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Insomnia symptoms and obesity are associated with aggression independent of depression in patients with epilepsy

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ABSTRACT

Purpose: : There has been little research conducted into aggression in persons with epilepsy (PWE). We determine whether sleep disturbances and obesity are associated with aggression in PWE independent of psychological distress.

Methods: : This was a cross-sectional study. The Aggression Questionnaire (AQ-K), the Insomnia Severity Index (ISI), the Epworth Sleepiness Scale (ESS), the Patient Health Questionnaire-9 (PHQ-9), and the Generalized Anxiety Disorder-7 (GAD-7) were utilized in the study. A stepwise linear regression analysis was used.

Results: : A total of 104 participants (49% men) were included. Mean AQ-K score was 51.4 (SD 12.6). PHQ-9 scores ≥10 and GAD-7 scores ≥7 were noted in 26.9% and 24.0% of participants, respectively. In a stepwise linear regression model, AQ-K scores were positively associated with PHQ-9 scores ≥10 ($p = 0.002$), ISI scores ($p = 0.007$), body mass index (BMI) ($p = 0.001$), and composite scores of epilepsy severity ($p = 0.013$). This model explained 46.6% of the variance in the AQ-K. In the subscale analyses, different variables were identified as independent factors associated with different subscales of the AQ-K. For example, physical aggression was related to a PHQ-9 score ≥10, men, and perampanel usage, whereas hostility was related to a GAD-7 score ≥7, polytherapy, and BMI.

Conclusions: : Insomnia symptoms and obesity were related to overall aggressive behavior in PWE independent of depressive symptoms. The individual subscales of the AQ were correlated differently with the various factors including male sex, obesity, depressive symptoms, anxiety, insomnia symptoms, epilepsy severity, polytherapy, and the use of perampanel.

1. Introduction

Aggression can be defined as “overt motor behavior enacted with the intent to do harm or injury to a person or object, with the expectation that harm will occur” [1]. Interictal aggression related to epilepsy has been well described in the literature and is not a new concept. Although interictal dysphoric disorder, a mood disorder found in persons with epilepsy (PWE), has been a matter of debate [2], a symptom cluster characterized by periodical mood changes and outbursts of irritability and aggressive behavior was considered one of the key symptoms of this disorder [3]. However, relatively little attention has been paid to aggression in PWE compared to depression, anxiety, and psychosis. Although it is assumed that aggression is common in PWE, the prevalence of interictal aggressive behavior in PWE remains unknown [4], and may change depending on the definition of aggressive behavior, epilepsy subtypes, and the origin of the study population. Recently, behavioral symptoms such as irritability, aggression, and tantrum were observed in 10.6% of 4085 adults with epilepsy [5]. Patients with temporal lobe epilepsy in particular exhibited a rate of violent acts of ~7% [6]. Since the adverse behavioral effects of some newer antiepileptic drugs (AEDs) have been widely recognized [4,7], the number of studies on this topic is now increasing.

Aggression in PWE has been suggested to have a complex and multifactorial background, especially involving psychosocial, AED-related, and epilepsy-related factors [7]. The link between aggressive behavior and psychiatric disturbance especially depression has been well documented [8,9]. A recent Swedish population-based longitudinal study showed an association between a diagnosis of depression and violent crime [8]. A large Italian study using the Aggression Questionnaire (AQ) showed that psychiatric disturbances were

Abbreviations: AED, antiepileptic drug; AQ-K, Korean version of Aggression Questionnaire; BMI, body mass index; ESS, Epworth Sleepiness Scale; GAD-7, Generalized Anxiety Disorder-7; ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9; PWE, persons with epilepsy; SD, standard deviations

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significantly associated with aggression in PWE [9]. Some AEDs, especially topiramate, levetiracetam, and perampanel, are well known to be able to induce aggressive behavior in PWE [4,5,7]. Epilepsy-related factors are also related to aggressive behaviors in PWE. In a large Italian study, AED polytherapy and epilepsy duration were found to be associated with aggression in PWE [9].

