10) scale were completed by patients. The control subjects completed the K-NDDI-E, K-GAD-7, and K-FSS scales.

2.3. Questionnaires

2.3.1. The K-NDDI-E

The K-NDDI-E is a quick, reliable, and validated screening tool for major depressive disorder (MDD) in epilepsy patients [23]. This is a six-item measure using a four-point scale (1–4) to evaluate the degree to which an epilepsy patient has been bothered by depression-related problems over the previous 2 weeks. The total scores range from 6 to 24, and higher scores indicate a more intense level of depression. A total score of 12 or more is suggestive of MDD, and the Cronbach's α coefficient is 0.898 [23].

2.3.2. The K-GAD-7

The GAD-7 is a self-report questionnaire used for the rapid detection of generalized anxiety disorder [24]. This is seven-item measure uses a four-point scale (0–3) to assess the degree to which a subject has been bothered by anxiety-related problems over the previous 2 weeks. The total GAD-7 scores range from 0 to 21, and higher scores indicate a more intense level of anxiety. The present study utilized the K-GAD-7, which can be downloaded from the Patient Health Questionnaire website [www.phqscreeners.com; [25]. The K-GAD-7 has been validated, a total score of 7 or more in the Korean version of the measure is suggestive of generalized anxiety disorder, and the Cronbach's α coefficient is 0.924 [26].

2.3.3. The QOLIE-10

The QOLIE-10 is a 10-item self-administered questionnaire specifically designed to measure QOL in patients with PCE [27]. This measure consists of subscales that address epilepsy effects, mental health, and role functioning, and higher scores are indicative of a better QOL. The present study utilized the K-QOLIE-10. The Cronbach's α coefficient of the Korean version is 0.843 for the epilepsy effects and role function subscales and 0.606 for the mental health subscale [27].

2.3.4. The K-FSS

The FSS consists of nine items that assess fatigue on a scale from 0 to 7 [28]. After summing the scores of the nine items, the total score is divided by 9, yielding values from 0 to 7. The FSS is useful in clinical practice because it has fewer items than other questionnaires that evaluate fatigue and it is easy to score. The Cronbach's α coefficient of the Korean version of the FSS is 0.935, and a total score of 3.22 or more is suggestive of suffering from fatigue [29].

2.3.5. The PROMIS^{TM} and subscales

To improve the quality of the assessments of patient-reported outcomes, a cooperative group founded by scientists from several US-based academic institutions and the National Institutes of Health was created. This group developed the PROMIS^{TM} item banks, which precisely and efficiently measure patient-reported symptoms in individuals with various chronic diseases and conditions [30]. More advanced sleep-associated questionnaires that assess two different aspects of sleep-related problems have been developed from the PROMIS^{TM}: the PROMIS^{TM}-SRI and the PROMIS^{TM}-SD. The full version of the PROMIS^{TM} includes 16 PROMIS^{TM}-SRI items and 27 PROMIS^{TM}-SD items, whereas the short forms of the PROMIS^{TM}-SRI and PROMIS^{TM}-SD each has eight items. The convergent and discriminant validities of the short forms of PROMIS^{TM}-SD and PROMIS^{TM}-SRI reflect correlations with the full versions of PROMIS^{TM}-SD and F- PROMIS^{TM}-SRI, respectively [31]. The responders report the details of their sleep and sleep-related disturbances over the last 7 days using a five-point scale [31]; thus, total scores on the short forms of the PROMIS^{TM}-SRI and PROMIS^{TM}-SD each range from 0 to 40. For the final interpretation of these questionnaires, the individual items are summed and the corresponding *t*-scores are estimated from a nonlinear transformation. The Korean version of the short forms of PROMIS^{TM}-SRI and PROMIS^{TM}-SD were used in the present study.

2.4. Statistical analysis

The descriptive statistics, including counts, percentages, means, and standard deviations, are summarized in Table 1. Independent *t*-tests and chi-square tests were used to compare the K-FSS, K-NDDI-E, and K-GAD-7 scores of the epilepsy patients in all the subgroups with those of the control subjects. A one-way analysis of variance (ANOVA) was used to compare the scores among the study groups, and independent *t*-tests were used to compare each potential pair of groups. In order to obtain the most valid and accurate information possible, a p value <0.01 rather than <0.05 was considered to indicate statistical significance for all comparisons.

