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Research Article

Cortisol and Serotonin Patterns in Epilepsy: An Observational Study

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Abstract

Background: Cortisol and serotonin are known to be biomarkers for psychiatric disorders. Their effects on epilepsy patients' mental health need further study. ***Objective***: To assess the relationship between cortisol and serotonin levels in patients with focal and generalized epilepsy who also experience major depressive disorder (MDD), intermittent explosive disorder (IED), and mild depression. ***Methods***: This exploratory cross-sectional pilot study was conducted at IMS and Sum Hospital in Bhubaneswar. A total of 78 epileptic patients were evaluated; 26 had MDD, 26 had IED, and 26 experienced mild depression. Each group had 13 focal and 13 generalized epilepsy patients. Blood samples were collected at 8 A.M. after 48 hours of an epileptic attack. The Cobas e 601 system from Roche Diagnostics Corporation measured cortisol, while the BA E-8900 from Imussmol SAS, Pessac, France, measured serotonin. ***Results***: After investigation, focal epilepsy patients with MDD, IED, & mild depression experienced significant fluctuations in cortisol and serotonin, while generalized patients with these conditions showed significant cortisol variations but not in serotonin levels. Generalized patients with MDD showed higher cortisol levels than focal patients, while IED patients displayed the opposite trend. Furthermore, serotonin levels were lower in focal patients with MDD and IED than in generalized epilepsy, but the differences were not statistically significant. ***Conclusions***: Cortisol and serotonin levels were substantially related to psychiatric disorders in both types of epilepsy patients.

Keywords: Cortisol; Epilepsy; Focal; Generalized; Psychiatric disorders; Serotonin.

أنماط الكورتيزول والسيروتونين في الصرع: دراسة رصدية

الخلاصة

الخلفية: الكورتيزول والسيروتونين معروفان بأنهما علامات حيوية للاضطرابات النفسية. تأثيراتها على الصحة النفسية لمرضى الصرع تحتاج إلى مزيد من الدراسة. **الهدف**: تقييم العلاقة بين مستويات الكورتيزول والسيروتونين لدى المرضى المصابين بالصرع البؤري والعام الذين يعانون أيضا من اضطراب الاكتئاب الشديد (MDD)، واضطراب الانفجار المتقطع (IED)، والاكتئاب الخفيف. **الطرائق**: أجريت هذه الدراسة التجريبية الاستكشافية في IMS ومستشفى سوم في بوبانسوار. تم تقييم ما مجموعه 78 مريضا من الصرع؛ 26 منهم كانوا يعانون من MDD، و26 مصابين ب IED، و26 يعانون من اكتئاب خفيف. كان في كل مجموعة 13 مريضا بؤريا و13 مريضا بالصرع المعمم. تم جمع عينات الدم في الساعة 8 صباحا بعد 48 ساعة من نوبة الصرع. تم استخدام نظام Cobas e 601 لقياس الكورتيزول، وجهاز BA E-8900 لقياس السيروتونين. **النتائج**: أظهر مرضى الصرع البؤري المصابون ب MDD، وIDD، والاكتئاب الخفيف تقلبات كبيرة في الكورتيزول والسيروتونين، بينما أظهر المرضى المصابون بهذه الحالات تغيرات كبيرة في الكورتيزول ولكن دون تغيرات كبيرة في مستويات السيروتونين. أظهر المرضى المصابون باضطراب التفكيك الشديد مستويات أعلى من الكورتيزول مقارنة بمرضى البؤرة، بينما أظهر مرضى IDD الاتجاه المعاكس. علاوة على ذلك، كانت مستويات السيروتونين أقل لدى المرضى البؤريين المصابين ب MDD و IDD مقارنة بالصرع العام، لكن الفروقات لم تكن ذات دلالة إحصائية. **الاستنتاجات**: كانت مستويات الكورتيزول والسيروتونين مرتبطة بشكل كبير بالاضطرابات النفسية لدى كلا نوعي مرضى الصرع.