Sleep disturbances may be a potential risk factor affecting emotional function, and consequently resulting in reactive aggression and violence [10]. However, relatively little attention has been paid to the effects of sleep problems on aggression. Disturbed sleep is accompanied by emotional instability expressed by a greater irritability and short-temperedness. In most people this will not result in physical outbursts of aggression. However, this may be different in vulnerable individuals, such as epilepsy patients, who are frequently accompanied by psychiatric problems and sleep disturbances [10]. Persons with epilepsy have been consistently reported to have poor sleep quality, insomnia, and obstructive sleep apnea two to three times more commonly than healthy controls [11,12]. Some studies have reported a higher prevalence of excessive daytime sleepiness in PWE [13].

Another potential risk factor for aggression may be obesity, which is a major health problem worldwide. Obesity was found to be strongly associated with impulsivity, which is thought to be a risk factor for aggression [14]. Persons with epilepsy may have a greater risk for obesity than the general population because they are often sedentary and may be treated with weight gain-causing medications such as valproate, pregabalin, and perampanel [15]. Obesity is more common in patients with refractory epilepsy and in patients treated with polytherapy [15]. Little research has been conducted into associations between sleep disturbances or obesity and aggression in PWE.

The measurement of aggression seems to depend on definition, so that different instruments may measure different aspects of aggression. The AQ developed by Buss and Perry is one of the most popular self-report questionnaires for the measurement of aggression, and has the four-factor structure measuring physical aggression, verbal aggression, anger, and hostility [16]. The individual subscales of the AQ may correlate differently with the potential risk factors for aggression. For example, the original study of the AQ showed that men were much more physically aggressive than women, somewhat more verbally aggressive, and just a little more hostile [16].

Therefore, the purpose of this study was to determine whether sleep disturbances and obesity are associated with aggression in PWE independent of psychological distress such as depressive symptoms or anxiety. Referring to the literature [4,5,7–10,14], it was expected that aggression would be correlated with various clinical factors such as psychological distress, some AEDs, epilepsy-related variables, sleep disturbances, and obesity in PWE and the individual components of aggression would be differently correlated with various risk factors for aggression.

2. Methods

2.1. Subjects

This was a cross-sectional study conducted at a single university hospital in Korea. Inclusion criteria were as follows: patients aged over 18; with a diagnosis of epilepsy; who had been taking antiepileptic medication for at least one year; willing to complete self-reported questionnaires. A revised 2014 definition of epilepsy was used in this study, whereby it is defined by either: 1) two unprovoked seizures occurring more than 24 h apart, or 2) one unprovoked seizure and a minimum risk of 60% for another occurring in the next 10 years [17]. Because there was limited information about the recurrence risk after a single seizure in some clinical circumstances, a diagnosis of epilepsy after a single seizure was made in this study supported by the findings of electroencephalography or magnetic resonance imaging [17]. The new International League Against Epilepsy classifications of seizures and epilepsy were applied in this study [18,19]. The participants were asked to fill out questionnaires when visiting their neurologist at the outpatient clinic. Demographic and clinical data were collected by conducting interviews and reviewing medical files. Patients were excluded if they had experienced a seizure in the 48 h before the request to fill out the questionnaire, or if they were unable to read or understand the questionnaire. Written informed consent was obtained from all participants. The study was reviewed and approved by the Institutional Review Board of Asan Medical Center.

2.2. Assessment tools

The AQ is a validated instrument for assessing aggression [16], which consists of 29 items categorized into four subdomains: physical aggression (9 items), verbal aggression (5 items), anger (7 items), and hostility (8 items). Each item is evaluated using a 5-point Likert scale ranging from 1 (never) to 5 (always). Single domain scores can be added together to obtain a total score. The validated Korean version of the AQ (AQ-K) was used in this study [20]. During the validation process of the AQ-K, a decision was made to omit two of the original items from the anger subscale ('some of my friends think I'm a hothead' and 'sometimes I fly off the handle for no good reason') because they related more to verbal aggression and hostility than anger. As a result, the AQ-K evaluates aggression using 27 items [20]. A total score of the AQ-K ranges from 27 to 135, with a higher score representing a higher level of aggression. In the validation study of 552 college students (age 26.6 ± 3.2 years), the mean score of the AQ-K was 68.2 (standard deviation [SD] 13.3) [20].