To determine the relationship between K-FSS scores and each study variable, a Pearson's correlation coefficient analysis was used to select the variables that were correlated with these scores; a p value <0.05 was considered to indicate statistical significance. Using the selected variables, a stepwise multiple regression analysis was performed to identify the best combination of predictors of a high K-FSS score; a p value <0.01 was considered to indicate statistical significance, and dummy variables were used as the categorical variables. Because QOL is the ultimate psychosocial reflection of the lives of epilepsy patients, the effect of K-QOLIE-10 scores may have obscured the results of the stepwise regression. For this reason, K-QOLIE-10 scores were not included in the stepwise regression analysis even though this score was significantly correlated with the K-FSS score. A collinearity statistical analysis was also conducted as a redundancy check. SPSS software (version 21, IBM Inc.; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

3. Results

3.1. Characteristics of epilepsy patients and control subjects

The demographic, socioeconomic, clinical, and psychosocial characteristics of epilepsy patients and control subjects are

summarized in Table 1. Although the experimental and control subjects were matched by age and gender, there were a number of significant differences ($p < 0.001$) between the two sets of subjects. The epilepsy patients were more likely to have concurrent medical diseases; less likely to be married, have a job, or have a drivers' license; had fewer total years of total education; and had a lower level of income.

3.2. Comparisons between epilepsy subgroups and control subjects

The K-FSS, K-NDDI-E, and K-GAD-7 scores of the epilepsy patients, the epilepsy subgroups, and the control subjects are shown in Table 2. There were significant differences in the K-FSS, K-NDDI-E, and K-GAD-7 scores between the epilepsy patients and the controls ($p < 0.01$). The comparisons between each potential pair of the three epilepsy subgroups and the control group revealed that the K-FSS, K-NDDI-E, and K-GAD-7 scores were higher in the UCE subgroup than in the control group and that the K-NDDI-E scores were higher in the PCE subgroup than in the control group ($p < 0.01$ for all comparisons). The comparisons of each potential pair among the three epilepsy subgroups revealed that the K-FSS, K-NDDI-E, and K-GAD-7 scores were higher in the UCE subgroup than in the WCE subgroup ($p < 0.01$).

3.3. Pearson's correlation coefficients for the relationship between K-FSS scores and each study variable

The study variables that were significantly correlated with the K-FSS scores are listed in Table 3. The K-FSS scores were higher in the following subgroups of epilepsy patients: those with no job, a low household income, no driver's license, who were unmarried, who had an early age of onset, who had no seizure freedom, who were undergoing a polytherapy, and who were undergoing the co-administration of psychiatric drugs. The K-FSS scores were also higher in epilepsy patients with high PROMIS-SRI, PROMIS-SD, K-NDDI-E, and K-GAD-7 scores and in epilepsy patients with low total K-QOLIE-10 scores. However, the duration of AED medication use and drug load of AEDs were not associated with KFSS scores.

3.4. Predictors of the K-FSS score

The stepwise multiple regression analysis in the present study produced a model with two variables that explained 44.9% of the variance. The strongest predictors of K-FSS scores were PROMIS-SRI ($\beta = 0.526$, $p < 0.01$) and K-NDDI-E ($\beta = 0.232$, $p < 0.01$; Table 4) scores. The standardized β value revealed that the effect of PROMIS-SRI scores on K-FSS scores were 2.27 times stronger than that of K-NDDI-E scores. Because the redundancy check showed that the variance inflation factors were less than 10 for the two significant variables, their effects were independent of each other.

Table 3
Variables correlated with K-FSS scores in epilepsy patients.

Variable	p value (r)[a]
Job	0.008 (−0.162)
Drivers' license	0.015 (−0.148)
Married but no divorce or bereavement	0.004 (−0.175)
Age at onset	0.016 (0.147)
Household income	0.019 (−0.143)
AED regimen, monotherapy	0.016 (−0.147)
Seizure control	<0.001 (−0.211)
Co-administration of psychiatric drugs	<0.001 (0.283)
PROMIS-SD	<0.001 (0.519)
PROMIS-SRI	<0.001 (0.643)
K-QOLIE-10	<0.001 (−0.546)
K-NDDI-E	<0.001 (0.497)
K-GAD-7	<0.001 (0.498)

[a] Pearson's correlation analysis was used for the analysis.
K-FSS: Korean version of Fatigue Severity Scale, AED: antiepileptic drug, PROMIS-SRI: short form of Patient-Reported Outcomes Measurement Information System Sleep-Related Impairment, PROMIS-SD: short form of Patient-Reported Outcomes Measurement Information System Sleep-Disturbance, K-QOLIE-10: Korean version of Quality of Life in Epilepsy Inventory-10, K-NDDI-E: Korean version of Neurological Disorders Depression Inventory for Epilepsy, K-GAD-7: Korean version of Generalized Anxiety Disorder-7

4. Discussion

The present study demonstrated that the fatigue experienced by epilepsy patients was more severe than that experienced by the healthy control subjects. A previous study found that the severity of fatigue is higher in epilepsy patients than in healthy controls but the numbers of subjects in each group in that study were relatively small [1]. The present study included 270 epilepsy patients and 200 healthy control subjects, which is a greater number of participants than included in other studies investigating fatigue in epilepsy patients [1,16,17]. This may render the differences in fatigue observed in epilepsy patients and controls in the present study more reliable and valid. Additionally, the present study also compared the degree of fatigue of each epilepsy subgroup with age- and sex-matched control subjects. The K-FSS scores of the UCE subgroup, but not of the PCE or WCE subgroups, were significantly higher than those of the control group. The present study also assessed numerous variables describing various characteristics of the subjects, including socioeconomic and seizure-related variables, depression, anxiety, and sleep-related problems, to identify the predictors of fatigue more accurately. The results show that the fatigue in epilepsy patients

Table 2
Fatigue, depression, and anxiety in epilepsy patients compared with control subjects.

