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ORIGINAL ARTICLE

HPA axis function in patients with right and left focal lateralized epilepsy.

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Abstract

OBJECTIVES: There is a complex, reciprocal link between epilepsy and the hypothalami pituitary-adrenal (HPA) axis. This study aimed to evaluate the role of the HPA axis in individuals with focal epilepsy, including those with right- or left-hemispheric lateralized epilepsy.

MATERIAL AND METHODS: The study comprised 60 individuals with focal epilepsy, ages 18 to 85, with seizures coming from a single hemisphere, no destructive lesions on cranial magnetic resonance imaging, and 32 healthy persons. Blood was drawn from the patient and control groups at 8.00 for serum cortisol level and at 23.00 for serum melatonin level. The Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale were administered to both the patient and control groups.

RESULTS: Patients showed decreased melatonin levels ($p < 0.001$) and poorer sleep quality ($p = 0.035$). The cortisol level of the patients was found to be lower than the cortisol level of healthy individuals, although it was not statistically significant ($p = 0.107$). Cortisol and melatonin levels did not significantly differ between patients with seizures coming from the right or left hemisphere. The patients with seizures originating from the left hemisphere had a longer duration of epilepsy disease ($p = 0.013$), higher seizure frequency ($p = 0.013$), lower age of first seizure onset ($p = 0.038$), and a higher rate of polytherapy ($p = 0.05$).

CONCLUSION: Low cortisol and melatonin levels in patients with focal epilepsy may be an indicator of disruption in the HPA axis. There is no significant difference in the HPA axis function between patients with focal epilepsy according to the epileptic hemisphere.

Abbreviations:

HPA axis	- Hypothalami pituitary-adrenal axis
MRI	- Magnetic Resonance Imaging
PET-CT	- Positron Emission Tomography and Computed Tomography
EEG	- Electroencephalogram
ESS	- Epworth sleepiness scale
PSQI	- Pittsburgh sleep quality index
PWRHS	- Patients with right hemispheric seizures
PWLHS	- Patients with left hemispheric seizures
CNS	- Central Nervous System
GABA	- gamma-aminobutyric acid
ACTH	- Adrenocorticotropic hormone
COVID-19	- Coronavirus disease 2019

INTRODUCTION

The most common triggers of seizures in people with epilepsy are emotional stress and lack of sleep (Gunn & Baram, 2017; Nakken *et al.* 2005). The body's physiological response to emotional stress is controlled by the HPA axis, a neuroendocrine pathway. There is a complex and bidirectional interaction between the stress-HPA axis and epileptic seizure (Cano-López & González-Bono, 2019; Zobel *et al.* 2004).

Patients with epilepsy often experience sleep difficulties due to disruption of the HPA axis. The interaction between sleep and the HPA axis is also complex and bidirectional (Nicolaides *et al.* 2020). HPA axis hyperactivity is tightly linked to decreased sleep duration or quality (Balbo *et al.* 2010). Melatonin, a physiological modulator of the HPA axis, has antiseizure drug potential (Khan *et al.* 2020; Mareš *et al.* 2013). Studies have shown that melatonin level is low before a seizure and that there is a significant increase in its level after a seizure (Dabak *et al.* 2016). Sleep disturbance and seizure frequency in epileptic patients may be related to melatonin levels (Jain *et al.* 2015).

The HPA axis is a crucial neuroendocrine mechanism linked to numerous psychiatric disorders including depression and bipolar disorder as well as numerous neurological conditions like dementia and migraines (Murri *et al.* 2016; Druzhkova *et al.* 2022; Keller *et al.* 2017; Leistad *et al.* 2007; Milligan Armstrong *et al.* 2021). There is no study in the literature evaluating the HPA axis by performing hemispheric lateralization among people who have focal epilepsy. Therefore, this study aimed to evaluate the relationship between HPA axis function and focal epilepsy based on the characteristics of sleep-wake cycles and cortisol-melatonin levels in all patients with focal epilepsy as well as in patients with right or left-hemisphere lateralized focal epilepsy.

