Original Article / *Özgün Araştırma*

DOI: 10.4274/haseki.galenos.2019.4922
Med Bull Haseki 2019;57:195-200

Effect of Antiepileptic Drug Treatment on Thyroid Hormone Levels in Epilepsy Patients

Epilepsi Hastalarında Antiepileptik İlaç Tedavisinin Tiroid Hormon Düzeylerine Etkisi

Aytül Mutlu

İstanbul Haseki Training and Research Hospital, Clinic of Neurology, İstanbul, Turkey

Abstract

Aim: Antiepileptic drugs (AEDs) can have an effect on hormone metabolism and function, and alter serum levels of some hormones. This study aimed to determine the effects of AEDs on thyroid function test results in epilepsy patients.

Methods: The study included 82 epilepsy patients aged 18-45 years. Serum free thyroxin (fT4), free triiodothyronine (fT3), and thyroid-stimulating hormone (TSH) levels were measured in all the participants. Thyroid hormone levels in subgroups were investigated. In addition, Serum AED and thyroid hormone levels and duration of AED use and thyroid hormone levels were analyzed.

Results: Although there were differences in thyroid hormone levels among patient subgroups, the differences did not reach statistical significance. There was no significant correlation between the duration of AED use and thyroid function parameters in the monotherapy subgroup. The only correlation observed between serum AED levels and thyroid function test results was that decreased serum fT4 level was associated with decreased carbamazepine level in blood.

Conclusion: In this study, we found a significant decrease in fT4 level with only increased serum carbamazepine level. Different results in our study and similar studies in the literature showed that there could be many different physiological and environmental factors affecting thyroid hormone levels.

Keywords: Antiepileptic drugs, epilepsy, thyroid hormones

Öz

Amaç: Antiepileptik ilaçlar (AEİ) hormon metabolizması ve fonksiyonu üzerinde etkili olabilir ve kan seviyelerini değiştirebilirler. Bu çalışmada, epilepsi hastalarında AEİ'nin tiroid hormon düzeyleri üzerine etkisinin araştırılması planlandı.

Yöntemler: Çalışmamıza yaşları 18-45 arasında olan 83 hasta alındı. Tüm hastalarda serumda Serbest Tiroksin (fT4), Serbest Triiodotironin (FT3) ve tiroid stimüle edici hormon (TSH) düzeyleri ölçüldü. Altgruplar arasında tiroid hormon düzeyleri karşılaştırıldı. Ayrıca, AEİ kan düzeyleri ile tiroid hormon düzeyleri ve AEİ kullanım süreleri ile tiroid hormon düzeyleri arasında bağlantı olup olmadığı incelendi.

Bulgular: Hasta alt grupları arasında tiroid hormon düzeyleri arasında farklılıklar olsa da istatiksel olarak anlamlı sonuç bulunmadı. AEİ kullanımı süresi ile tiroid hormon düzeyleri arasında da istatiksel olarak anlamlı ilişki saptanmadı. Sadece, AEİ kan düzeyleri ile tiroid fonksiyon testleri arasında sadece karbamazapin (CBZ) kan düzeyinin artışı ile fT4 düzeyinin azalmasının istatiksel olarak anlamlı olduğu saptandı.

Sonuç: Bu çalışmada sadece CBZ serum düzeylerinin artmasına bağlı fT4 hormon düzeylerinin anlamlı derecede azaldığını saptadık. Çalışmamızda ve literatürdeki benzer çalışmalarda farklı sonuçların bulunması, tiroid hormon düzeylerini etkileyen bir çok farklı fizyolojik ve çevresel faktörlerin olabileceğini göstermiştir.

Anahtar Sözcükler: Antiepileptik ilaçlar, epilepsi, tiroid hormonları

Address for Correspondence/Yazışma Adresi: Aytül Mutlu
İstanbul Haseki Training and Research Hospital, Clinic of Neurology, İstanbul, Turkey
E-mail: meltemim98@yahoo.com ORCID ID: orcid.org/0000-0002-1710-0783
Received/Geliş Tarihi: 06 December 2018 **Accepted/Kabul Tarihi:** 04 March 2019

Introduction

Epilepsy is a common neurological disease characterized by episodic cerebral dysfunction associated with abnormal electrical discharge of neurons in the brain occurring due to various reasons (1,2). Epilepsy requires long-term treatment with antiepileptic drugs (AEDs). Long-term AED treatment can cause metabolic disorders, organ toxicity, endocrine disorders, cognitive dysfunction, and psychiatric disorders. Epileptic seizures and AEDs both can disrupt endocrine and reproductive systems. It has been reported in previous studies that especially epileptic discharges from the temporal lobe and AEDs may cause changes in hormone levels by affecting the hypothalamo-pituitary axis through nerve pathways and may affect the endocrine system (3,4).

