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Sex differences in the relationship between aggression and symptoms of depression and anxiety in adults with refractory focal epilepsy

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ABSTRACT

Purpose: To determine whether sex affects the relationship between aggression and symptoms of depression and anxiety in adults with refractory focal epilepsy.
Methods: This cross-sectional study was conducted in 85 adults with refractory focal seizures, which are defined as one or more seizures recurring per month even when the patient is treated with two or more antiseizure medications. We used the Buss-Perry Aggression Questionnaire (AQ) and the Hospital Anxiety and Depression Scale (HADS) to evaluate aggression and symptoms of depression and anxiety, respectively. We performed multivariate linear regression and analysis of covariance with interaction terms. HADS-depression and HADS-anxiety scores were separately evaluated to avoid multicollinearity between both of them.
Results: The HADS-depression and HADS-anxiety scores, male sex, an antiseizure medication load of ≥3, and the use of pregabalin were independently correlated with at least one of the AQ total and subscale scores. These models for depressive and anxiety symptoms explained 34.2% and 32.5%, respectively, of the variance of the AQ total score. Although the AQ total scores did not differ between the sexes, sex significantly affected the relationships between aggression and symptoms of depression and anxiety. Specifically, HADS-depression and HADS-anxiety scores were positively associated with the AQ total scores, especially scores of verbal aggression and anger subtypes, in men but not in women.
Conclusions: These findings support the importance of including anger management and other strategies targeted toward aggression in the development of psychological interventions to reduce anxiety and depression in adults with refractory focal epilepsy. Tailoring those interventions to the needs of males and females will be important to consider.

1. Introduction

Epilepsy is a common chronic disorder of the brain that affects approximately 50 million people of all ages worldwide [1], which accounts for 0.5% of the global burden of disease [2]. Experiencing recurrent seizures can result in psychiatric symptoms, such as anxiety and depression, which are more strongly related to poor health-related quality of life (HRQoL) than seizures themselves in patients with epilepsy [3]. Indeed, psychiatric symptoms are up to 10 times more common in patients with epilepsy than in the general population [4,5]. Moreover, seizure frequency is correlated with the level of anxiety and depression [6].

Aggression can be defined as "an overt behavior or signal of imminent behavior with the capacity to inflict physical harm on another individual" [7]. Studies on aggression in the field of epilepsy have attracted increasing attention because some antiseizure medications (ASMs), especially topiramate, levetiracetam, and perampanel, have been recognized as having the potential to induce aggressive behavior in patients with epilepsy [8–10]. Traditionally, men are considered more aggressive than women, and this preponderance of men is linked to testosterone. However, a recent review indicated that overall aggression scores do not differ between the sexes; rather, men are more physically aggressive, whereas women are more indirectly aggressive [11]. Moreover, a recent meta-analysis did not find a strong relationship between aggression and testosterone [12]. In patients with epilepsy, most studies have shown no significant differences in overall aggression between the

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sexes [13–15], although a recent study revealed that overall aggression and all of its subtypes, except anger, were more severe in men than in women [8].

Various correlates of aggression in patients with epilepsy have been suggested, which include demographic, psychosocial, seizure-related, and ASM-related factors [13–15]. In particular, a significant relationship between depression and aggression has been consistently documented in patients with epilepsy [14,15]. For example, a recent study conducted in South Korea found that depression is the strongest correlate of aggression in adults with epilepsy [15]. However, it remains unclear whether sex affects the relationship between aggression and depression in patients with epilepsy.

Epilepsy is highly heterogeneous; the etiology of epilepsy is diverse, and seizure frequency and severity are also highly variable. Approximately half of all epilepsy patients are not able to control seizures following an initial ASM treatment; moreover, seizures continue to recur in one-third of patients despite adequate ASM trials [16,17]. Patients with uncontrolled epilepsy are more aggressive than those with controlled epilepsy [14], and the level of aggression also significantly correlates with the severity of epilepsy [15]. Thus, our study aimed to determine whether sex affects the relationship between aggression and symptoms of depression and anxiety in patients with refractory focal epilepsy.