MATERIAL AND METHODS

Participants and procedure

The study was conducted between November 2020 and April 2021, while the COVID19 pandemic was ongoing. This prospective study included patients with focal epilepsy who applied to the epilepsy outpatient clinic at Istanbul Medeniyet University Goztepe Prof. Dr. Süleyman Yalçın City Hospital. The study included 60 patients with clinically focal seizures with a focal epileptogenic focus between the ages of 18 and 85 who were treated with the appropriate anti-seizure medication and 32 healthy volunteers. Cranial MRI and PET-CT imaging, and video EEG recordings were examined to determine the epileptic focus compatible with the clinical seizures of the included patients, and the patients were diagnosed with focal epilepsy, then the epileptic hemisphere was lateralized. Cases with primary generalized epileptic activity, cases with multifocal epileptic foci, and cases with lesions of other destructive diseases in the cerebral hemisphere were not included in the study.

In face-to-face interviews with the patients, gender, age, education level, marital status information, degree of mental retardation, and hand dominance characteristics were noted. In the etiology of seizures, perinatal risk status (low birth weight, preterm, toxins exposure, persistent maternal illness, and certain maternal illnesses), presence of parental consanguinity, trauma history, central nervous system infection history, and febrile convulsion history were learned. If there was a history of trauma, central nervous system infection and/or febrile convulsion, age was also noted. The age at which recurrent seizures first occurred, the nature and frequency of the aura, whether the seizures occurred during sleep, seizure frequency, and antiepileptic drug information were recorded in the patient follow-up form created for clinical follow-up.

The Epworth sleepiness scale (ESS) and the Pittsburgh sleep quality index (PSQI) were used in a face-to-face interview by the same clinician to gather data on sleep-wake cycles.

Istanbul Medeniyet University Goztepe Prof. Dr. Süleyman Yalçın City Hospital's ethical committee gave its approval (date:26/10/2020-decision no:2020/0632). The "Information and Consent Form for Participants" prepared for the study was read and signed by the patients.

Cortisol and melatonin measurement

Blood was taken from the patients at 08:00 for serum cortisol level measurement and at 23:00 for serum melatonin level measurement after at least 1 month had passed since the last epileptic seizure. 3 ml of venous blood from the patients was drawn into gel tubes. After the samples were taken into the tube, within 30 minutes, they were centrifuged for 10 minutes at 1000 rpm at 2-8°C. The supernatant was removed from the tube's top and put into Eppendorf tubes, where it was maintained cool and preserved until analysis at -80°C. Blood specimens were studied in the biochemistry laboratory with Elabscience Human Cortisol Kit Catalog No for ELISA: E-EL-0157 96T and Human MT(Melatonin) Kit Catalog No for ELISA: E-EL-H2016 96T, by the storage conditions.

Applied surveys

PSQI is a scale created to provide a quantitative measurement of sleep quality and to define sleep quality as good or bad (Buysse *et al.* 1989). Consisting of a total of 24 questions, this scale evaluates the previous month's sleeping quality. Evaluation is made on a total of 21 points. A total score greater than 5 means that sleep quality is poor (Agargun MY, 1996).

The ESS is a scale created to evaluate the daytime sleepiness of the person. The probability of napping during 8 different activities of daily living that the person did in the previous month is evaluated. In this

scale, the highest score that can be obtained is 24, and scores of 10 and above indicate excessive daytime sleepiness (Izci *et al.* 2008; Johns, 1992).

STATISTICAL ANALYSIS

Kolmogorov-Smirnov test of normality (if number of patients >50) and/or Shapiro-Wilk test (if number of patients ≤50) were used to compare patient-control groups and patient subgroups for numerical continuous variables. Using Levene's test, also evaluated was the homogeneity of group variances. When parametric test assumptions were satisfied, an independent samples t-test was conducted, and these variables' averages and standard deviations were utilized to describe them. In cases where the parametric test assumptions were not met, the median (25^{th} percentile-75^{th} percentile: interquartile range of distribution) was defined and an analysis using the Mann-Whitney U test was performed. Frequencies and percentages were employed to identify

Tab. 1. Comparison of patients and healthy control group demographics and comparison of clinical features of patients according to lateralized hemisphere