The Insomnia Severity Index (ISI) consists of 7 items that assess difficulty falling asleep and staying asleep, problems waking up too early, satisfaction with current sleep pattern, interference with daily functions, noticeability of impairment attributed to sleep problems, and distress caused by sleep problems [21]. Each item is rated on a 5-point Likert scale ranging from 0 to 4. The total score of the ISI ranges from 0 to 28, with a higher score indicating greater insomnia severity. The validated Korean version of the ISI used in this study has previously been shown to demonstrate excellent internal consistency, good test-retest reliability, and adequate convergent and divergent validities [21]. In the validation study, a cutoff score of 15.5 on the ISI was optimal for discriminating patients with insomnia [21].

Daytime sleepiness was assessed using the validated Korean version of the Epworth Sleepiness Scale (ESS) [22], consisting of eight questions regarding how often an individual dozes during daily activities. Each answer is rated on a 4-point scale ranging from 0 (never dozed) to 3 (high chance of dozing). The total score of the ESS ranges from 0 to 24, with a higher score indicating a greater sleep propensity during the day. In the validation study, the mean ESS score of the healthy controls was 5.07 (SD 2.93) [22].

The Patient Health Questionnaire-9 (PHQ-9) is a 9-item self-reported scale used to assess and grade the severity of depression [23]. Each item is rated on a 4-point Likert scale ranging from 0 (absence of symptom) to 3 (presence of symptom nearly every day) in the last 2 weeks. Total PHQ-9 score is obtained from the sum of the scores of the 9 items, and ranges from 0 to 27. A higher PHQ-9 score indicates a greater risk of depression. The Korean version of the PHQ-9 has been previously validated [23]. A PHQ-9 score ≥ 10 is considered indicative of depression.

The Generalized Anxiety Disorder-7 (GAD-7) is a 7-item self-reported scale used for the rapid detection of generalized anxiety disorder [24]. Subjects are asked to respond to questions about how much they have been affected by anxiety-related problems over the past 2 weeks. Each item is rated on a 4-point Likert scale ranging from 0 to 3. Total GAD-7 score ranges from 0 to 21, and a higher score indicates more intense anxiety. The Korean version of the GAD-7 was previously validated in PWE [24]. A GAD-7 score ≥ 7 is considered indicative of an anxiety disorder.

2.3. Epilepsy severity measurement

Composite epilepsy severity score was determined here based on seizure type, seizure frequency, and the number of antiepileptic drugs, as in Lee et al. [25]. Seizure type was scored 3 for generalized or focal to bilateral tonic–clonic seizures, 2 for focal impaired awareness seizures, 1 for focal aware seizures, and 0 where there had been an absence of seizures for at least 1 year. When patients exhibited more than one type of seizure, the most severe was used. Seizure frequency was scored 3 for weekly or daily seizures, 2 for monthly seizures, 1 for 1–11 seizures a year, and 0 where there had been an absence of seizures for at least 1 year. Medication regimen was scored 3 for a regimen comprising 3 or more antiepileptic drugs, 2 for duotherapy, 1 for monotherapy, and 0 where a patient was receiving no medication. The composite epilepsy severity score ranges from 0 to 9, with a higher score reflecting a greater epilepsy severity.