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INTRODUCTION

Epilepsy is seen more as a rapidly expanding mental illness than as a long-term neurological condition that disrupts the normal functioning of nerve cells in the brain. Comorbid mental disease is common among epilepsy patients; in fact, one-third of these people also suffer from anxiety and mood problems. Depression, anxiety, and cognitive impairment are among the most common psychiatric comorbidities with temporal lobe epilepsy in comparison to other types of epilepsy [1]. Cortisol and serotonin are measurable indicators that act as biomarkers for mental disorders and epilepsy [2-6]. In addition to describing shared processes underlying the mechanism development of both disorders, the psychiatric-epilepsy link incorporates many medical & experimental information points. The high prevalence of psychiatric comorbidities, including depression, anxiety, and abnormal cognition among epileptic patients, stems directly from their hyperexcitable neurons and vulnerability to seizures. In these situations, the hypothalamic-pituitary-adrenal axis is activated, synthesizing adrenal glucocorticoids, which result in cortisol secretion into the bloodstream and continuously affect the brain. Stressful events such as seizures have been shown to elevate hypothalamic-pituitary-adrenal (HPA) axis hormones and cortisol

during the post-ictal phase following a focal or generalized epilepsy episode (Figure 1) [7].

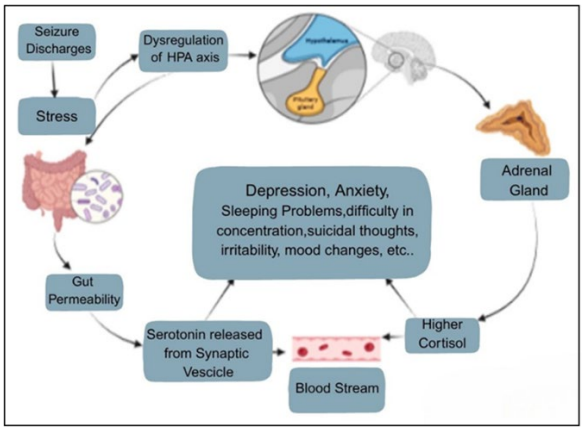

Figure 1: HPA axis and GUT axis are connected for higher cortisol and serotonin [7].

In a review of 38 studies on epilepsy, Cano-Lopez and Gonzalez-Bono found that 77% indicated elevated cortisol levels in epilepsy patients, highlighting both their stress response and a lack of brain connectivity [8]. Research has demonstrated that high morning cortisol levels worsen circadian seizures. Furthermore, studies have established a connection between the cortisol awakening response and seizure occurrences at a plateau level [9]. Serotonin is created from its only precursor, tryptophan, and maximum serotonin is secreted by enterochromaffin cells in the digestive tract, released in response to stimuli [10,11]. Glucocorticoids, produced by the HPA axis, increase the permeability of the intestinal barrier and alter the composition, distribution, and energy metabolism of microbiomes, a phenomenon called microbiota dysbiosis. Stress disrupts the microbiota that regulates tryptophan metabolism, decreasing the brain's serotonin synthesis and short-chain fatty acid pathways, ultimately reducing serotonin levels [10,12]. Past evidence suggests that seizures occur more frequently when serotonin levels are low, and at high levels, seizure incidence is low [13]. Researchers found significantly unworthy 5-HT-transporter performance in the insula and fusiform gyrus in depressive TLE patients. Researchers found that in the raphe nuclei, insula, cingulate gyrus, and hippocampus, TLE patients who had lower levels of 5-HT were more likely to have depressive symptoms [14]. There is little research on cortisol and serotonin in stressed epilepsy patients in India. In 1994, researchers identified a nonspecific rise in cortisol levels in cases of generalized tonic-clonic seizures [15]. During research on the effects of yoga on depression patients, Thirthalli *et al*. found that these individuals exhibited elevated levels of cortisol [16]. An Indian researcher discovered that serotonin levels were elevated during the postictal stage following generalized tonic-clonic seizures and focal to bilateral tonic-clonic seizure episodes, in contrast to the interictal levels [5]. Indian researchers identified reduced serotonin levels in depressive patients exhibiting suicidal intentions [17]. There is a lack of research on the association between cortisol and serotonin and seizure-induced stressful events in eastern India. Research has proven that both cortisol & serotonin have a positive relationship with epileptic discharges as well as with psychiatric issues. Therefore, we decided to measure both cortisol and serotonin after epileptic activities to explore the deeper relationship of epilepsy with psychiatric problems.