Thyroid hormone levels may vary depending on life cycle like menopause and age, and environmental factors. Thyroid hormones play an important role in maintaining lipid and carbohydrate metabolism, cell growth and development. Hypothyroidism, even the subclinical form, is associated with an increase in the risk of coronary heart disease. The prevalence of AED-induced thyroid dysfunction and its long-term consequences remain uncertain, primarily because thyroid function tests are not routinely performed in clinical practice. AEDs can affect hormone levels by altering their metabolism and function; as such, AEDs can also affect thyroid function (5), as first reported by Strandjord et al. (6) in 1981. Subsequently, many other studies highlighting the importance of routine thyroid function testing in patients with epilepsy have reported that long-term AED therapy could alter thyroid hormone balance and lead to hypothyroidism. Consequently, the present study aimed to determine the effects of AED treatment on thyroid function test results in epilepsy patients receiving AED monotherapy and polytherapy.

Methods

In this randomized study, we included 82 patients aged 18-45 years who were diagnosed with epilepsy according to clinical and electroencephalography findings in the epilepsy outpatient clinic of the neurology department of our hospital. All patients have been using the same AEDs for ≥6 months and had serum AED levels at within the therapeutic range. Patients on regular medication other than AEDs, serum drug levels beyond the therapeutic limit, hypoalbuminemia or hyper-albuminemia, hypoglycemia or hyperglycemia, abnormal liver enzyme function test results, and patients with a chronic disease other than epilepsy were excluded from the study.

Blood samples were collected after a 48-72 hours seizure-free period. The patients were subgrouped according to AED regimen, as follows: monotherapy: n=44 and polytherapy: n=38. Free thyroxin (fT4), free triiodothyronine (fT3), and thyroid-stimulating hormone (TSH) levels were measured and compared between the monotherapy and polytherapy patient subgroups. In addition, AED blood and thyroid hormone levels and duration of AED use were investigated. The study protocol was approved by our hospital ethics committee, on 20/08/2014 with the decision no:138 and all the participants provided written informed consent. Assessment of thyroid function

An fT4 level of 0.61-1.12 ng dL^{-1}, an fT3 level of 2.5-3.9 pg mL^{-1}, and a TSH level of 0.38-5.33 mIU L^{-1} were considered normal.

Statistical Analyses

SPSS for Windows v.15.0 was used for statistical analysis. Categorical variables are shown as number and percentage, and numerical variables are shown as mean ± standard deviation and range. Student's t-test was used to compare normally distributed numerical data between two independent groups, and the Mann-Whitney U test was used otherwise. Normally distributed numerical variables were independently tested via One-Way ANOVA for multiple group comparisons, and via the Kruskal-Wallis test if the variables were not normally distributed. Patient subgroup analysis was performed using Tukey's test and the Mann-Whitney U test with Bonferroni correction. Correlations between numerical variables were analyzed via Spearman's correlation coefficient, due to the absence of parametric test conditions. The associations/relationships between the categorical variables were determined using the chi-square test. The level of statistical significance was set at $p<0.05$.

Results

The patient group included 44 monotherapy patients (29 female and 15 male) with a mean age of 25.3±6.5 years and 38 polytherapy patients (26 male and 12 female) with a mean age of 30.7±7.9 years. The mean age in the monotherapy patient subgroup was significantly lower than in the polytherapy subgroup ($p=0.002$). The male-to-female ratio in the polytherapy subgroup was higher than in monotherapy subgroups. There was no significant difference in the type of seizure, age at the first seizure and mean duration of illness between the monotherapy and polytherapy subgroups ($p=0.152$ and $p=0.214$, respectively). 34.1% of patients in the monotherapy subgroup received valproic acid (VPA), 27.3% carbamazepine (CBZ), 18.2% lamotrigine (LTG), and 20.5% received levetiracetam (LEV). 28.9% of patients in the polytherapy subgroup were treated with CBZ+LEV, 13.2% with CBZ+VPA, 28.9% with LEV+VPA,

10.5% with LTG+CBZ, 10.5% with LTG+LEV, and 7.9% with LTG+VPA. 22.7% of patients in the monotherapy subgroup used the same medication for ≤1 year, 56.8% for 1-5 years, and 20.5% for >5 years (Table 1). The duration of drug use in patients of the polytherapy subgroup was not evaluated because of the different duration of use for each drug.