	Patient (n=60)	**PWRHS (n=19)**	**PWLHS (n=41)**	***p* value (PWRHS-PWLHS)**	**Healthy individual (n=32)**	***p* value (Patient -Healthy individual)**
	n(%) or median (25^{th} percentile - 75^{th} percentile)					
Epileptic hemisphere	60 (%100)	**19 (%31.7)**	**41 (%68.3)**	**<0.01¶**	-	-
Age (years)	37.5 (26.2-42.7)	37 (22-46)	38 (30-42)	0.545*	40.5 (25-50)	0.294*
Sex (Female/Male)	25/35 (%41.7/%58.3)	7/12 (%36.8/%63.2)	18/23 (%43.9/%56.1)	0.606†	19/13 (%59.4/%40.6)	0.105†
Hand dominance (Right/Left)¢	51/9 (%85/%15)	17/2 (%89.5/%10.5)	34/7 (%82.9/%17.1)	0.705††	31/1 (%96.9/%3.1)	0.156††
Educational level (%)						
Elementary School -Secondary School	**38 (64.4)**	10 (52.6)	28 (70)	0.193†	**8 (25)**	**0.001†**
High school- University	**21 (35.6)**	9 (47.4)	12 (30)		**24(75)**	
Marital standing (Married/Single)	**26 /34 (43.3/56.7)**	10 /9 (52.6/47.4)	16/25 (39/61)	0.322†	**21/11(65.6/34.4)**	**0.042†**
Mental retardation						
None Yes	45 (%75) 15 (%25)	17 (%89.5) 2 (%10.5)	28 (%68.3) 13 (%31.7)	0.070††		
History of febrile convulsion (yes)	28 (%46.7)	8 (%42.1)	20 (%48.8)	0.630†		
Febrile convulsion age (years)	1.5 (0.6-2)	2 (0.95-3)	1.5 (0.6-2)	0.292*		
Head trauma (yes)	16 (%26.7)	6 (%31.6)	10 (%24.4)	0.550†		
Head trauma age (years)	8 (5-11)	10 (5-11)	7 (4-9)	0.154*		
CNS Infection (yes)	4 (%6.7)	1 (%5.3)	3 (%7.3)	-		
CNS Infection age (years)	1.3 (0.4-2.7)	2 (2-2)	0.7 (0.3-3)	0.655*		
Perinatal risk (yes)	12 (%20)	5 (%26.3)	7 (%17.1)	0.493††		
Parental consanguinity (yes)	14 (%23.3)	5 (%26.3)	9 (%22.0)	0.749††		
Age of first seizure onset (years)	12.5 (5-21)	**16 (12-34)**	**11 (3-18)**	**0.038***		
Disease duration (years)	15 (7.2-30)	**10 (6-20)**	**22 (10-33)**	**0.013***		
Longest seizure-free time (years)	1 (0.08-2.5)	1 (0.25-2)	0.48 (0.08-3)	0.608*		
Seizure frequency (per month)	1.5 (0.25-5.75)	**0.33 (0.25-2)**	**4 (0.5-8)**	**0.013***		
Seizure in sleep (yes)	40 (%65.2)	13 (%68.4)	27 (%65.9)	0.844†		
Therapy (Mono/Poly)	24 (%40)/ 36 (%60)	11 (%57.9)/ 8 (%42.1)	13 (%31.7)/ 28 (%68.3)	**0.05†**		

PWRHS: Patients with right hemispheric seizures PWLHS: Patients with left hemispheric seizures ¶ One-sample t-test. *Mann Whitney U test. †Pearson Chi-Square. ††Fisher's Exact Test. Statistically significant was defined as $p < 0.05$. ¢ We did not have patients with equal dominance of both hands.