2. Materials and methods

2.1. Subjects

The study was a cross-sectional study. Subjects were recruited from an outpatient clinic of a single tertiary hospital from June 2016 to November 2017. Inclusion criteria were as follows: 1) adults aged ≥19 years; 2) diagnosis of focal epilepsy; 3) one or more seizures recurring per month, even while taking two or more ASMs; and 4) ability to read and understand self-report questionnaires. Subjects who had a seizure within the 72 hours before study recruitment were excluded. Clinical information was obtained from patient's medical files. Written informed consent was acquired from all subjects. The study protocol was reviewed and approved by the Institutional Review Board of Asan Medical Center.

2.2. Measures

To measure individual differences in aggression, we used the Buss-Perry Aggression Questionnaire (AQ) [18]. The AQ consists of 29 items, which are categorized into four subscales: physical aggression (nine items), verbal aggression (five items), anger (seven items), and hostility (eight items) [18]. Each item is scored on a five-point Likert scale, ranging from 1 (extremely uncharacteristic of me) to 5 (extremely characteristic of me). In the Korean version of the AQ, the following two items from the anger subscale of the original AQ are excluded because they are more related to verbal aggression and hostility than to anger: "some of my friends think I'm a hothead" and "sometimes I fly off the handle for no good reason" [19]. Therefore, the Korean version of the AQ evaluates aggression using 27 items, with a total score ranging from 27 to 135 [19]. Higher scores indicate a higher level of aggression.

The Hospital Anxiety and Depression Scale (HADS) was developed to assess the degree of anxiety and depression in individuals with a somatic disease [20]. To avoid overlap with symptoms of somatic diseases, the HADS excludes physical symptoms, such as fatigue, loss of appetite, and insomnia, which are common adverse effects of ASMs. The HADS consists of 14 items, which are categorized into two subscales: HADS-anxiety (HADS-A; seven items) and HADS-depression (HADS-D; seven items) [20]. Each item was scored on a four-point Likert scale, ranging from 0 (no distress) to 3 (significant distress), according to how the individual felt during the past week. The total score of each subscale, therefore, ranges from 0 to 21, with higher scores representing a higher level of depression and anxiety [21].

2.3. Drug load measurement of ASM

The drug load of ASM was calculated as a sum of the ratios of the prescribed/defined daily doses of each ASM included in the treatment regimen [22]. The defined daily dose was defined as the assumed average maintenance dose per day for a drug used for its main indication in adults [23]. The drug load of ASM for each individual was categorized into low (drug load of <3) and high (drug load of ≥3).

2.4. Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences, version 21.0 (IBM Corp., Armonk, NY, USA). A two-tailed $p < 0.05$ was considered statistically significant. Data were compared using Student's *t*-tests or Pearson's correlation tests. To determine whether symptoms of depression and anxiety are independently associated with aggression, multivariate linear regression analyses were conducted with each AQ total and subscale score as a dependent variable and HADS-D and HADS-A scores as independent variables. To avoid multicollinearity between independent variables, HADS-D and HADS-A scores were entered separately into a linear regression model. Confounding variables included age, sex, and variables with a relationship of $p < 0.05$ with at least one of AQ total and subscale scores in the univariate analyses. Potential confounding variables were the presence or absence of psychiatric history, seizure frequency (weekly vs. monthly), recurrence of focal to bilateral tonic-clonic seizures (FBTCS) during the past year, ASM drug load of ≥3, and use of individual ASM. We included the use of certain ASM as one of the potential confounding variables only if the ASM was used in more than 20% of the subjects. We determined the presence of multicollinearity using a variance inflation factor of <3 and a condition index of <20. Assumptions of the linear regression after fitting the model were tested using a normal probability–probability plot.