2.4. Statistical analysis

Data are presented as mean ± SD for numerical variables, and numbers and percentages for nominal variables. The potential factors independently associated with aggressive symptoms in PWE were assessed using multivariate linear regression analyses. Here, the dependent variables included the total AQ-K score and the scores of each domain of the AQ-K. The independent variables included demographic, psychological, sleep-related, epilepsy-related, and medication-related variables. Demographic variables included age, sex, and body mass index (BMI). Psychological variables included depression, defined by a PHQ-9 score ≥ 10, and anxiety, defined by a GAD-7 score ≥ 7. Sleep-related variables included ISI and ESS scores. Epilepsy-related variables included age at seizure onset, duration of epilepsy, type of epilepsy and seizures, seizure frequency in the last year, recurrence of generalized or focal to bilateral tonic-clonic seizures in the last year, and composite score of epilepsy severity. Medication-related variables included the number of AEDs and the use of individual AEDs prescribed in more than 15% of the participants. Univariate analyses were conducted using an unpaired *t*-test or Pearson correlation test depending on the types of independent variables. Variables with $p < 0.05$ on univariate analysis were then entered into a stepwise linear regression model with an entry criterion set at $b < 0.05$. Multicollinearity was determined for all stepwise regression models by calculating the variance inflation factor. Any regression model with a variance inflation factor > 5 was excluded based on the presence of significant multicollinearity. All statistical tests conducted were two-tailed, and $p < 0.05$ was considered significant. Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 21.0 (International Business Machines Corp., Armonk, NY, USA).

3. Results

3.1. Subjects

A total of 104 participants were included in this study (Table 1). Of these, 51 (49%) were men, and 53 (51%) were women. The mean age of the participants was 40.9 years old (SD 12.9). The mean number of AEDs was 2.3 (SD 1.1, range 1–5). The mean AQ-K score was 51.4 (SD 12.6). Of the 104 participants, 28 (26.9%) and 25 (24.0%) had depressive symptoms (PHQ-9 score ≥ 10) and anxiety (GAD-7 score ≥ 7), respectively. The mean scores of the ISI and ESS were 7.3 (SD 6.2) and 5.7 (SD 4.1), respectively.

3.2. Factors associated with total AQ-K scores

Based on univariate analyses, AQ-K total scores were positively correlated with ISI score ($r = 0.489$, $p < 0.001$), composite score of epilepsy severity ($r = 0.356$, $p < 0.001$), ESS score ($r = 0.331$, $p = 0.001$), and BMI ($r = 0.275$, $p = 0.005$) (Table 2). Participants with a PHQ-9 score ≥ 10 ($p < 0.001$), GAD-7 score ≥ 10 ($p < 0.001$), higher seizure frequency ($p = 0.007$), AED polytherapy ($p = 0.01$), or the presence of generalized or focal to bilateral tonic clonic seizures ($p = 0.023$) had higher AQ-K total scores (Table 3).

When variables with $p < 0.05$ in the univariate analyses were entered into a stepwise linear regression model, depressive symptoms (PHQ-9 score ≥ 10), ISI score, BMI, and composite score of epilepsy severity were identified as independent factors associated with higher AQ-K total scores (Table 4). This model explained 46.6% of the variance in AQ-K total scores.

3.3. Factors associated with individual AQ-K subscale scores

Variables with $p < 0.05$ in the univariate analyses are shown in Table 2 and 3, and these were entered into a stepwise linear regression

Table 1
Subject characteristics (n = 104).