METHODS

Study design and setting

In this exploratory cross-sectional pilot study, we look at how different groups of people with epilepsy, with the same mental illness, or those who share the same epilepsy and other psychiatric problems relate to one another in terms of cortisol and serotonin. Seizure types were classified according to the International League Against Epilepsy (ILAE) 2017 operational classification. Focal to bilateral tonic-clonic seizures were considered under focal epilepsy based on focal onset, following ILAE criteria. 52 epilepsy patients were selected, who were split evenly between major and mild depression, with each subgroup including 13 with focal and another 13 with generalized epilepsy. Depressive, anxiety, and cognitive conditions were diagnosed based on DSM-5 criteria. To evaluate symptom severity and psychiatric impact on daily activities, standardized rating scales, including the Hamilton Depression Scale (HAM-D) and the Hamilton Anxiety Scale (HAM-A), were used. Additionally, the cognitive function was assessed using the Montreal Cognitive Scale (MOCA). To minimize circadian variation, blood samples were collected in the morning at a single time point (8:00 A.M.) at least 48 hours after the most recent epileptic episode. Sampling was not timed to coincide with seizure occurrence, and seizure-free (interictal) samples were not specifically collected. When available, the exact time of the last seizure before blood collection was recorded.

Inclusion criteria

The inclusivity criterion stipulates that patients must be over 18. Every patient was diagnosed with epilepsy and one of the psychiatric symptoms out of these 3 psychiatric diseases, i.e., major depression, mild depression, and intermittent explosive disorder. We selected another 26 patients with IED; each subgroup included the same 13 focal and 13 generalized epilepsies.

Exclusion criteria

Exclusion criteria encompass epilepsy patients with a history of suicide. Intoxicated individuals should be disregarded. Individuals who have previously suffered a stroke or trauma were excluded. Patients undergoing neurosurgery were likewise ineligible. No significant differences in cortisol and serotonin levels were found between frontal and temporal lobe epilepsy; however, because of the small sample size, within-seizure focus subgroups limited the statistical power. That's why seizure focus was not included as a variable in this analysis. Participants were not excluded based on the use of current medications. As a preliminary approach, due to the high prevalence of polytherapy usage, the systematic recording of antiseizure medication type,

dose, and duration as covariates was not included in this analysis.

Outcome measurements

All three groups were measured for cortisol and serotonin to gain a deeper understanding of the relationship between epilepsy and psychiatric problems. The cortisol measurement system Cobas e 601 from Roche Diagnostics Corporation and the serotonin kit BA E-8900 iummusol SAS in Pessac, France, were used to determine cortisol and serotonin levels and intensity. To better understand the nature of the connection between serotonin & cortisol, a statistical analysis was performed to investigate the association. Within the scope of this investigation, alterations are identified that shed light on whether or not cortisol affects the density and responsiveness of serotonin.

Ethical considerations

The institutional ethics committee of SUM & IMS Hospital, SOA University has approved the study protocol. All epilepsy patients, whether focal or generalized, completed a written consent form and gave their consent to participate.

Statistical analysis

Although cortisol and serotonin are continuous variables, they were categorized into clinically relevant groups (low, normal, high) to facilitate groupwise comparisons with psychiatric outcomes, improve clinical interpretability, and account for potential non-normal distributions. Chi-square statistical analysis assessed the relationship between cortisol & serotonin levels in various epilepsy groups with distinct psychiatric conditions while also evaluating the effectiveness of these levels among different epilepsy patients facing dissimilar psychiatric issues. To investigate the impact of cortisol and serotonin levels on the same epilepsy groups, which included patients suffering from a variety of psychiatric conditions, we utilized a one-way ANOVA. A p-value less than 0.05 was considered significant.

RESULTS

Most patients with focal and generalized symptoms, aged approximately 18–38 years, exhibited MDD, IED, and mild depression; however, generalized patients in this age group showed higher levels of MDD and IED symptoms than focal patients. Focal patients showed excessive, persistent depression compared to generalized patients (Table 1).

Table 1: Sociodemographic characteristics of participants

Variable	Focal with MDD	Generalized with MDD	Focal with IED	Generalized with IED	Focal with Mild depression	Generalized with mild depression
Age (year)						
18-38	61.5	84.6	53.8	92.3	76.9	69.2
39-59	38.5	15.4	46.2	7.7	23.1	30.8
Male	53.8	69.2	76.9	38.5	84.6	100
Female	46.2	30.8	23.1	61.5	15.4	

Values are presented as percentage.