Potential interactions of sex with HADS-D and HADS-A scores for AQ scores were tested using analysis of covariance with interaction terms. These interaction models were adjusted by confounding variables that showed an association of $p < 0.05$ with at least one of the AQ total and subscale scores in the multivariate linear regression analysis. Partial eta-squared scores of 0.01, 0.06, and 0.14 or higher were indicative of small, medium, and large effect sizes, respectively.

3. Results

3.1. Subjects

Eighty-five subjects (36 women and 49 men) with refractory focal epilepsy were included in the study. The mean age of the subjects was 41.7 ± 10.7 years (Table 1). Thirty-four (40%) subjects had known etiology of epilepsy, and 33 (38.8%) had a recurrence of FBTCS during the past year. The mean drug load of ASM was 2.9 ± 1.0, and a drug load of ≥3 was noted in 38 (44.7%) subjects. Levetiracetam was the most common ASM (57.6%), followed by valproate (54.1%) and carbamazepine (50.6%). The mean HADS-A and HADS-D scores were 7.5 ± 4.4 and 7.6 ± 4.1, respectively. There were no sex differences in HADS-A scores (7.6 ± 4.5 in males vs.

Table 1
Subject characteristics (n = 85).

Age, years, mean (SD)	41.7 (10.7)
Sex, male, n (%)	49 (57.6)
Age at seizure onset, years, mean (SD)	20.2 (11.8)
Duration of epilepsy, years, mean (SD)	21.5 (12.5)
Etiology of epilepsy, n (%)	
Central nervous system infection	17 (20.0)
Hippocampal sclerosis	5 (5.9)
Traumatic	4 (4.7)
Vascular	3 (3.5)
Malformation of cortical development	3 (3.5)
Perinatal	2 (2.4)
Unknown etiology	51 (60.0)
Seizure frequency in the last year, n (%)	
1–3 per month	53 (62.4)
≥1 per week	32 (37.6)
FBTCS recurrence in the last year, n (%)	33 (38.8)
Number of antiseizure medications, n (%)	
Two	25 (29.4)
Three	38 (44.7)
Four	18 (21.2)
Five	4 (4.7)
Antiseizure medication load, mean (SD)	2.9 (1.0)
Antiseizure medication load ≥3, n (%)	38 (44.7)
Individual antiseizure medication prescribed, n (%)	
Levetiracetam	49 (57.6)
Valproic acid	46 (54.1)
Carbamazepine	43 (50.6)
Topiramate	30 (35.3)
Oxcarbazepine	27 (31.8)
Pregabalin	22 (25.9)
Zonisamide	12 (14.1)
Lamotrigine	10 (11.8)
Others*	15 (17.6)
Histories of psychiatric disorders, n (%)	10 (11.8)
Video-EEG monitoring, n (%)	38 (44.7)
History of epilepsy surgery, n (%)	10 (11.8)
Focal neurological deficit, n (%)	4 (4.7)
HADS-A scores, mean (SD)	7.5 (4.4)
HADS-D scores, mean (SD)	7.6 (4.1)
HADS-A score ≥8, n (%)	39 (45.9)
HADS-D score ≥8, n (%)	43 (50.6)
AQ-K, mean (SD)	57.5 (16.0)
Physical aggression	17.3 (5.8)
Verbal aggression	10.9 (4.1)
Anger	12.7 (3.4)
Hostility	16.1 (5.7)

AQ-K, Korean version of Aggression Questionnaire; EEG, electroencephalography; HADS-A, Hospital Anxiety Depression Scale-Anxiety; HADS-D, Hospital Anxiety Depression Scale-Depression; FBTCS, focal to bilateral tonic-clonic seizures; n, number; SD, standard deviation.

* Phenytoin, clobazam, lorazepam, and phenobarbital were prescribed individually less than 10%.