Body mass index, Kg/m^2, mean (SD)	24.4 (4.0)
Occupational status, n (%)	
Housewife	24 (23.1)
Student	6 (5.8)
Employed	51 (49.1)
Unemployed	23 (22.1)
Age at seizure onset, years, mean (SD)	22.1 (12.7)
Duration of epilepsy, years, mean (SD)	18.8 (12.3)
Epilepsy type, n (%)	
Generalized, idiopathic	17 (16.3)
Focal	83 (79.8)
CNS infection	10 (9.6)
Hippocampal sclerosis	9 (8.7)
Traumatic	8 (7.7)
Vascular	5 (4.8)
MCD	5 (4.8)
Tumor	2 (2.0)
Unknown etiology	44 (42.4)
Unknown	4 (3.8)
Seizure type, n (%)	
Focal aware	14 (13.5)
Focal impaired awareness	54 (51.9)
Generalized or focal to bilateral TCS	36 (34.6)
Seizure frequency in the last year, n (%)	
Seizure-free	37 (35.6)
1-11 per year	46 (44.2)
1 or more per month	21 (20.2)
Composite scores of epilepsy severity, mean (SD)	4.44 (2.38)
AED polytherapy, n (%)	72 (69.2)
Individual AEDs prescribed, n (%)	
Levetiracetam	61 (58.7)
Valproic acid	37 (35.6)
Carbamazepine	22 (21.2)
Topiramate	23 (22.1)
Oxcarbazepine	39 (37.5)
Lamotrigine	21 (20.2)
Perampanel	16 (15.4)
Others*	20 (19.2)
Histories of psychiatric disorders, n (%)	15 (14.4)
Insomnia Severity Index scores ≥ 16, n (%)	15 (14.4)
Epworth Sleepiness Scale scores ≥ 11, n (%)	16 (15.4)
AQ-K, mean (SD)	
Physical aggression	15.2 (4.4)
Verbal aggression	10.4 (3.4)
Anger	11.7 (3.4)
Hostility	14.1 (4.8)

AED, antiepileptic drug; AQ-K, Korean version of Aggression Questionnaire; n, number; SD, standard deviation; TCS, tonic clonic seizures.
The range of possible scores of the measures: Composite scores of epilepsy severity 0–9, Insomnia Severity Index 0–28, Epworth Sleepiness Scale 0–24, and AQ-K 27–135.
* Zonisamide, lacosamide, pregabalin, clobazam, phenoabarbital, lorazepam, phenytoin, and ethosuximide were prescribed individually less than 10%.

Table 2
Correlation coefficients showing $p < 0.05$ between numeric variables and the scores of the Aggression Questionnaire in patients with epilepsy (n = 104).

	Total	Physical aggression	Verbal aggression	Anger	Hostility
Body mass index, Kg/m^2	0.275**	0.215*	0.274**	0.109	0.258**
Insomnia Severity Index	0.489***	0.359**	0.213*	0.543***	0.425***
Epworth Sleepiness Scale	0.331**	0.232*	0.136	0.298**	0.359***
Composite scores of epilepsy severity	0.356***	0.242*	0.137	0.388***	0.344***

The range of possible scores of the measures: Composite scores of epilepsy severity 0–9, Insomnia Severity Index 0–28, Epworth Sleepiness Scale 0–24, and AQ-K.27–135.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

model for individual subscales of the AQ-K. Different variables were identified as independent factors associated with different subscales of the AQ-K (Table 5). A PHQ-9 score ≥ 10 was significantly associated with all subscales except hostility ($p = 0.057$). In contrast, a GAD-7 score ≥ 7 was related only to hostility. Male sex and the use of perampanel were associated with only physical aggression. ISI score was associated with anger, whereas BMI was related to verbal aggression and hostility. Composite score of epilepsy severity and AED polytherapy were associated with anger and hostility, respectively. These models for physical aggression, verbal aggression, anger, and hostility explained 35.2%, 15.5%, 42.3%, and 35.4% of the variance in the individual subscales of the AQ-K, respectively.

