



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



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## 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.

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## 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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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 $\pm$ SD (range) or percentage (%)		<i>p</i> value <sup>a</sup>
	Epilepsy patients ( $n = 270$ )	Controls ( $n = 200$ )	
Age, years	39.8 $\pm$ 12.4 (19–70)	40.3 $\pm$ 12.3 (19–70)	0.677
Gender, male	168 (62.2%)	125 (62.5%)	1.000
Education, years	12.9 $\pm$ 2.8 (6–20)	14.8 $\pm$ 2.4 (6–20)	<0.001
Job, yes	130 (48.1%)	137 (68.5%)	<0.001
Household income, $\geq 1$ (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 $\pm$ 13.1 (1–63)		
Duration of epilepsy, years	14.7 $\pm$ 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 $\pm$ 10.0 (1–54)		
AED regimen, monotherapy	125 (46.3%)		
AED load	1.3 $\pm$ 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 $\pm$ 10.4 (28.9–76.5)		
PROMIS-SRI	48.3 $\pm$ 9.9 (30.0–80)		
K-QOLIE-10 overall score	75.5 $\pm$ 20.0 (7.5–100)		

<sup>a</sup> 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

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