7.3 ± 4.4 in females; p = 0.712) and HADS-D scores (7.6 ± 4.5 in males vs. 7.3 ± 4.4 in female; p = 0.622). The HADS-A and HADS-D scores of ≥8 were noted in 39 (45.9%) and 43 (50.6%) subjects, respectively. There were also no sex differences in the percentage of HADS-A scores of ≥8 (n = 24, 49.0% in males vs. n = 15, 41.7% in females; p = 0.504) and HADS-D scores of ≥8 (n = 26, 53.1% in male vs. n = 17, 47.2% in female; p = 0.595). The mean AQ total score was 57.5 ± 16.0.

3.2. Correlates of aggression in the multivariate linear regression models

Univariate analyses showed that HADS-D and HADS-A scores, sex, a presence of psychiatric history, ASM drug load of ≥3, use of pregabalin, use of levetiracetam, and use of carbamazepine were significantly correlated with at least one of AQ total and subscale scores (Table 2).

In the separate multivariate linear regression models, both HADS-D and HADS-A scores were positively correlated with AQ total score (both p < 0.01) (Table 3). With regard to AQ subscales, the HADS-D score was correlated with physical aggression (p = 0.002) and hostility (p < 0.001), whereas the HADS-A score was correlated with verbal aggression (p = 0.027) and hostility (p < 0.001). These models for depressive and anxiety symptoms explained 34.2% and 32.5%, respectively, of the variance of the AQ total score.

Among confounding variables, male sex, an ASM drug load of ≥3, and the use of pregabalin were independently correlated with at least one of AQ total and subscales (Table 3). Male sex and an ASM drug load of ≥3 were significantly correlated with verbal aggression and anger, respectively, in both models (all p < 0.05). The use of pregabalin was positively correlated with verbal aggression and anger in both models (all p < 0.05), and positively correlated with AQ total scores only in the model for depressive symptoms (p < 0.05).

3.3. Interaction between sex and psychological distress for aggression

Interactions of sex with HADS-D and HADS-A scores were significant for AQ total score in both the unadjusted and adjusted models (both interactions p < 0.05; Table 4). Specifically, in the adjusted model, the positive relationships of HADS-D and HADS-A scores with AQ total scores were significant in men (both p < 0.001; partial η^2 = 0.221 and 0.192, respectively) but not in women. With regard to the subscale score of the AQ, both the unadjusted and adjusted models showed that verbal aggression and anger subscale scores were significantly correlated with HADS-D and HADS-A scores in men but not in women (all interaction p values <0.05; Table 5). By contrast, in the adjusted models, the relationships of HADS-D score with physical aggression and hostility subscale scores did not differ between the sexes, although they reached trend significance (p = 0.082 and p = 0.091, respectively). The relationships of HADS-A score with physical aggression and hostility subscale scores did not differ between the sexes in both the unadjusted and adjusted models (all p values > 0.1). Each model for total and subscale scores was adjusted by variables with an association of p < 0.05 with at least one of AQ total and subscale scores in the multivariate analysis (an ASM drug load of ≥3 and use of pregabalin).

4. Discussion

Using the AQ, in the univariate analyses, we found no sex differences in the magnitude of overall aggression or its subtypes, except verbal aggression, in patients with refractory focal epilepsy. Men had a significantly higher level of verbal aggression than women even after controlling for several covariates. Although the level of overall aggression did not differ between the sexes in the present study, sex significantly affected the relationships between aggression and symptoms of depression and anxiety in patients with refractory focal epilepsy. Based on both univariate and multivariate analyses, symptoms of depression and anxiety were positively associated with overall aggression, specifically verbal aggression and anger, exclusively in men. The reason for such a sex difference is unclear. In general, depression and anxiety are reported more often in women than in men throughout their lifespan. For example, the lifetime prevalence of anxiety disorder and major depressive disorder is 1.5 times higher in women than in men [24,25]. However, in our study population with refractory focal epilepsy, there were no sex differences in anxiety and depressive symptoms. Further studies are needed to clarify the sex difference in relationships between

Table 2
Univariate analyses of age, sex, and variables with p < 0.05 in association with at least one of overall aggression and its subtypes in patients with refractory focal epilepsy (n = 85).