More male patients showed MDD and mild depression symptoms than female patients. In a generalized group, female patients displayed more IED symptoms than male patients; in contrast, the focal group showed the opposite pattern. Both Fisher's exact test and chi-square analysis revealed a significant association between cortisol and serotonin in patients with focal epilepsy with mild depression and in those with generalized epilepsy with IED. In contrast, only the chi-square test detected additional significant associations between these two hormones in focal epilepsy with MDD and generalized epilepsy with mild depression. No statistical approach showed any meaningful associations between these two hormones in focal epilepsy with IED and in generalized epilepsy with MDD (Table 2).

Table 2: Association of cortisol with serotonin in the same group of epilepsy

Epilepsy types with psychiatric disorders	Hormone	Mean	*p*-value	Fisher's exact test
Focal epilepsy with MDD	Cortisol Serotonin	1.77 0.23	0.041	0.108
Focal epilepsy with IED	Cortisol Serotonin	1.85 0.15	0.140	0.295
Focal epilepsy with mild depression	Cortisol Serotonin	1.38 0.77	0.012	0.035
Generalized epilepsy with MDD	Cortisol Serotonin	1.92 0.31	0.488	1.0
Generalized epilepsy with IED	Cortisol Serotonin	1.77 0.46	0.012	0.014
Generalized epilepsy with Mild depression	Cortisol Serotonin	1.31 0.69	<0.0001	0.001

Among patients with focal epilepsy, cortisol levels did not vary significantly across HAM-D severity groups (F= 2.18, p= 0.127); however, significant variation was found across MOCA categories (F= 4.51, p= 0.018), with elevated cortisol levels linked to increasing cognitive impairment. By contrast, serotonin levels showed significant differences across both HAM-D (F= 9.76, p< 0.001) and MOCA (F= 9.74, p< 0.001), displaying a consistent decline of serotonin level with increasing depression and cognitive severity. In individuals with generalized epilepsy, cortisol levels showed significant differences across both depression

(F= 5.55, p= 0.008) and MOCA (F= 23.32, p< 0.001) severity groups, while serotonin levels showed significant variation in MOCA (F= 9.27, p< 0.001), but not with HAM-D groups (F= 0.85, p= 0.435) (Table 3).

Table 3: Comparison of cortisol and serotonin levels in the same groups of epilepsy with different psychiatric disorders

Epilepsy Type	Hormone	Grouping	Severity	Low (%)	Normal (%)	High (%)	Mean±SD	*p*-value	Levene p
Focal	Cortisol	HAM-D	Mild	0	57	43	17.41±3.89	0.127	0.776
			Moderate	0	44	56	19.68±5.53		
			Severe	0	6	94	21.61±2.62		
		MOCA	Mild	0	44	56	16.97±3.67	0.018	0.776
			Moderate	0	20	80	21.13±4.35		
			Severe	0	0	100	21.78±4.47		
Focal	Serotonin	HAM-D	Mild	14	86	0	128.29±44.82	<0.001	0.096
			Moderate	50	50	0	90.73±62.14		
			Severe	94	6	0	37.79±12.69		
		MOCA	Mild	39	61	0	125.73±44.68	<0.001	0.045
			Moderate	70	30	0	65.1±54.9		
			Severe	100	0	0	35.64±9.98		
Generalized	Cortisol	HAM-D	Mild	0	71	29	16.15±5.63	0.0079	0.056
			Moderate	0	31	69	17.72±5.39		
			Severe	0	13	88	22.53±2.88		
		MOCA	Mild	0	90	10	12.53±3.12	<0.001	0.065
			Moderate	0	26	74	20.63±3.97		
			Severe	0	0	100	22.77±3.08		
Generalized	Serotonin	HAM-D	Mild	60	40	0	89.54±97.13	0.435	0.11
			Moderate	56	44	0	73.76±50.15		
			Severe	46	46	8	59.08±53.26		
		MOCA	Mild	38	62	0	118.47±33.51	<0.001	0.70
			Moderate	61	39	0	63±50.17		
			Severe	63	25	12	39.06±27.65		

MDD: Major depressive disorder, IED: Intermittent explosive disorder. Modified this table.

Generalized epilepsy patients had higher cortisol levels than focal patients; those with MDD showed this, while IED patients showed the opposite pattern. However, serotonin levels were lower in generalized epilepsy patients with MDD & IED compared to those with focal epilepsy. In the mild depression group, focal epilepsy patients had lower serotonin than generalized epilepsy patients. Focal epilepsy patients with mild depression had higher cortisol than generalized patients (Table 4).