4. Discussion

We identified a number of factors associated with aggression in PWE: male sex, obesity, depressive symptoms, anxiety, insomnia symptoms, epilepsy severity, polytherapy, and the use of perampanel. Aggression-associated factors were found to be different for each domain of the AQ-K. As expected, insomnia symptoms and obesity were related to overall aggressive behavior in PWE independent of depressive symptoms. Among these aforementioned factors, depressive symptoms were found to be the most important for overall aggression and all domains of aggression, except for hostility. Our findings were consistent with the previous studies, which showed a significant relationship between depression and aggressive behavior in non-epilepsy and epilepsy populations [8,9]. It has been suggested that common pathogenic pathways exist between epilepsy and depression [26] and that the common neurotransmitter systems and brain regions might exist between epilepsy and aggression [4]. For these reasons, depression can facilitate aggressive behavior, which can be a direct consequence of depression [9]. However, it is possible that potential mediators may exist in the relationship between depression and aggression. A Korean study in PWE (n = 266) using the AQ-K showed that the strongest factor associated with aggression was perceived stigma, followed by anxiety and depressive symptoms [27]. In additional analysis using a structural equation model, perceived stigma exerted a direct effect on aggression, but depressive symptoms only had an indirect effect on aggression through perceived stigma [27].

As we expected that sleep problem and obesity may be a potential risk factor for aggression [10,14], this study found that insomnia symptoms and obesity were significantly related to aggression, particularly anger and verbal aggression/hostility, respectively, in PWE independent of depressive symptoms. Similarly, in a large Korean study of a middle-aged population, sleep problems such as difficulty maintaining sleep were identified as factors associated with trait anger, measured by the Spielberger Trait Anger Scale [28]. In a US study, college students with poor subjective sleep quality, as measured by the Pittsburgh Sleep Quality Index (cut-off score > 8), experienced significantly more anger, measured by the Profile of Mood States [29]. Sleep disturbance may impair prefrontal cortical functioning, thereby weakening the top-down inhibition of aggressive impulses [30]. Therefore, it is important to identify individuals more vulnerable to the emotional consequences of poor sleep, as promoting better sleep in these individuals may reduce the frequency or severity of aggressive outbursts. With respect to obesity, obese/overweight adolescents have been found to be more likely to engage in risky behaviors [31]. Obesity is also a major risk factor for obstructive sleep apnea. In a recent study, obesity and overweight comorbid with obstructive sleep apnea increased the risk of externalizing behaviors such as aggression [32]. Neuroimaging studies have documented lower perfusion in the orbitofrontal cortex, medial/ventrolateral prefrontal cortex, and middle/superior frontal gyri in impulsive and obese individuals [33], showing this obesity-impulsivity connection.

Our study found that aggression was associated with overall epilepsy severity, which was determined based on seizure type, seizure frequency, and number of antiepileptic drugs. Our findings are consistent with the findings of Chen et al. [5], who showed that behavioral symptoms including aggression are associated with a history of intractable epilepsy, static encephalopathy, and secondarily generalized seizures. In addition, we found that AED polytherapy was significantly associated only with hostility, but not other domains such as physical aggression, verbal aggression, or anger. This is in line with a large Italian study using the same AQ, which found AED polytherapy to be a risk factor only for hostility, but not other domains [9]. Long-term polytherapy may influence higher-order cortical functions, and can affect patients' psychological and behavioral functions. In contrast, a Korean study did not find that AED load was related to aggression in PWE [27]. However, further analyses were not performed to identify relationships between AED load and each domain of the AQ-K.

In our study, male sex, depressive symptoms, and the use of perampanel were all associated with physical aggression in PWE. Similarly, a large Italian study using the AQ in PWE also showed that men were more physically aggressive, whereas women were more hostile [5]. A link between testosterone and aggression has been well established in human. Book et al. [34] conducted a meta-analysis of 45 independent studies, and found a weak, but positive, relationship between testosterone and human aggression. Testosterone may interact with the serotonin system and increase neuronal activity in the amygdala, hypothalamus, and periaqueductal gray matter [35], which are all brain areas involved in aggressive behavior.

In our study, perampanel was found to be related to physical aggression, but topiramate and levetiracetam did not show this association. The recent short-term prospective studies assessed the effects of perampanel on aggression in PWE, measured using the AQ, and demonstrated that patients receiving perampanel were more aggressive, especially in physical aggression [36,37]. Concomitant administration of levetiracetam and topiramate did not seem to aggravate aggressive behavior by PWE receiving perampanel [36,38]. But a recent study showed that concomitant use of topiramate is rather protective against aggression in patients receiving perampanel for focal epilepsy [37]. In addition, in a recent study, Chen et al. [5] attributed levetiracetam to more aggressive behavior, and lamotrigine to less aggressive behavior. Kato et al. [39] also found that lamotrigine improved aggression in

Table 3
Comparisons of the scores of the Aggression Questionnaire between categories of nominal variables in patients with epilepsy (n = 104).