	Mean ± SD (range)				
	Total patients with epilepsy ($n = 270$)	UCE ($n = 49$)	PCE ($n = 78$)	WCE ($n = 143$)	Controls ($n = 200$)
K-FSS	3.1 ± 1.5 (1.0–7.0)[b]	3.8 ± 1.6 (1.1–6.7)[b,**]	3.1 ± 1.4 (1.0–6.7)	2.9 ± 1.4 (1.0–7.0)	2.7 ± 1.3 (1.0–6.6)
K-NDDI-E	10.1 ± 4.5 (6–24)[b]	12.5 ± 5.7 (6–24)[b,**]	10.2 ± 4.4 (6–24)[b]	9.2 ± 3.8 (6–24)	8.7 ± 2.9 (1–18)
K-GAD-7	4.7 ± 5.4 (0–21)[b]	7.6 ± 6.2 (0–21)[b,**]	5.3 ± 5.9 (0–21)[a,*]	3.4 ± 4.2 (0–21)	3.5 ± 3.6 (0–19)

[a] $p < 0.05$, Comparisons with controls.
[b] $p < 0.01$, Comparisons with controls.
[*] $p < 0.05$, Comparison with WCE.
[**] $p < 0.01$, Comparison with WCE.
A one-way ANOVA was used for the comparisons of the scores of WCE, PCE, and UCE patients with those of the control subjects. Independent t-tests were performed to compare the scores between the epilepsy patients and control subjects and between each potential pair of the three subgroups of epilepsy patients and control subjects. UCE: uncontrolled epilepsy, PCE: poorly controlled epilepsy, WCE: well-controlled epilepsy, K-FSS: Korean version of Fatigue Severity Scale, K-NDDI-E: Korean version of Neurological Disorders Depression Inventory for Epilepsy, K-GAD-7: Korean version of Generalized Anxiety Disorder-7, SD: standard deviation

Table 4
Predictors of K-FSS scores in epilepsy patients according to a multiple stepwise regression analysis.

Variable	Standardized coefficients (ß)	p value	Collinearity (VIF)	Adjusted R^2
				0.449
PROMIS-SRI	0.526	<0.001	1.340	
K-NDDI-E	0.232	<0.001	1.340	

K-FSS: Korean version of Fatigue Severity Score, PROMIS-SRI: short form of Patient-Reported Outcomes Measurement Information System Sleep-Related Impairment, K-NDDI-E: Korean version of Neurological Disorders Depression Inventory for Epilepsy, VIF: variance inflation factor

was primarily associated with sleep-related impairments and depression.

Two previous studies found that sleep-related problems are crucial predictors of fatigue in epilepsy patients, but the particular aspects of the sleep-related problems differ among studies. Neves et al. [16] included sleep quality and daytime sleepiness as candidate variables in their analysis and found that sleep quality, but not daytime sleepiness, was a significant predictor of fatigue in epilepsy patients. In contrast, Hamelin et al. [17] found that daytime sleepiness was an important predictor of fatigue in epilepsy patients, although this study did not include sleep quality as a candidate predictor. The present study utilized advanced forms of questionnaires to evaluate sleep quality and daytime sleepiness: the PROMIS-SD and PROMIS-SRI, respectively. PROMIS-SRI scores were significant predictors of fatigue in epilepsy patients, but PROMIS-SD scores were not, which is concordant with the findings of Hamelin et al. [17].

Epilepsy and depression have a bidirectional relationship and, as a corollary of this relationship, depression is often comorbid with epilepsy. It has been found that 9–37% of epilepsy patients suffer from depression [32], and several studies have shown that fatigue in epilepsy patients is determined by the presence of depression [9,16]. Neves et al. [16] determined that depression and sleep quality are significant predictors of fatigue in epilepsy patients and that the effects of depression are stronger than those of sleep quality. In the present study, sleep-related impairments, but not sleep quality, was a significant predictor of fatigue, and this effect was 2.27 times stronger than that of depression.

The present study compared the degrees of fatigue between each potential pair of the three epilepsy subgroups and the control group and found that K-FSS scores were significantly higher in the UCE subgroup than in the control group. However, the K-FSS scores of the PCE and WCE subgroups did not differ from that of the control group. These findings suggest that fatigue may be more severe in epilepsy patients when their seizures are not controlled. On the other hand, the stepwise multiple regression analysis in the present study showed that seizure control was not a significant predictor of fatigue in epilepsy patients.