Table 4: Comparison of Cortisol and serotonin levels in different epilepsy groups with the same psychiatric disorder

Epilepsy with psychiatric disorder	Hormone	Normal	Higher	lower
Focal with MDD	Cortisol	23.1	76.9	-
Generalized with MDD		7.7	92.3	-
Focal with MDD	Serotonin	23.1	-	76.9
Generalized with MDD		30.8	-	69.2
Focal with IED	Cortisol	15.4	84.6	-
Generalized with IED		23.1	76.9	-
Focal with IED	Serotonin	15.4	-	84.6
Generalized with IED	-	30.8	7.7%	61.5
Focal with mild depressive	Cortisol	61.5	38.5	-
Generalized with mild depressive	-	69.2	30.8	
Focal with mild depressive	Serotonin	76.9	-	23.1
Generalized with mild depressive		69.2	-	30.8

DISCUSSION

It is currently unanswerable whether seizures cause stress or stress causes seizures, as this relationship is bidirectional. Recent research has validated the role of cortisol in epilepsy [18], and patients who experience more frequent seizures tend to have elevated cortisol levels [19]. In another research, cortisol was found to be negatively associated with the functional activities of stress-sensitive seizure patients [20]. Patients with temporal lobe epilepsy (TLE) demonstrate decreased serotonin binding at 5-HT1A receptors in the orbitofrontal cortex, thalamus, neocortex, fusiform gyrus, and raphe hippocampus [21]. Epilepsy patients exhibited reduced transcriptional efficiency of 5-HTT, with particularly significant effects observed in both the insula and fusiform gyrus on the side affected by their epilepsy [21]. As per a previous meta-analysis, epileptic patients over the age of 18 experience the highest rates of depression; conversely, other research has identified a significant prevalence of depression among patients below 18 years of age [22]. In terms of gender differences, female epilepsy patients experiencing depression were more significantly affected than their male counterparts [23,24]. Table 1 shows that two groups of epilepsy patients aged 18-38 years, each with three types of psychiatric disorders, were more affected. Except for generalized epilepsy with IED, this study found that male epilepsy patients were more affected than female patients. Females predominated in this specific group. As shown in Table 2, two types of epilepsy disorder patients who were also suffering from three different types of psychiatric disorders were studied, and both hormones were tested simultaneously during the post-seizure period. Except for patients with focal epilepsy and interictal epileptiform discharges (IED) or generalized epilepsy with major depressive disorder (MDD), the other epilepsy groups with various psychiatric conditions showed a significant p-value between the two