	AQ-K, r or mean (SD)	Physical aggression, r or mean (SD)	Verbal aggression, r or mean (SD)	Anger, r or mean (SD)	Hostility, r or mean (SD)
HADS-D scores	0.462***	0.418***	0.230*	0.253*	0.550***
HADS-A scores	0.430***	0.298**	0.313**	0.297**	0.497***
Age, years	0.054	0.081	0.081	0.129	−0.065
Male vs. female	59.7 (17.7) vs. 54.6 (13.0)	18.2 (6.3) vs. 16.1 (4.9)	11.7 (4.6) vs. 9.8 (2.9)*	12.6 (3.2) vs. 12.9 (3.8)	17.2 (6.4) vs. 15.8 (4.6)
Psychiatric histories: yes vs. no	65.8 (21.5) vs. 56.4 (15.0)	19.8 (6.6) vs. 17.0 (5.7)	11.9 (5.8) vs. 10.8 (3.8)	15.3 (3.9) vs. 12.4 (3.2)*	18.8 (7.1) vs. 16.3 (5.5)
ASM load: ≥3 vs. <3	53.3 (12.0) vs. 61.0 (18.0)*	15.7 (4.8) vs. 18.6 (6.3)*	10.2 (3.5) vs. 11.5 (4.4)	11.7 (2.9) vs. 13.6 (3.6)*	15.7 (4.1) vs. 17.4 (6.8)
CBZ use: yes vs. no	54.8 (14.2) vs. 60.3 (17.4)	16.5 (5.4) vs. 18.1 (6.2)	10.4 (3.4) vs. 11.4 (4.6)	12.6 (3.4) vs. 12.9 (3.5)	15.4 (4.6) vs. 17.9 (6.6)*
PGB use: yes vs. no	63.6 (21.2) vs. 55.4 (13.3)	19.0 (7.5) vs. 16.7 (5.0)	12.6 (5.0) vs. 10.3 (3.6)*	14.1 (4.0) vs. 12.3 (3.1)*	18.0 (7.6) vs. 16.1 (4.9)
LEV use: yes vs. no	54.5 (12.6) vs. 61.7 (19.1)*	16.1 (5.0) vs. 19.0 (6.5)*	10.1 (2.9) vs. 11.9 (5.1)	12.2 (3.2) vs. 13.4 (3.6)	16.1 (5.2) vs. 17.3 (6.4)

AQ-K, Korean version of Aggression Questionnaire; ASM, antiseizure medication; CBZ, carbamazepine; HADS-A, Hospital Anxiety Depression Scale-Anxiety; HADS-D, Hospital Anxiety Depression Scale-Depression; LEV, levetiracetam; PGB, pregabalin; r, correlation coefficients; SD, standard deviation.
*p < 0.05; **p < 0.01; ***p < 0.001

Table 3
Multivariate linear regression showing variables associated with aggression in patients with refractory focal epilepsy (n = 85).