Tab. 2. Comparison of cortisol-melatonin levels, PSQI, and ESS of the patients and the controls

	Patient (n=60)	PWRHS (n=19)	PWLHS (n=41)	*p* value (PWRHS-PWLHS)	Healthy individual (n=32)	*p* value (Patient-Healthy)
	Median (25th percentile - 75th percentile)					
Cortisol (µg/dL)	15.4 (11.9-20)	14.9 (10.6-17.9)	14.7 (12.6-20)	0.418	16.8 (13-24)	0.107
Melatonin (ng/L)	**27.1 (18.8-95.6)**	20.8 (14.9-93.4)	23.2 (18.3-28.3)	0.905	**78.1 (32.8-143.4)**	**<0.001**
PSQI	**6 (3-8.7)**	6 (3-7)	6 (3-9)	0.375	**4 (2-5.7)**	**0.035**
ESS	4 (2-7.75)	3 (2-8)	4 (1.5-7.5)	0.737	4 (2-6)	0.636

PWRHS: Patients with right hemispheric seizures PWLHS: Patients with left hemispheric seizures. Mann Whitney U test was performed on the entire table. Statistically significant was defined as $p < 0.05$. PSQI: Pittsburgh Sleep Quality Index ESS: Epworth Sleepiness Scale

categorical variables, and the Pearson Chi-square Test or Fisher's Exact Test was used to analyze how they related to one another.

For continuous variables with non-normal distributions and ordinal variables, "Spearmen's correlation coefficient" was utilized during the correlation analysis. When examining two-category variables and continuous variables, the "point-biserial correlation coefficient" was used.

For all statistical analyses, $p < 0.05$ was regarded as significant using IBM SPSS Statistics (version 25.0 for Windows, Chicago, IL, USA.

RESULTS

The study included 32 healthy individuals and 60 patients with focal epilepsy. Seizures of 41(68.3%) patients originated from the left hemisphere. The number of patients with left hemispheric seizures was significantly higher ($p < 0.01$) (Table 1).

When patients and healthy individuals were compared, and when patients with right hemispheric seizures (PWRHS) were compared with patients with left hemispheric seizures (PWLHS), the distributions of age, gender, and hand dominance were not significantly different from one another ($p > 0.05$). The educational level of healthy people was found to be much greater than that of patients ($p = 0.001$). The proportion of single people among epilepsy patients was significantly greater ($p = 0.042$). Although not statistically significant, mental retardation was more common in PWLHS ($p = 0.07$) (Table 1).

PWRHS had a significantly higher age of the first seizure ($p = 0.038$). Disease duration and monthly seizure frequency were noticeably higher in PWLHS ($p = 0.013$; $p = 0.013$, respectively) (Table 1).

Twenty-four (40%) patients were receiving monotherapy and thirty-six (60%) patients were getting multiple therapies. Patients who received polytherapy were more numerous in the PWLHS group than in the PWRHS group, and the difference was statistically significant ($p = 0.05$) (Table 1).

The median cortisol level for patients with epilepsy was 15.4 (11.9-20) µg/dL compared to 16.8 (13-24) µg/dL for healthy individuals, with no statistically significant difference between them ($p = 0.107$). Cortisol levels of PWRHS and PWLHS were also not statistically different ($p = 0.418$) (Table 2).

The median melatonin level for patients with epilepsy was 27.1 ng/L (18.8-95.6) compared to 78.1 ng/L (32.8-143.4) for healthy individuals ($p < 0.001$). However, there was no difference in melatonin levels between PWRHS and PWLHS ($p = 0.905$) (Table 2).

The median PSQI score of patients with epilepsy was significantly higher than the median PSQI score of healthy individuals ($p = 0.035$). ESS scores of patients with epilepsy and healthy individuals were not statistically different ($p = 0.636$). Both PSQI and ESS scores of PWRHS and PWLHS were not statistically different (Table 2).

In the group of PWRHS, mental retardation, and seizure frequency showed a very strong positive correlation ($r = 0.724$, $p < 0.001$). The age at which the first seizure occurred and the frequency of seizures revealed a moderately significant negative correlation ($r = -0.503$, $p = 0.028$). Seizure frequency and age of head trauma had a very strong positive correlation ($r = 0.818$, $p = 0.047$). The longest seizure-free duration and seizure frequency had a very strong negative correlation ($r = -0.782$, $p < 0.001$).