No correlations between fatigue and epilepsy-related variables, including seizure type, seizure freedom, and factors associated with AED treatment, have been observed in previous studies [1,16–18]. Of these studies, one observed that the number of AEDs and the number of seizures tended to increase fatigue, but these relationships did not exhibit statistical significance [1]. To date, only one study has found a high frequency of seizures to be a significant predictor of fatigue in epilepsy patients, but the study did not include psychosocial factors or sleep-related problems in the multiple regression analysis [12].

There is a vicious cycle between sleep-related problems and seizure control. Seizures are likely a primary cause of sleep-related problems, and sleep-related problems may aggravate seizure control states [33–35]. A few studies have investigated seizure precipitants in epilepsy patients, and these found that fatigue and sleep deprivation tended to precipitate seizures [14,15]. Thus, it is impossible to ignore the association between fatigue and seizure control in epilepsy patients. In the context of these findings, our observation suggests important associations among fatigue, sleep-related problems, and seizure control. This study found a partial relationship among these variables; the stepwise regression analysis showed that K-FSS scores were determined by PROMIS scores and that K-FSS scores were higher in UCE patients but not in WCE patients compared with control subjects (Table 2). Furthermore, PROMIS-SRI scores were higher in the UCE subgroup than in the WCE subgroup (Table 5). These findings may be interpreted to mean that fatigue has an indirect relationship with seizure control. Although seizure control per se may not directly be involved with the experience of fatigue, the seizure control state may influence the fatigue of epilepsy patients via indirect mechanisms that are mediated by sleep-related impairments.

Patients with UCE are more likely to be given additional AEDs than are those with WCE and patients who receive more AEDs may be associated with greater levels of fatigue than those given lesser amounts of AEDs [1]. This association was also evident in the correlation analysis in the present study; in which the K-FSS scores were higher in the epilepsy patients who underwent polytherapy than in those who underwent monotherapy. AED loads were not correlated with K-FSS scores and, despite the relationship between K-FSS scores and drug number, K-FSS scores were not predicted by drug number. This suggests that the drug number may also have indirect effects on fatigue by influencing sleep-related impairments, in a similar way to the effects of seizure control on fatigue.

As observed in this and previous studies [9,16,17], sleep-related problems and depression may intensify fatigue in epilepsy patients. Thus, screening for depression and sleep-related

Table 5
Differences in sleep-related problems among the epilepsy subgroups according to seizure control in epilepsy patients.

	Mean ± SD (range)		
	UCE (n = 49)	PCE (n = 78)	WCE (n = 143)
PROMIS-SD[a]	51.86 ± 11.05 (28.90–76.50)**	49.34 ± 10.06 (28.90–76.50)	47.01 ± 10.01 (28.90–76.50)
PROMIS-SRI[b]	53.39 ± 10.27 (30.00–76.90)**	49.22 ± 9.56 (30.00–73.30)*	46.07 ± 9.33 (30.00–80.00)

A one-way ANOVA was conducted for the comparisons of the scores among WCE, PCE, and UCE patients. Independent t-tests were performed to compare the scores between each potential pair of the three subgroups. UCE: uncontrolled epilepsy, WCE: well-controlled epilepsy, PCE: poorly controlled epilepsy, PROMIS-SD: short form of Patient-Reported Outcomes Measurement Information System-Sleep Disturbance, PROMIS-SRI: short form of Patient-Reported Outcomes Measurement Information System Sleep-Related Impairment, SD: standard deviation

[a] $p < 0.05$, Comparison among all three subgroups.
[b] $p < 0.01$, Comparison among all three subgroups.
* $p < 0.05$, Comparison with WCE.
** $p < 0.01$, Comparison with WCE.

problems should be conducted in epilepsy patients to prevent fatigue. The present results also indicate that fatigue in epilepsy patients may be more severe than fatigue in healthy people when the seizures of the patients are not controlled and, therefore, fatigue levels must be considered when seizure control is an issue. The fatigue of epilepsy patients may be reduced by improving sleep hygiene and treating depression and, more specifically, the present study showed that the fatigue of UCE patients may be ameliorated by improving seizure control. Conversely, the reduction of fatigue may also aid in the control of seizures. Sleep-related problems, depression, and fatigue have been shown to impair QOL in epilepsy patients [9,33,36,37]; thus, it is possible that reducing fatigue and depression and improving sleep hygiene and seizure control may lead to enhanced QOL in epilepsy patients.

Conflic of interest statement

The authors report no financial interests or potential conflicts of interest related to the present study.

Acknowledgments

The authors report no financial interests or potential conflicts of interest related to the present study.

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