The thyroid hormones levels were higher in patients of the monotherapy subgroup receiving VPA than in other subgroups. In addition, thyroid hormones levels were lower in polytherapy subgroup than in monotherapy subgroups. The difference was not statistically significant (Table 2).

There was not a significant correlation between the duration of AED use and the level of thyroid function parameters in the monotherapy subgroup (Table 3).

Analysis of the correlation between AED blood levels and thyroid hormone levels showed a significant negative correlation between the CBZ blood level and fT4 level (p=0.016) (Table 4). There was no statistical significance between AED blood levels and thyroid hormone levels in patients using polytherapy (Table 5).

Table 1. General characteristics of patients

		Monotherapy subgroup		Polytherapy subgroup		
		Mean ± SD		Mean ± SD		p
Age (years)		25.3±6.5* (18-38)		30.7±7.9 (19-44)		0.002
Age at first seizure (years)		14.9±8.9 (0-34)		17.9±10.2 (0-36)		0.152
Duration of disease (years)		10.4±7.6 (1-33)		12.7±8.3 (1-37)		0.214
Duration of AED use (months)		487.5±545.8 (6-2304)		-		-
		n	%	n	%	p
Gender	Male	15	34.1	26	68.4	0.055
	Female	29	65.9	12	31.6	-
Seizure type	Generalized onset	38	86.4	30	78.9	-
	Focal onset	5	11.4	3	7.9	-
	Focal onset + secondary generalized	0	0.0	4	10.5	-
	Unknown onset	1	2.3	1	2.6	-
AEDs	CBZ	12	27.3	-	-	-
	LTG	8	18.2	-	-	-
	LEV	9	20.5	-	-	-
	VPA	15	34.1	-	-	-
	CBZ+LEV	-	-	11	28.9	-
	CBZ+VPA	-	-	5	13.2	-
	LEV+VPA	-	-	11	28.9	-
	LTG+CBZ	-	-	4	10.5	-
	LTG+LEV	-	-	4	10.5	-
	LTG+VPA	-	-	3	7.9	-
Duration of medication use	0-1 year	10	22.7	-	-	-
	1-5 years	25	56.8	-	-	-
	>5 years	9	20.5	-	-	-

AED: Antiepileptic drugs, CBZ: Karbamazapin, LTG: Lamotrigine, LEV: Levetiracetam, VPA: Valproic acid, SD: Standard deviation
*Bonferroni corrected alpha level of significance is p<0.0033

Table 2. Hormone levels according to group.

	CBZ monotherapy	LTG monotherapy	LEV monotherapy	VPA monotherapy	Polytherapy subgroup
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
fT3	3.15±0.37	3.11±0.39	3.23±0.26	3.39±0.38	3.09±0.29
fT4	0.78±0.14	0.81±0.16	0.79±0.08	0.84±0.14	0.74±0.14
TSH	2.22±1.22	2.19±1.68	1.80±0.52	2.39±1.47	2.00±1.00

fT4: Free thyroxin, fT3: Free triiodothyronine, TSH: Thyroid-stimulating hormone, SD: Standard deviation, LTG: Lamotrigine, LEV: Levetiracetam, VPA: Valproic acid

Table 3. Hormone levels according to duration of AED use in the monotherapy subgroup

		Duration of AED Use			
		≤1 year	1-5 years	≥5 years	
		Mean ± SD	Mean ± SD	Mean ± SD	p
Monotheraphy	fT3	3.28±0.37	3.22±0.36	3.25±0.38	0.996
	fT4	0.84±0.14	0.79±0.14	0.81±0.12	0.632
	TSH	1.92±0.82	2.29±1.26	2.21±1.78	0.595

fT4: Free thyroxin, fT3: Free triiodothyronine, TSH: Thyroid-stimulating hormone, AED: Antiepileptic drugs, SD: Standard deviation

Table 4. The correlation between antiepileptic drug (monotherapy) blood levels and thyroid hormone levels.