In the group of PWLHS, head trauma age - length of time between seizures and seizure frequency was strongly negatively correlated ($r = -0.715$, $p = 0.030$; $r = -0.778$, $p < 0.001$ respectively). Aura frequency and seizure frequency were strongly positively correlated ($r = 0.867$, $p < 0.001$). Seizure frequency and the history of febrile seizures-perinatal risk status showed a slightly significant positive correlation ($r = 0.328$, $p = 0.036$; $r = 0.320$, $p = 0.042$, respectively) (Table 3).

ESS and PSQI were slightly positively correlated in all epilepsy patients ($r = 0.330$, $p = 0.010$). Cortisol levels and antiepileptic drug use were slightly negatively correlated in all epilepsy patients ($r = -0.276$, $p = 0.033$) (Table 4).

Tab. 3. Seizure frequency and demographic-laboratory data correlation analysis according to lateralized hemispheres

	Right hemisphere seizure frequency (monthly)		Left hemisphere seizure frequency (monthly)	
	r	***p***	**r**	***p***
Age (years)	-0.007 λ	0.977 λ	0.048 λ	0.764 λ
Gender (female/male)	0.113 Ψ	0.645 Ψ	-0.067 Ψ	0.677 Ψ
Hand dominance (right/left)*	-0.032 Ψ	0.897 Ψ	0.032 Ψ	0.840 Ψ
Mental retardation (yes/no)	**0.724 Ψ**	**<0.001 Ψ**	0.245 Ψ	0.123 Ψ
Age of first seizure onset (years)	**-0.503 λ**	**0.028 λ**	-0.182 λ	0.255 λ
Febrile seizure history (yes/no)	-0.181 Ψ	0.458 Ψ	**0.328 Ψ**	**0.036 Ψ**
Febrile convulsion age (years)	0.553 λ	0.155 λ	0.420 λ	0.065 λ
Head trauma (yes/no)	-0.165 Ψ	0.501 Ψ	-0.161 Ψ	0.315 Ψ
Head trauma age (years)	**0.818 λ**	**0.047 λ**	**-0.715 λ**	**0.030 λ**
CNS infection (yes/no)	0.028 Ψ	0.910 Ψ	0.036 Ψ	0.823 Ψ
CNS infection age (years)	-	-	0.500 λ	0.667 λ
Perinatal risk (yes/no)	0.401 Ψ	0.089 Ψ	**0.320 Ψ**	**0.042 Ψ**
Disease duration (years)	0.270 λ	0.263 λ	0.199 λ	0.212 λ
Aura frequency (monthly)	0.643 λ	0.062 λ	**0.867 λ**	**<0.001 λ**
Longest seizure-free time (years)	**-0.782 λ**	**<0.001 λ**	**-0.778 λ**	**<0.001 λ**
Seizure during sleep (present/absent)	0.167 Ψ	0.494 Ψ	0.164 Ψ	0.305 Ψ
Cortisol (µg/dL)	0.252 λ	0.297 λ	0.253 λ	0.110 λ
Melatonin (ng/L)	-0.035 λ	0.887 λ	0.181 λ	0.257 λ
Pittsburgh Sleep Quality Index (score)	0.151 λ	0.538 λ	0.066 λ	0.684 λ
Epworth sleepiness scale (score)	-0.160 λ	0.513 λ	-0.110 λ	0.496 λ

r: Correlation coefficient. λ: Spearmen correlation analysis. Ψ: Point Biserial correlation analysis
Statistically significant was defined as $p < 0.05$. ¢ We did not have patients with equal dominance of both hands

In the correlation analyses performed according to the lateralized hemisphere, between the ESS and the PSQI, there was a moderately significant positive correlation in the group of PWRHS (r = 0.486, $p = 0.035$) (Table 5).

