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The Relationship Between Pituitary Gland Dimensions, Thyroid Functions, and Seizure Activity in Patients with Epilepsy

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Abstract

Objective: Morphological and functional changes in hormonal systems may present as the cause and/or result of epileptic seizures. The purpose of the present research is to evaluate the relationship between the structure of the pituitary gland, thyroid functions, and seizure activity in patients with epilepsy.

Methods: It was designed as a hospital-based, retrospective, and case–control study. No secondary epilepsy patients (18-65 years) were included in the study. Disease duration, seizure frequency, and antiepileptic treatments were questioned. Electroencephalography findings were grouped as normal, nonspecific, slow wave activity, and epileptic activity. Seizure types were determined. The pituitary gland was measured with coronal T2-magnetic resonance imaging sequences. Pituitary gland width, height, and intercavernous distance were obtained. Thyroid-stimulating hormone, free triiodothyronine, and free thyroxine results were recorded.

Results: There were 63 patients (mean age of 43.11 ± 12.38 years) and 44 healthy volunteers in the study. Pituitary gland width and intercavernous distance were lower in epilepsy patients compared to the control group ($P = .012$ and $P = .006$). Thyroid function test results were similar in the patient and control groups ($P > .05$). There was a negative correlation between the number of seizures in the last 1 month and the width of the pituitary gland ($P = .008$, $r = -0.331$). There was no relationship between other clinical features, antiepileptic therapy, and pituitary measurements and thyroid functions.

Conclusion: The lower width of the pituitary gland and its relationship with the frequency of seizures support that seizure activity is associated with structural features of the hormonal system in patients with epilepsy.

Keywords: Epilepsy, pituitary, seizure, antiepileptic drugs, thyroid hormones

INTRODUCTION

Epilepsy is a common neurological disease that affects more than 65 million people in the worldwide.[1] Anticonvulsant treatments have been used for many years to reduce disease-related seizures.[2] Studies have proved that these treatments have different effects on thyroid hormone levels.[3]

Thyroid-stimulating hormone (TSH) is secreted from the pituitary gland and modulates T3 and T4 secretion in the thyroid gland. Differences in pituitary gland morphology may be detected in hypothyroid patients with magnetic resonance imaging (MRI).[4] Changes in serum hormone levels may occur due to epileptic seizures, and this may affect the hypothalamic-pituitary-thyroid axis.[5-7] Many hormone levels increase especially in the postictal period. This supports the relationship between epileptic seizures and hypothalamus-pituitary-thyroid and gonadal axis.[8] The GABAergic system, which is associated with the etiopathogenesis of epileptic seizures, is also effective on the thyroid system. There is a complex relationship between the GABAergic system and hypothalamus-pituitary-thyroid axis.[9]

The relationship between hormonal changes and seizure activity is known. This helps us to understand the cause of seizures. The purpose of the present research is to evaluate the structural features of the pituitary gland and its relationship with thyroid hormones and seizure activity. The results will help to reveal the structural and functional features of the hypothalamic-pituitary-thyroid axis in patients with epilepsy.

METHODS

The study was performed in patients with no secondary epilepsy who had been followed up in the neurology clinic for at least 1 year. It was designed as a retrospective, case–control study. Ethical approval was obtained from the local ethics committee of Selcuk University for clinical trials before the study (Date: May 26, 2021, Decision no: 2021/257). The study process adhered to the Helsinki Declaration and good clinical practice guidelines.

For the study, electronic files from 2016 to 2021 were scanned and data from 460 epilepsy patients were analyzed. Patients with secondary (brain tumor, metabolic disorders, stroke, etc.) epilepsy, endocrinologic, psychiatric, and structural brain diseases were excluded from the study. In addition, patients whose tests (MRI, electroencephalography (EEG), and serum thyroid hormones) could not be performed in the last 6 months were

excluded from the study. All patients were between the ages of 18 and 65. According to the current criteria, 63 epilepsy patients were identified. Forty-four healthy volunteers of similar age and gender were also included in the study as a control group.