	AQ-K		Physical aggression		Verbal aggression		Anger		Hostility	
	B	SE	B	SE	B	SE	B	SE	B	SE
Model 1										
HADS-D scores	1.427**	0.398	1.427**	0.398	0.131	0.109	0.122	0.092	0.699***	0.143
Age, years	0.071	0.148	0.071	0.148	0.043	0.041	0.018	0.034	−0.036	0.053
Male	4.689	3.212	4.689	3.212	2.087*	0.882	−0.148	0.744	0.816	1.151
Psychiatric history	3.967	4.918	3.967	4.918	0.203	1.350	2.145	1.139	0.881	1.763
ASM load ≥3	−5.357	3.291	−5.357	3.291	−1.190	0.903	−1.639*	0.762	−0.667	1.180
PGB use	7.702*	3.488	7.702	3.488	2.157*	0.958	1.912*	0.808	1.525	1.250
LEV use	−3.934	3.329	−3.934	3.329	−1.025	0.914	−0.407	0.771	−0.687	1.193
CBZ use	−3.402	3.192	−3.402	3.192	−1.002	0.876	−0.240	0.739	−1.161	1.144
Model 2										
HADS-A scores	1.226**	0.376	0.275†	0.145	0.226*	0.100	0.170*	0.085	0.555***	0.139
Age, years	0.159	0.152	0.068	0.059	0.058	0.040	0.029	0.034	0.005	0.056
Male	5.380	3.239	2.224†	1.250	2.099*	0.858	−0.119	0.730	1.176	1.195
Psychiatric history	5.055	4.939	1.346	1.907	0.093	1.308	2.116	1.113	1.500	1.823
ASM load ≥3	−5.390	3.343	−2.128	1.291	−0.975	0.885	−1.514*	0.754	−0.772	1.234
PGB use	6.993	3.559	2.049	1.374	1.941*	0.943	1.764*	0.802	1.239	1.314
LEV use	−3.682	3.369	−1.685	1.301	−1.042	0.892	−0.408	0.759	−0.547	1.243
CBZ use	−3.224	3.270	−1.289	1.262	−0.688	0.866	−0.051	0.737	−1.196	1.207

AQ-K, Korean version of Aggression Questionnaire; ASM, antiseizure medication; B, unstandardized coefficients; CBZ, carbamazepine; HADS-A, Hospital Anxiety Depression Scale-Anxiety; HADS-D, Hospital Anxiety Depression Scale-Depression; LEV, levetiracetam; PGB, pregabalin; SE, standard error.
Notes: HADS-D and HADS-A scores were separately analyzed in models 1 and 2, respectively.

Table 4
Analysis of covariance showing interactions of sex with symptoms of depression and anxiety and their effects on aggression in patients with refractory focal epilepsy (n = 85).

			Interaction effects of HADS-D or HADS-A scores on AQ-K scores					
Independent variable	Model	Subgroups	Interaction p-value	B	SE	95% CI	p-value	Partial eta^2
HADS-D score	Crude	Women	0.012	0.823	0.530	−0.231–1.878	0.124	0.029
		Men		2.716	0.517	1.688–3.744	<0.001	0.254
	Adjusted[a]	Women	0.026	0.679	0.516	−0.348–1.706	0.192	0.021
		Men		2.406	0.508	1.395–3.417	<0.001	0.221
HADS-A score	Crude	Women	0.022	0.569	0.536	−0.498–1.637	0.292	0.014
		Men		2.212	0.452	1.312–3.112	<0.001	0.228
	Adjusted[a]	Women	0.026	0.396	0.520	−0.640–1.431	0.449	0.007
		Men		1.931	0.445	1.045–2.817	<0.001	0.192

AQ-K, Korean version of Aggression Questionnaire; B, unstandardized coefficients; CI, confidence interval; HADS-A, Hospital Anxiety Depression Scale-Anxiety; HADS-D, Hospital Anxiety Depression Scale-Depression; SE, standard error.
Notes: Effect size partial eta^2 small: 0.01, moderate: 0.06, large: 0.14 or higher.
[a] These models were adjusted by antiseizure medication load ≥3 and the use of pregabalin.

aggression and symptoms of depression and anxiety in patients with refractory focal epilepsy. To the best of our knowledge, there are no data comparable to those in the current study.

Several ASMs are well-established for managing aggression in patients with psychiatric disorders [26]. In particular, a review of controlled trials in adults with repetitive or impulsive aggression

Table 5
Analysis of covariance showing interactions of sex with symptoms of depression and anxiety and their effects on subtypes of aggression in patients with refractory focal epilepsy (n = 85).