	Total, mean (SD)	Physical aggression, mean (SD)	Verbal aggression, mean (SD)	Anger, mean (SD)	Hostility, mean (SD)
Male vs. female	53.7 (12.9) vs. 49.2 (12.1)	16.6 (4.6) vs. 13.9 (3.8)**	11.2 (3.8) vs. 9.7 (2.7)*	11.7 (3.4) vs. 11.8 (3.6)	14.3 (4.9) vs. 13.8 (4.6)
PHQ-9 scores ≥10 vs. < 10	63.6 (12.9) vs. 46.9 (9.2)***	18.9 (5.2) vs. 13.9 (3.2)***	12.1 (3.8) vs. 9.8 (3.0)**	14.8 (3.2) vs. 10.6 (2.8)***	17.8 (5.4) vs. 12.3 (3.7)***
GAD-7 scores ≥7 vs. < 7	63.2 (13.2) vs. 47.7 (9.9)***	18.8 (5.6) vs. 14.1 (3.2)***	11.8 (3.6) vs. 10.0 (3.2)*	14.5 (3.4) vs. 10.1 (3.0)***	18.1 (5.5) vs. 12.8 (3.7)***
Seizure frequency in the last year (≥1/month vs. 1–11/month, vs. no seizure)	56.7 (14.0) vs. 52.8 (13.0) vs. 43.6 (9.7)**	17.1 (5.4) vs. 15.4 (4.4) vs. 14.0 (3.4)*	10.7 (3.5) vs. 10.8 (3.5) vs. 9.8 (3.2)	12.9 (3.2) vs. 12.3 (3.9) vs. 10.3 (2.5)**	16.0 (5.5) vs. 14.4 (4.3) vs. 12.6 (4.5)*
Presence of GTCS or FBTCS in the last year (yes vs. no)	55.7 (14.8) vs. 49.2 (10.8)*	16.1 (5.5) vs. 14.8 (3.6)	11.3 (3.7) vs. 10.0 (3.1)	13.1 (4.0) vs. 11.0 (2.9)**	15.2 (4.8) vs. 13.4 (4.7)
AED poly- vs. monotherapy	53.5 (12.5) vs. 46.6 (11.8)*	15.6 (4.5) vs. 14.4 (4.2)	10.5 (3.3) vs. 10.2 (3.5)	12.4 (3.3) vs. 10.3 (3.3)**	15.1 (4.9) vs. 11.8 (3.6)**
Use of perampanel (yes vs. no)	54.9 (15.9) vs. 50.8 (12.0)	17.3 (5.9) vs. 14.8 (4.0)*	10.8 (3.6) vs. 10.4 (3.4)	11.9 (3.2) vs. 11.7 (3.5)	15.0 (6.1) vs. 13.9 (4.5)

AED, antiepileptic drug; PHQ-9, Patient Health Questionnaire-9; SD, standard deviation; GTCS, generalized tonic clonic seizures; FBTCS, focal to bilateral tonic clonic seizures.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

Table 4
Stepwise linear regression showing factors associated with aggression in patients with epilepsy (n = 104).