Age, gender, and dominant hand of the patients were recorded. Disease duration (years) of epilepsy was questioned. Disease duration was divided into 2 groups as 0-5 years and 5 years and more. The frequency of seizures in the last month and antiepileptic treatments of the patients were assessed. According to antiepileptic treatments, the patients were divided into 2 groups as monotherapy and polytherapy.

The EEG records of the patients in the last 6 months were analyzed using a digital system. Results were divided into 4 groups as normal, nonspecific, slow wave activity, and epileptic activity. Seizure types were divided into 5 groups as focal onset-aware, focal onset-impaired awareness, generalized onset-motor, generalized onset-nonmotor, and other. These groups were revised into 3 groups as focal onset, generalized onset, and others.

Coronal T2-weighted turbo spin echo (1.5 T MRI, TR: 3600, TE: 87 ms; slice thickness: 5 mm; gap: 1.5 mm) was used to determine the dimensions of the pituitary gland (Siemens; Erlangen, Germany). Morphological structure was measured and recorded digitally as in the literature.[10] Pituitary gland width, height, and intercavernous distance were obtained.

Blood was obtained after at least 8 hours of fasting. Dry tubes were used for hormonal analysis. Blood samples were analyzed with Beckman Coulter AU5800 device (Beckman Coulter Inc., Hialeah) (nephelometric method). Serum concentrations of thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), and free thyroxine (fT4) were obtained.

Statistical Analysis

Data were analyzed with Statistical Package for the Social Sciences version 18.0 (IBM Inc, Chicago, IL USA). In descriptive analyses, categorical data were presented as numbers (n) and percentage (%), and numerical data were presented as mean ± standard deviation, median (1-3 quartile), and minimum–maximum. Normality of numerical data was analyzed with Kolmogorov–Smirnov and Shapiro Wilk tests. In normally distributed numerical data, 2 independent groups were compared with independent-samples *t* test and more than 2 groups with one-way analysis of variance test. In non-normally distributed numerical data, 2 independent groups were compared with the Mann–Whitney *U* test and in more than 2 groups with the Kruskal–Wallis test. The relationship between 2 numerical variables was analyzed with Pearson's or Spearman's correlation test. The correlation relation (*r*) were as follows: 0.05-0.30 (weak), 0.30-0.40 (weak and moderate), 0.40-0.60 (moderate), 0.60-0.70 (strong), 0.70-0.75 (very strong), and 0.75-1.00 (perfect correlation). A *P* value <.05 was considered statistically significant (95% CI).

RESULTS

One hundred and seven patients, including 63 patients with epilepsy and 44 healthy volunteers, were included in the study. The gender distribution of epilepsy patients was 50.8% female and 49.2% male. The mean age of the patients was 43.11 ± 12.38 years. Gender and age distribution of the patient and control groups were similar ($P > .05$). The median duration of epilepsy was determined as 3.00 (1.00-5.00) years.

Table 1. Sociodemographic Characteristics, Disease Activity, and Antiepileptic Treatments in Patients with Epilepsy

	Number	Percentage
Gender		
Female	32	50.8
Male	31	49.2
Dominant Hand		
Right	57	90.5
Left	6	9.5
Disease year		
0-5	42	66.7
5 and more	21	33.3
Seizure activity (for the last 1 month)		
No	50	79.4
Yes	13	20.6
Electroencephalography		
Normal	40	63.5
Non-specific	6	9.5
Slow wave	2	3.2
Epileptic activity	15	23.8
Antiepileptic treatments		
No	4	6.3
Monotherapy	42	66.7
Polytherapy	17	27.0
Antiepileptic treatments		
Levetiracetam	27	64.3
Valproate	5	11.9
Carbamazepine	5	11.9
Lamotrigine	3	7.1
Other	2	4.8
Seizure type		
Focal onset, Aware	6	9.5
Focal onset, impaired awareness	7	11.1
Generalized onset, motor	27	42.9
Generalized onset, nonmotor	4	6.3
Unknown onset and unclassified	19	30.2

Sociodemographic characteristics, disease activity, and antiepileptic treatments in patients with epilepsy were presented (Table 1).