DISCUSSION

HPA axis and epilepsy

Stress is an important factor affecting HPA axis function in epilepsy (Sawyer & Escayg, 2010). As expected, epilepsy patients are exposed to a chronic type of stress. A single seizure as an acute stressor can acutely alter HPA axis function or chronic recurrent seizures may change the way the HPA axis works in a different way than a single seizure (Herman *et al.* 2016) It has been reported that acute stress has both an increasing and decreasing effect on seizure sensitivity, depending on the seizure induction method and the type of acute stressor used, whereas chronic stress constantly has a proconvulsive effect (Sawyer & Escayg, 2010). In an animal study in which epileptic seizures were induced in non-epileptic mice reported that the HPA axis was activated and the cortisol level increased. It was concluded that seizures, as an acute stressor, cause deficiencies in the basic inhibitory mechanism that controls the HPA axis, resulting in overstimulation of the axis (O'Toole *et al.* 2014). Frequent seizures and high cortisol levels can worsen limbic damage and trigger the epileptogenic cycle, which can further impair HPA axis function (Herman *et al.* 2016; O'Toole *et al.* 2014). High cortisol levels are observed in epilepsy patients as a result of hyperactivity of the HPA axis during a seizure, and the elevated cortisol levels decrease within hours (Tunca *et al.* 2000). Since the blood sample in our study was taken at least one month after the last seizure, it is an expected result that the cortisol level was not high, but it may be lower than normal.

Another factor known to cause HPA axis dysfunction is insomnia. It is known that melatonin production is suppressed and excessive activation of the HPA axis is triggered by insomnia (Lateef & Akintubosun, 2020). In a study investigating the relationship between melatonin and the HPA axis, it was reported that the amount of GABA in the hypothalamus was raised by exogenous melatonin administration, and the melatonin's ability to regulate sleep was correlated with the hypothalamic GABA concentration (Si *et al.* 2020). Like

Tab. 4. Correlation analysis of the PSQI, ESS, melatonin, and cortisol levels in all patients

	Cortisol (µg/dL)	Melatonin (ng/L)	PSQI (score)	ESS (score)	Therapy (Mono/Poly)
Cortisol (µg/dL)	1				
Melatonin (ng/L)	r = -0.037; $p = 0.781^{\lambda}$	1			
PSQI (score)	r = -0.171; $p = 0.192^{\lambda}$	r = 0.051; $p = 0.699^{\lambda}$	1		
ESS (score)	r = -0.216; $p = 0.097^{\lambda}$	r = 0.109; $p = 0.299^{\lambda}$	**r = 0.330; $p = 0.010^{\lambda}$**	1	
Therapy (Mono/Poly)	**r = -0.276; $p = 0.033^{\Psi}$**	r = -0.089; $p = 0.50^{\Psi}$	r = 0.171; $p = 0.192^{\Psi}$	r = 0.088; $p = 0.502^{\Psi}$	1

$^{\lambda}$: Spearman correlation analysis $^{\Psi}$: Point Biserial correlation analysis r: Correlation coefficient.
Statistically significant was defined as $p < 0.05$. PSQI: Pittsburgh Sleep Quality Index ESS: Epworth Sleepiness Scale

cortisol, melatonin has been shown to exert a regulatory effect on HPA axis function via GABA receptors. During a rat study, it was discovered that the HPA axis was regulated and infantile spasms were prevented by the administration of ACTH and/or melatonin (Wan *et al.* 2021).

There are studies to explain the pathogenesis of epilepsy in focal epilepsy patients through the HPA axis, inflammatory and neurotrophic factors, and to evaluate the coexistence of depressive disorder (Mazarati *et al.* 2009; Druzhkova *et al.* 2022). However, there are no clinical studies evaluating the relationship between focal epilepsy and HPA axis activity relative to the lateralized hemisphere.

In our study, cortisol and melatonin levels were investigated to evaluate HPA axis function in individuals with focal epilepsy. Cortisol values of all patients were compared with the cortisol values of healthy individuals, and between them, no discernible differences existed. This may be due to the possible high cortisol level in the healthcare personnel in our control group, as the study was conducted under stressful working conditions while the COVID-19 pandemic was ongoing. On the other hand, healthcare workers waking up too early for work may cause a significant decrease in cortisol levels at 8:00 in the morning when the blood sample is taken.