	Total scores of the Aggression Questionnaire (n = 104)				
	B	SE	beta	VIF	p value
PHQ-9 score ≥ 10	9.271	2.891	0.328	1.858	0.002
Insomnia Severity Index	0.544	0.199	0.266	1.688	0.007
Body mass index, Kg/m^2	0.829	0.245	0.258	1.033	0.001
Composite scores of seizure severity	1.090	0.428	0.202	1.124	0.013

B, unstandardized coefficients; beta, standardized coefficients; PHQ-9, Patient Health Questionnaire-9; SE, standard error; VIF, variance inflation factor.
The range of possible scores of the measures: Composite scores of epilepsy severity 0–9, Insomnia Severity Index 0–28, PHQ-9 0–27, and AQ-K.27–135.

patients with temporal lobe epilepsy. This was particularly notable with respect to anger, which represents the emotional component of aggression in the AQ.

A number of limitations should be noted when interpreting the results of our present study. Firstly, our analyses reflect relationships at a single time point and therefore do not provide evidence for causal or temporal relationships. Secondly, intelligence was not assessed in our patients, although we did exclude those who were unable to read or understand the questionnaire. Low intelligence has been considered one of the major risk factors of violence among epilepsy patients [9]. Thirdly, information about the level of education of our patients was missing. A lower level of education has also been shown to be significantly related to more aggressive behavior [9]. In addition, PWE possessing a high school degree have been shown to have larger cognitive reserves and more adequate behavior than those with fewer years of formal education [40]. Fourthly, this study was based on self-report measures. The participants clearly understood that the purpose of the study was to measure aggressive behavior. Thus, dishonesty can be an issue, because the participants were aware of socially desirable responses. Sleep disturbances were also assessed only subjectively by using questionnaires. Previously diagnosed sleep disorders and their treatment were not taken into consideration, and polysomnography was not performed. Lastly, we did not include individuals without epilepsy or healthy controls in our study, and thus did not determine whether Korean PWE are more aggressive than healthy controls although the mean score of the AQ-K in this study (51.4 ± 12.6) was lower than that in the Korean validation study (68.2 ± 13.3) [20]. A previous Korean study revealed that the degree of aggression was significantly higher in PWE than controls [27]. In contrast, an Italian study showed that PWE had slightly less aggressive responses than the general Italian population [9].

5. Conclusions

Insomnia symptoms and obesity were found to be related to overall aggressive behavior in PWE independent of depressive symptoms. The individual subscales of the AQ were correlated differently with the various factors including male sex, obesity, depressive symptoms, anxiety, insomnia symptoms, epilepsy severity, polytherapy, and the use of perampanel. The identification and management of modifiable risk factors for aggression is essential for effective patient care.

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Table 5
Stepwise linear regression showing factors associated with the subscales of the Aggression Questionnaire in patients with epilepsy (n = 104).

	Physical aggression			Verbal aggression			Anger			Hostility		
	B	SE	beta	B	SE	beta	B	SE	beta	B	SE	beta
PHQ-9 score ≥ 10	4.566***	0.804	0.464	2.088**	0.699	0.276	1.852*	0.792	0.240	2.427	1.264	0.227
GAD-7 score ≥ 7	–	–	–	–	–	–	–	–	–	2.884*	1.300	0.260
Male	2.095**	0.713	0.240	–	–	–	–	–	–	–	–	–
Body mass index, Kg/m^2	–	–	–	0.207**	0.078	0.244	–	–	–	0.236*	0.097	0.197
Insomnia Severity Index	–	–	–	–	–	–	0.196***	0.054	0.354	–	–	–
Composite scores of seizure severity	–	–	–	–	–	–	0.377**	0.116	0.261	–	–	–
AEDs polytherapy	–	–	–	–	–	–	–	–	–	2.191*	0.851	0.213
Use of perampanel	2.214*	0.979	0.183	–	–	–	–	–	–	–	–	–

AEDs, antiepileptic drugs; B, unstandardized coefficients; beta, standardized coefficients; GAD-7, Generalized Anxiety Disorder-7; SE, standard error.
The range of possible scores of the measures: Composite scores of epilepsy severity 0–9, Insomnia Severity Index 0–28, PHQ-9 0–27, GAD-7 0–21, and AQ-K.27–135.

Declaration of Competing Interest

The authors declare no conflicts of interest in relation to this study.

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