hormones. According to earlier research, epilepsy and psychiatric disorders were interconnected, and cortisol and serotonin were researched separately in the presence of both diseases [3,25-28]. According to prior studies, cortisol levels were correlated with individuals who have epilepsy, as well as with those who experience depression or other psychiatric disorders [1]. Table 3 showed significant differences in cortisol levels in cognitive impairment among patients with both focal and generalized epilepsy, while a significant association was observed only in generalized epilepsy. These findings were consistent with those of Rider et al., who discovered that individuals with epilepsy (but not a specific type of epilepsy) who have two types of psychiatric disorders, namely depression & anxiety disorders, at the same time exhibit an acute increase in serum cortisol levels after a seizure attack [3]. Druzhkova *et al*. also discovered a significant correlation between rising cortisol levels and deteriorating cognitive impairment in epilepsy patients [1]. Table 3 showed that focal epilepsy exhibited a significant variability in serotonin level in relation to both depression and cognitive impairment, which was detected in focal epilepsy; however, in the generalized epilepsy patients, it was found to be linked with only cognitive issues and not with depressive severity. Earlier investigations indicated that lower levels of serotonin were associated with various psychiatric disorders, i.e., depression, and cognitive functions that express lower brain connectivity [29,30], as well as with epilepsy [5]. Prior investigations have shown that specific epilepsy patients (whether focal or generalized seizure types) with lower serotonin levels exhibited a higher correlation with comorbid depression [25]. Earlier studies indicated that patients with temporal lobe epilepsy and major depressive disorder (MDD) showed decreased binding to their receptors, such as 5-hydroxytryptamine-1A (5-HT1A) receptors, as determined through functional connectivity weighted analysis (FCWAY) [31]. Table 4 showed that approximately 76.9% of focal and 92.3% of generalized epilepsy patients with major depressive disorder (MDD) exhibit higher cortisol levels, a finding supported by of Afifi *et al*. study [26]. People who have focal epilepsy with major depressive disorder (PMDD) had higher levels of cortisol than people with epilepsy who exhibited a positive response on the Beck Depression Inventory-II (BDI-II) [1]. Previous and recent studies indicated that cortisol levels rose during acute stress; however, researchers had observed a decrease in cortisol levels when specific therapies were applied to patients or individuals not experiencing stress [32,33]. Similar to earlier research, Table 4 indicated that 38.5% of individuals with focal epilepsy and 30.8% of those with generalized epilepsy who experienced mild depression had elevated cortisol levels. However, the remaining patients in the mild depression of both epilepsy groups showed normal cortisol levels. This finding aligns with the Shao study, which found no significant association between acute stress and cortisol levels [34]. Individuals with intermittent explosive disorder displayed heightened aggression, suggesting an overproduction of glucocorticoids when faced with stress [35]. Previous studies indicated that the aggressive group had elevated serum and plasma cortisol levels [36,37]. According to Table 4, 84.6% of patients with focal and 76.9% of generalized epilepsy with intermittent explosive disorders showed elevated cortisol levels, contrasting with the findings observed in epilepsy patients with MDD. This study also evaluated serotonin levels while measuring cortisol levels and found that patients with generalized seizures (69.2%) exhibited lower serotonin levels than those with focal seizures (76.9%), who also had a major depressive disorder (MDD). According to previous research, cortisol influences serotonin regulation by increasing serotonin transporter expression and uptake, but chronically elevated cortisol in stress or depression may impair this process in patients with MDD and generalized anxiety disorders [38]. Various studies have suggested a decrease in tryptophan, along with diminished availability of the 5-HT transporter, indicating reduced serotonin levels in patients with IED who exhibit highly aggressive behavior [27,39]. This study specifically showed that 84.6% of focal epilepsy patients have lower serotonin levels, compared to 61.5% of individuals experiencing generalized seizures with IED. A prior investigation demonstrated that those who have recovered from depression may experience a rapid return of temporary depressive symptoms, potentially leading to relapses into moderate or mild forms of major depression [40] due to tryptophan depletion. Earlier findings suggested that serotonin does not significantly relate to depression, as two comprehensive investigations of the SERT gene and two systematic reviews examining the serotonin metabolite 5-HIAA found no connection with depression [41]. Table 3 showed that mild depressive patients can have both normal and lower serotonin levels. Among these patients, 76.9% with focal mild depression had normal serotonin levels compared to those with generalized mild depression. However, 30.8% of individuals with generalized depression tend to have lower serotonin levels compared to focal individuals (23.1%).

Study Limitation

Anti-seizure medications can influence mood, cognition, and psychiatric outcomes. Antiseizure medications were not recorded and included in this analysis due to the exploratory nature of the pilot study and the high prevalence of polytherapy. Future research with a larger sample size should reconsider this, incorporating statistical adjustment. Although blood samples were collected within 48 hours after the recent epileptic event, samples were not specifically collected after the post-ictal or during the inter-ictal event. Therefore, the extent to which residual seizure-related hormonal fluctuations influenced psychiatric comorbidities remains unclear. Future studies should control for seizure timing and sampling relating to seizures in different periods to understand seizure-related hormonal fluctuation to assess the severity of psychiatric comorbidities.

Conclusion

Epilepsy and psychiatric disorders exhibit a bidirectional relationship, with both cortisol and serotonin contributing to the stabilizing processes involved in most cases. The presence of different types of epilepsy, along with various psychiatric disorders, is associated with variations in cortisol and serotonin levels. This observational study will help in clinical settings for treating patients. Further research will uncover the reasons behind hormonal fluctuations in three groups. This study has some limitations, primarily due to the use of a smaller sample size, which affects the overall understanding of the results; additionally, incorporating other serum tests and genetic studies would enhance the findings. These findings raise several questions, such as which pathways become active after an epileptic attack or during periods of stress and depression? Why are these hormone levels found to differ across various epilepsy studies? Therefore, future research is needed.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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