	AED blood level			
	CBZ		VPA	
	rho	P	rho	P
fT3	-0.184	0.315	0.121	0.501
fT4	-0.423	0.016	0.282	0.112
TSH	0.010	0.956	-0.290	0.101

fT4: Free thyroxin, fT3: Free triiodothyronine, TSH: Thyroid-stimulating hormone, AED: Antiepileptic drugs, CBZ: Karbamazapin, VPA: Valproic acid

Table 5. The correlation between antiepileptic drugs (polytherapy) blood levels and thyroid hormone levels

		fT3*	fT4	
		P	P	
CBZ	LTG	0.728	0.994	0.671
	LEV	0.302	1.000	0.570
	VPA	0.025	0.828	0.678
	Polytherapy	0.856	0.957	0.691
LTG	LEV	0.268	0.999	0.923
	VPA	0.042	0.996	0.498
	Polytherapy	0.954	0.752	0.839
LEV	VPA	0.144	0.936	0.355
	Polytherapy	0.223	0.927	0.829
VPA	Polytherapy	0.007	0.142	0.459

CBZ: Karbamazapin, LTG: Lamotrigine, LEV: Levetiracetam, VPA: Valproic acid
*Bonferroni corrected alpha level of significance is p<0.0033.

Discussion

There is a very complex relationship between the endocrine system, and epilepsy and use of AEDs. Seizure activity can affect hormonal balance, and hormone levels and the balance can affect seizure activity (7-9). Several mechanisms related to AED-induced thyroid dysfunction, including competitive binding of thyroid hormones to thyroxine-binding globulin, increased peripheral conversion of T4 to active T3, and alterations in the hypothalamic-pituitary axis have been postulated (3,7). AEDs have a negative effect on the hepatic P-450 enzyme system, which might be due to accelerated clearance of thyroid hormones (10). It is thought that changes in thyroid hormone levels observed in epilepsy patients might primarily be due to AEDs (11,12). Many studies have reported the toxic effects of AEDs on thyroid function, and many retrospective studies reported that epilepsy patients remained clinically euthyroid despite changes in thyroid function (12-15). In the present study, although the thyroid hormone levels in the monotherapy subgroup patients receiving VPA were moderately higher and the thyroid hormone levels in the polytherapy subgroup was moderately lower, we did not find a statistically significant difference. There was no significant correlation between the duration of AED use and the thyroid function parameters in the monotherapy and polytherapy subgroups. The only correlation observed between AED blood levels and thyroid hormone levels was a significant negative correlation between the CBZ blood level and fT4 level (p=0.016). In the literature, findings regarding the effect of VPA on thyroid function are inconsistent; some studies reported an association between VPA and increased thyroid hormone levels, whereas others reported lowered levels or no effect at all (15-18). The effect of VPA on serum thyroid hormone levels could not be fully explained. Studies on the effect of VPA on the thyroid hormones showed different results, an association between VPA and decreased and increased hormones levels has been reported by different studies (15-18). It has been reported that VPA may affect thyroid hormone levels due to its enzymatic inhibitory effect rather than the induction of microsomal enzymes in the liver (16). It is emphasized that this may be due to the GABA ergic feature of VPA because it can increase the level of TSH. GABA is an inhibitor of somatostatin release, and somatostatin inhibits TSH secretion. VPA is also highly bound to plasma proteins, causing T4 to detach from its location (15). Apak et al. (15) observed that the T4 level was significantly decreased in patients receiving VPA. However, no change was detected in fT4, T3, fT3 and TSH levels. They reported that T4 and fT4 levels were significantly decreased in patients treated with phenytoin, with no change in T3, fT3 and TSH levels. There were no significant changes in T3, fT3 and TSH levels in the group of patients receiving CBZ, however, a significant decrease was found in T4 and fT4 levels. The highest decrease in T4 levels was observed in

patients using CBZ, VPA and phenytoin, respectively. Zhang et al. (16) and Adhimoolan and Arulmozhi (17) reported that the use of VPA and phenytoin lowered the fT4 level. Eirís-Puñal et al. (18) observed that the mean T4 and fT4 levels in epilepsy patients treated with CBZ and VPA were lower than in healthy controls. Moreover, it has been reported that 26% of 51 patients treated with VPA developed subclinical hypothyroidism (18). Bayar et al. (19) reported that the mean fT4 and T3 levels were significantly lower in patients using CBZ compared to that in controls, while the mean levels of fT3 and T4 were significantly higher in patients using VPA than in controls.