It has been reported that melatonin levels are low in patients with resistant epilepsy and that low melatonin levels are affected by long-term antiepileptic drug use and the duration of epilepsy. In our study, it was observed that the melatonin level of the patient group was quite low, and this supports the literature (Paprocka *et al.* 2010; Khan *et al.* 2020; Vasileva, 2021). However, there was no meaningful correlation between melatonin level, frequency of seizures, and medicines

Tab. 5. Correlation analysis of the cortisol level, melatonin level, PSQI, and ESS in patients according to lateralized hemisphere

		Cortisol (µg/dL)	Melatonin (ng/L)	PSQI (score)	ESS (score)	Therapy (Mono/Poly)
Right hemisphere	Cortisol (µg/dL)	1				
	Melatonin (ng/L)	r = -0.168; $p = 0.490^{\lambda}$	1			
	PSQI (score)	r = -0.136; $p = 0.579^{\lambda}$	r = 0.085; $p = 0.730^{\lambda}$	1		
	ESS (score)	r = -0.288; $p = 0.232^{\lambda}$	r = 0.391; $p = 0.097^{\lambda}$	**r = 0.486; $p = 0.035^{\lambda}$**	1	
	Therapy (Mono/Poly)	r = 0.326; $p = 0.173^{\Psi}$	r = -0.039; $p = 0.876^{\Psi}$	r = 0.045; $p = 0.856^{\Psi}$	r = 0.167; $p = 0.495^{\Psi}$	1
Left hemisphere	Cortisol (µg/dL)	1				
	Melatonin (ng/L)	r = -0.006; $p = 0.968^{\lambda}$	1			
	PSQI (score)	r = -0.219; $p = 0.168^{\lambda}$	r = 0.031; $p = 0.848^{\lambda}$	1		
	ESS (score)	r = -0.233; $p = 0.143^{\lambda}$	r = -0.167; $p = 0.298^{\lambda}$	r = 0.284; $p = 0.072^{\lambda}$	1	
	Therapy (Mono/Poly)	r = 0.226; $p = 0.155^{\Psi}$	r = -0.075; $p = 0.642^{\Psi}$	r = 0.186; $p = 0.244^{\Psi}$	r = -0.038; $p = 0.812^{\Psi}$	1

$^{\lambda}$: Spearman correlation analysis $^{\Psi}$: Point Biserial correlation analysis r: Correlation coefficient.
Statistically significant was defined as $p < 0.05$. PSQI: Pittsburgh Sleep Quality Index ESS: Epworth Sleepiness Scale

utilized. The fact that patients with focal epilepsy have low levels of melatonin, an essential HPA axis modulator, indicates that the HPA axis is dysfunctional in these patients. This again makes us think that the preservation of the function of the axis may have a place in the management of epilepsy and that new studies should be conducted on this subject.

Hemispheric lateralization

Right and left cerebral hemispheres differ in anatomical, functional organization, and features (Geschwind & Galaburda, 1985). In addition to the structural asymmetry between the hemispheres of higher cortical functions such as speech and memory, it is known that there are differences between the hemispheres in the activity of neurotransmitters such as choline acetyltransferase, GABA, and norepinephrine (Glick *et al.* 1982; Labar *et al.* 2001)

In the literature, it has been reported that the left cerebral hemisphere is more likely to cause focal epilepsy, and left-sided lesions had a higher prevalence of temporal lobe epilepsy (Currie *et al.* 1971; Dean *et al.* 1997; Scott, 1985). It has been emphasized that the left hemisphere is more vulnerable to the onset of seizures in childhood, laterality plays a role, not gender, at the start age of seizures, and the left hemisphere is more prone to the development of epilepsy (Strauss *et al.* 2019). It is reported that the left hemisphere is more epileptogenic, the duration of ictal seizures is longer, the frequency of seizures is higher, and the duration of epilepsy is longer (He *et al.* 2020; Seethaler M *et al.* 2021; Varatharajah *et al.* 2021; Varoglu, 2024).