The pituitary gland width and intercavernous distance were lower in the epilepsy patient group compared to the control group ($P = .012$ and $P .006$, respectively). There was no statistical difference between pituitary gland height and thyroid function tests in the patient and control groups ($P > .05$) (Table 2).

There was no statistical difference between age, dominant hand, disease duration, morphometric measurements of the pituitary gland, and thyroid function tests in patients with epilepsy ($P > .05$). In epilepsy patients, a negative weak–moderate correlation was detected between the number of seizures in the last 1 month and the pituitary gland width ($P = .008$, $r = -0.331$).

Pituitary width, pituitary height, intercavernous distance, and thyroid function test results were similar in patients with epilepsy according to gender ($P = .189$, $P = .640$, $P = .390$, $P = .456$, $P = .209$, $P = .900$, respectively). There was no difference in pituitary width, pituitary height, intercavernous distance, and thyroid function tests according to

Table 2. The Measurements of Pituitary Gland and Thyroid Functions in the Patient and Control Groups.

	Patient Group	Control Group	*t*/*z*	*P*
Pituitary gland width (mm)	15.11 ± 2.25	15.99 ± 1.28	−2.327	.012*
Pituitary gland height (mm)	4.34 ± 0.77	4.41 ± 0.68	−0.507	.614
Intercavernous distance (mm)	17.51 ± 2.24	18.68 ± 1.90	−2.805	.006*
TSH (mU/mL)	1.93 (1.33-2.91)	1.64 (1.33-2.28)	−1.240	.215
T3 (mU/mL)	3.28 ± 0.37	3.36 ± 0.35	−0.932	.355
T4 (mU/mL)	0.90 (0.80-1.03)	0.95 (0.83-1.12)	−0.888	.375

Data are presented as mean ± standard deviation or median (1-3 quartiles).
*Statistical significant value; *Student's *t*-test.
TSH, thyroid-stimulating hormone; T3, triiodothyronine; T4, thyroxine; mm, millimeter; mU, milliunits; mL, milliliters.

seizure type ($P > .05$). According to EEG results, no statistical difference was detected in pituitary width, pituitary height, intercavernous distance, and thyroid function tests ($P > .05$).

There was no difference in pituitary gland width, pituitary gland height, intercavernous distance, and thyroid functions according to antiepileptic options in patients with epilepsy ($P = .558$, $P = .860$, $P = .082$, $P = .058$, $P = .089$, $P = .054$, respectively). In addition, a statistically significant correlation was not detected between thyroid function tests and pituitary gland width, pituitary gland height and intercavernous distance ($P > .05$).

DISCUSSION

It is known that there is a complex and causal relationship between hormonal mechanisms and epileptic seizures. Endocrinological disorders induce epileptic seizures. Seizure activity also changes hormone levels. Scientific studies have often focused on hormonal levels in the postictal period.[11,12] Many factors such as seizure type, EEG changes, and antiepileptic treatments have been associated with hormonal levels, but the causal relationship between them has not been conclusively confirmed.