In the above studies, different results were found in the fT3 and fT4 levels in patients receiving VPA and CBZ monotherapy. Similar to our study, most studies reported normal TSH but altered fT4 levels associated with AEDs (20). Many other studies reported that CBZ therapy could affect thyroid hormone balance in epilepsy patients, in particular, by decreasing the fT4 level but not altering the fT3 or TSH levels (13,18,21,22). The effect of CBZ on thyroid hormones may be related to that CBZ blocks TRH-mediated stimulation of TSH release. CBZ reduces the fT4 and fT3 levels by increasing the hormone binding protein level as well as by its enzyme inducing effect. One of the reasons for no alteration in TSH levels may be that normal T3 level prevented an increase in TSH (19). In the present study, thyroid hormone levels did not differ in the monotherapy subgroup treated with CBZ; however, a significant negative correlation was observed between CBZ blood level and fT4 level. Additionally, in a small number of patients in the monotherapy subgroup receiving LEV and LTG, there was no change in thyroid hormone levels. Adhimoolam and Arulmozhi (17) observed that LEV did not affect fT4, fT3 and TSH levels in epilepsy patients. Shih et al. (23) reported lowered fT4 levels in epilepsy patients receiving LEV. Furthermore, they observed that female gender, advanced age and long-term AED polytherapy were the risk factors for the development of low thyroid hormone levels. They also reported that CBZ was responsible for decreased fT4 levels (23). Thyroid hormone levels in the present study was lower in the polytherapy subgroup, however, the difference was not statistically significant. The literature includes only a few studies on the effect of AED polytherapy on thyroid function. Chakova et al. (24) reported that AEDs altered thyroid function, especially in patients treated with polytherapy. Shih et al. (23) noted that the fT4 level was significantly lower in patients treated with AED polytherapy. Unlike many other studies, our study found no significant change in thyroid hormone levels in monotherapy and polytherapy subgroups. Different results in other studies may be attributed to the fact that thyroid hormone levels may vary depending on many factors (25). Yılmaz et al. (26) studied thyroid function in 223 epilepsy patients before and at the 1st, 6th, and 12th months of AED therapy. They reported decreased fT4 levels in patients receiving VPA at the 1st, 6th, and 12th months of treatment. Patients who received CBZ had a lower fT4 level at the 1st and 6th months of treatment, and a higher TSH level at the 6th and 12th months, and oxcarbazepine-treated patients had a lower fT4 level at the 1st month of treatment. In addition, patients treated with LEV had no change in fT4 and TSH levels. The researchers also reported that the frequency of subclinical hypothyroidism at the 12th month of treatment was 28% in valproate- and 21.4% in oxcarbazepine-treated patients whereas LEV was not associated with subclinical hypothyroidism. In the present study, there was no correlation between duration of AED use for ≤1 year, 1-5 years, and >5 years and change in thyroid hormone levels. Aparicio-Claure et al. (27) and Hamed (28) highlighted the importance of considering findings, such as decreased motivation, weakness, fatigue, and constipation, in patients using AEDs as initial clinical indicators of hypothyroidism. Jensovsky et al. (29) studied pediatric epilepsy patients and suggested that minor alterations in thyroid hormone function can lead to subclinical hypothyroidism-defined as normal thyroid hormone levels and a clinically euthyroid state. They also reported that such patients exhibit somatic symptoms, depression, slow thinking, poor memory, cognitive impairment, including a reduction in processing speed and poor memory, and subtle neuromuscular abnormalities. In the present study, there were no obvious clinical signs of thyroid dysfunction in the epilepsy patients. However, subclinical findings of thyroid dysfunction were not investigated in detail and thyroid ultrasonography was not performed.