			Interaction effects of HADS-D or HADS-A scores on AQ-K subscale scores											
			Physical aggression			Verbal aggression			Anger			Hostility		
Independent variable	Model	Subgroups	Interaction p-value	B	SE	Interaction p-value	B	SE	Interaction p-value	B	SE	Interaction p-value	B	SE
HADS-D score	Crude	Women	0.063	0.316	0.200	0.024	−0.022	0.146	0.019	<0.001	0.126	0.069	0.530**	0.184
		Men		0.845***	0.195		0.446**	0.142		0.422**	0.123		1.004***	0.179
	Adjusted[a]	Women	0.082	0.259	0.197	0.037	−0.054	0.143	0.026	−0.043	0.121	0.091	0.517**	0.187
		Men		0.741***	0.194		0.366*	0.140		0.340**	0.119		0.960***	0.184
HADS-A score	Crude	Women	0.217	0.182	0.211	0.002	−0.055	0.137	0.013	−0.007	0.122	0.198	0.449*	0.191
		Men		0.525**	0.178		0.514***	0.115		0.401***	0.103		0.773***	0.161
	Adjusted[a]	Women	0.250	0.113	0.206	0.003	−0.091	0.134	0.015	−0.051	0.118	0.228	0.425*	0.193
		Men		0.423*	0.176		0.448***	0.114		0.331**	0.101		0.730***	0.165

AQ-K, Korean version of Aggression Questionnaire; B, unstandardized coefficients; HADS-A, Hospital Anxiety Depression Scale-Anxiety; HADS-D, Hospital Anxiety Depression Scale-Depression; SE, standard error.
[a] These models were adjusted by antiseizure medication load ≥3 and the use of pregabalin.

in the absence of other disorders found that carbamazepine, oxcarbazepine, and phenytoin have significant effects on lowering aggression [27]. Conversely, perampanel, levetiracetam, and topiramate are widely recognized to induce aggressive behavior among patients with epilepsy [8–10,28]. Surprisingly, we found that patients who were taking pregabalin had a significantly higher overall aggression score (especially for subtypes of verbal aggression and anger) than those who did not. By contrast, patients who were taking levetiracetam had lower scores of overall aggression and physical aggression than those who were not although their statistical significance was lost in the multivariate analyses. Levetiracetam is well-documented to induce negative psychiatric and behavioral effects, such as depression, emotional instability, and aggression [8–10,29]. Pregabalin is considered an ASM that neither increases nor decreases psychiatric and/or behavioral symptoms as adverse effects [10]. Therefore, the negative association between levetiracetam and aggression and the positive association between pregabalin and aggression identified in the present study may be attributed to selection bias rather than the direct behavioral effects of ASMs.

The present study has several methodological limitations. First, the cross-sectional study design did not allow us to identify cause-and-effect relationships. Second, questionnaire-based studies are vulnerable to biases that affect retrospective self-reporting, which consequently decreases the reliability of memory-based measures [30]. When questionnaires, such as the AQ, encompass a prolonged period, access to episodic knowledge becomes limited. Third, we did not obtain information regarding the treatment of current mental problems from patients. Fourth, we did not consider temporal versus frontal lobe epilepsy as a covariate due to difficulty in localization of seizure focus without video-encephalography monitoring. Fifth, the AQ used in this study was not developed to measure indirect aggression; therefore, we were not able to evaluate the most common form of aggression in women. Sixth, there is no clinical threshold for aggression on the AQ, so, we are unable to determine how aggressive our study sample was. Finally, we did not provide data on the number of individuals who were approached to participate in the study or the overall response rate. Therefore, we lacked information about non-responders and could not determine whether non-response influenced our results.

In summary, the present study found that even though the magnitude of aggression did not differ between men and women, there were significant sex differences in the relationship between aggression and symptoms of depression and anxiety among adults with refractory focal epilepsy. Specifically, after controlling for covariates, symptoms of depression and anxiety were significantly correlated with aggression, especially verbal aggression and anger, in men but not in women. These findings further our understanding of associations between aggression and symptoms of depression and anxiety depending on sexes and could contribute to the development of successful sex-specific psychosocial interventions to improve the quality of life of adults with refractory focal epilepsy.

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