In the etiopathogenesis of epilepsy, there is a synchronized hyperexcitability of a neuron group. This neuronal hyperactivity induces hypothalamic functions. In this way, epileptic seizures can cause functional changes in the hypothalamo-pituitary-gonadal/thyroid/adrenal axis. [13-15] After generalized and focal seizures (especially in generalized seizures), follicle-stimulating hormone (FSH), prolactin, cortisol, and luteinizing hormone (LH) levels increase. In the postictal period, TSH level was detected to be high in some studies and normal in others.[16-18] An experimental study reports that epileptic seizures increase the thyrotropin-releasing hormone (TRH) level in extrahypothalamic brain areas (amygdala, hippocampus, piriform cortex, and anterior cortex).[19] Another experimental study shows that seizure activities change pituitary hormone levels with monoamine mechanisms.[20] Electroconvulsive treatment increases serum prolactin, adrenocorticotropic hormone, and thyrotropin levels.[21,22] Epileptic seizures change serum prolactin, thyrotropin, growth hormone, and cortisol levels with activating the hypothalamus-pituitary axis.[16,17] In a recent study, it was reported that the serum TSH level was also significantly higher in the postictal period.[18] However, references about hypothalamus and pituitary function in interictal periods are limited. In our study, we reported that thyroid function tests in the interictal period were at the same level as the control group and were not associated with seizure type and activity.

The relationship between the hypothalamus, pituitary, and thyroid gland is complex in patients with epilepsy. Hormones can trigger seizure activity. However, it is known that hormonal changes can occur in the postictal period after epileptic seizures. Neuronal hyperexcitability activates the hypothalamus during an epileptic seizure. This is associated with increased hormone levels in the postictal period. Serum hormone levels can change associated with many factors such as psychosocial factors, antiepileptic drugs, and comorbid diseases.[13] It has been reported that some antiepileptic treatments, especially valproic acid and carbamazepine, are associated with serum thyroid hormone levels.[13,23] In the current study, the relationship between antiepileptic type and serum thyroid hormone levels was not detected. Duration of antiepileptic treatment, anthropometric features, and comorbid diseases were not investigated in the study. In addition, a small number of patients were included in the groups. Statistically insignificant results may be associated with these factors.

There is a controlled mechanism between the hypothalamus-pituitary-thyroid axis. Thyrotropin-releasing hormone is secreted by neurons in the hypothalamus. Increased TRH stimulates TSH secretion in the anterior pituitary. TSH also induces the secretion of triiodothyronine and thyroxine from the thyroid gland. Increasing hormones suppress this mechanism with negative feedback and hormonal balance occurs. This mechanism may be impaired in many chronic diseases, especially in neuroendocrine diseases.[24,25] It is known that epileptic seizures also affect this mechanism. However, hormonal changes occur especially in the postictal period. Postictal serum hormone level suggests a possible hypothalamus and pituitary system activity.[16,17] Before the study, it was thought that there might be a relationship between seizure-EEG activity and serum thyroid hormone level based on this mechanism. However, no correlation was found between seizure frequency-EEG activity and serum thyroid hormone levels. This suggested a complex relationship between thyroid hormones and seizure activity in patients with epilepsy.

In the literature review, there are few studies investigating the structural features of the hypothalamus-pituitary-thyroid axis in epilepsy patients. Structural lesions of the hypothalamus, especially hypothalamic hamartoma, are associated with the type and frequency of epileptic seizures.[26,27] This current study is the first to evaluate the morphometric measurements of the pituitary gland and its relationship with seizure activity in patients with epilepsy. It was determined that the width of the pituitary gland was lower in patients with epilepsy. There was also a negative correlation between the width of the pituitary gland and the number of seizures in the last month. These results reveal the relationship between epilepsy and the structural features of the pituitary gland.

This study has several limitations. First, this study is retrospective and single-center. Second, the number of patients in the groups is small. Third, all hormones of the hypothalamus-pituitary-thyroid axis were

not studied. Fourth, morphometric measurements of the hypothalamus and thyroid gland were not performed. Fifth, the brain volume of the patients was not detected, and its ratio to the pituitary gland was not calculated. The measurements were not grouped as normal or pathological.

In conclusion, although the thyroid hormone level in epilepsy was detected to be similar to the control group, it is clear that there is a complex relationship between them. Pituitary gland width is lower in patients with epilepsy and this is negatively correlated with the number of seizures. These results support this complex hormonal relationship.

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