In terms of clinical features, in support of the literature; in our study, the proportion of patients who experienced left hemispheric seizures was noticeably higher, and these patients had a significantly lower age of onset of seizure, a higher monthly seizure frequency, a higher rate of polytherapy and a longer duration of epilepsy. The right hemisphere has been shown to reorganize in patients with an epileptic focal or congenital lesion in the left hemisphere to make up for the dysfunction in the left hemisphere (Kleen *et al.* 2013; Lidzba *et al.* 2017). In the correlation analysis of our study, patients with right hemisphere seizures showed a negative correlation between the age of first seizure onset and seizure frequency, however patients with left hemisphere seizures did not show this correlation. This result suggests that the left hemisphere cannot compensate for the right hemisphere and because the right hemisphere can effectively make up for the left hemisphere, in patients with left hemisphere seizures, there is no correlation between the age at which the first seizure occurs and the frequency of seizures. No statistically significant difference exists between the hemispheres in terms of the presence of etiological components. These findings are consistent with the idea that the left hemisphere is more susceptible to the initiation of epileptogenesis and more epileptogenic.

Epilepsy is more common in people with mental retardation than in the general population, as is widely known (Mcgrother *et al.* 2006). Although it was not significant, lateralization revealed a higher rate of mental retardation in PWLHS, but correlation analysis revealed a higher seizure frequency in mentally retarded patients who had seizures coming exclusively from the right hemisphere. This result suggests that the left hemisphere cannot compensate for the right hemisphere. Although patients with seizures coming from the left hemisphere had a higher likelihood of mental retardation, the lack of correlation between the presence of mental impairment and the frequency of seizures may suggest the presence of "functional asymmetry" between the hemispheres.

It has been reported that anatomical asymmetry between hemispheres in the cortical and subcortical structures of the brain may be related to body asymmetry. This asymmetry may result from the development of neuroplasticity under the influence of genetic or environmental factors, or may result from differences between genders due to the influence of sexual hormones (Renteria, 2012). Studies have concluded that there is asymmetry in cerebral anatomy and function in neurodevelopmental disorders such as attention deficit and hyperactivity disorder and dyslexia, and in psychiatric diseases such as schizophrenia, bipolar disorder and major depression (Oertel-knöchel & Linden, 2011). Anatomical, functional, and epileptogenic differences between hemispheres suggest that HPA axis functioning with neuroendocrine mechanisms may also differ between hemispheres.

There are no studies on whether there is a difference in the functioning of the HPA axis according to lateralization. In our study, to lateralize and investigate HPA axis function, the cortisol and melatonin levels of PWRHS and PWLHS were compared. It was discovered that there was no significant difference between them. Although the fact that there is no discernible difference between the hemispheres in terms of axis dysfunction, we believe that our study will be helpful for future research including more patients.

Epilepsy and sleep disorders

Patients with epilepsy frequently experience sleep difficulties, and excessive daytime sleepiness and insomnia are known to be more common than controls (Ismayilova *et al.* 2015). Adult epilepsy patients with subjective sleep disorder complaints were included in a study, and it was discovered that their PSQI scores were considerably higher than those of the control group, and ESS scores did not differ significantly between patients and controls (Shen *et al.* 2017) Similarly, in our study, the patients' PSQI scores were found to be substantially higher than those of the persons in the healthy control group, and it was noted that the patients' sleep quality was lower. The ESS was used to assess daytime sleepiness, but no significant differences were found between

the patient and healthy control groups. Healthy individuals in our control group were working in a shift system. It is known that disorders in the sleep-wake cycle are common in those who work in shift systems, including healthcare workers (Ettorre & Pellicani, 2020; Park *et al.* 2019). The reason why no difference was observed between the daytime sleepiness of the patient and control groups in our study may be that the healthy individuals in our control group were hospital personnel working in shifts and their sleep-wake cycles were disturbed.

CONCLUSION

Low cortisol and melatonin levels in patients with focal epilepsy may indicate HPA axis dysfunction. The fact that there was no significant difference in HPA axis function in the hemispheric comparison based on cortisol and melatonin levels of PWRHS and PWLHS shows that treating the HPA axis without paying attention to lateralization will work in the treatment of epilepsy.

When more extensive studies are conducted to elucidate the underlying neuropathology; we believe that the correction of HPA axis dysfunction can be beneficial in the control of seizures in all patients with focal epilepsy, regardless of lateralization, and especially in PWLHS with higher seizure frequency and worse prognosis.

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