Conclusion

There were nonsignificant changes in thyroid hormone levels in patients receiving antiepileptic treatment in monotherapy subgroup and polytherapy subgroup, however it was observed that increased serum CBZ levels were significantly associated with decreased fT4 levels. Based on the findings presented here, different results related to thyroid hormone changes in other studies performed in patients using AED suggest that there may be many different factors affecting thyroid hormone levels. Although the use of AEDs did not have a significant effect on thyroid functions, it was found that close monitoring of thyroid hormone levels was important in patients receiving epilepsy treatment, especially in high doses.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Özalp İ, Tunçbilek E, Tuncer M. Convulsions, Addiction Pediatrics Journal Hacettepe University Faculty of Medicine Department of Child Health and Diseases Department of Child Health 1994;15:529-551.
2. Oğul E. Basic and Clinical Neurology Oğul E (ed) Uludağ University Printing House Bursa 1996;171-188.
3. Dana-Heari J, Oxley J, Richens. A. Pituitary responsiveness to gonadotrophin-releasing and thyrotrophin-releasing hormones in epileptic patients receiving carbamazepine or phenytoin. Clin Endocrinol 1984;20:163-68.
4. Leśkiewicz M, Budziszewska B, Lasoń W. Endocrine effects of antiepileptic drugs. Przegl Lek 2008;65:795-8.
5. Kırımi E, Karasalihoğlu S, Boz A. Thyroid functions in children under long-term administration of antiepileptic drugs. Eastern Journal of Medicine 1999;4:23-6.
6. Strandjord RE, Aanderud S, Myking OL, Johannessen SI. Influence of carbamazepine on serum thyroxine and triiodothyronine in patients with epilepsy. Acta Neurol Scand 1981;63:111-21.
7. Timiras PS, Hill HF. Antiepileptic drugs hormone and epilepsy. Antiepileptic drugs: Mechanisms of Action 1980;655-66.
8. Mattson BH, Cramer JA. Epilepsy, sex hormones, and antiepileptic drugs. Epilepsia 1985;26:40-51.
9. Isojärvi JI, Pakarinen AJ, Myllylä VV. Effects of carbamazepine therapy on serum sex hormone levels in male patients with epilepsy. Epilepsia 1988;29:781-6.
10. Shih FY, Chuang MJ, Lu YT, Tsai WC, Fu TY, Tsai MH. Effects of antiepileptic drugs on thyroid hormone function in epilepsy patients. Seizure 2017;48:7-10.
11. Isojärvi JI, Pakarinen AJ, Myllylä VV. Thyroid function in epileptic patients treated with carbamazepine. Arch Neurol 1989;46:1175-8.
12. Isojärvi JI, Pakarinen AJ, Myllylä VV. Thyroid function with antiepileptic drugs. Epilepsia 1991;33:142-8.
13. Isojärvi JI, Turkka J, Pakarinen AJ, Kotila M, Rättyä J, Myllylä VV. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. Epilepsia 2001;42:930-4.
14. Strandjord RE, Aanderud S, Myking OL, Johannessen SI. Influence of carbamazepine on serum thyroxine and triiodothyronine in patients with epilepsy. Acta Neurol Scand 1981;63:111-21.
15. Apak İ, Tamam Y, Sevim M, Tamam B. Antiepileptik İlaçların Tiroid Hormon Düzeylerine Etkisi. Dicle Tıp Dergisi, 2006;33:145-52.
16. Zhang YX, Shen CH, Lai QL, et al. Effects of antiepileptic drug on thyroid hormones in patients with epilepsy: A meta-analysis, Seizure 2016;35:72-9.
17. Adhimoolam M, Arulmozhi R. Effect of antiepileptic drug therapy on thyroid hormones among adult epileptic patients: An analytical cross-sectional study. J Res Pharm Pract 2016;5:171-4.
18. Eirís-Puñal J, Del Río-Garma M, Del Río-Garma MC, Lojo-Rocamonde S, Novo-Rodríguez I, Castro-Gago M. Long-term treatment of children with epilepsy with valproate or carbamazepine may cause subclinical hypothyroidism. Epilepsia 1999;40:1761-6.
19. Bayar BD, Ataklı D, Ülker M, Yüksel B, Soysal A, Arpacı B. The effect of carbamazepine and valproic acid treatment on thyroid hormone function in epilepsy patients. Epilepsi 2008;14:181-5.
20. Svalheim S, Sveberg L, Mochol M, Taubøll E. Interactions between antiepileptic drugs and hormones. Seizure 2015;28:12-7.
21. Cansu A, Serdaroğlu A, Camurdan O, Hirfanoğlu T, Bideci A, Gücüyener K. The evaluation of thyroid functions, thyroid antibodies, and thyroid volumes in children with epilepsy during short-term administration of oxcarbazepine and valproate. Epilepsia 2006;47:1855-9.
22. Vainionpää LK, Mikkonen K, Rättyä J, Knip M, Pakarinen AJ, Myllylä VV, Isojärvi JI. Thyroid function in girls with epilepsy with carbamazepine, oxcarbazepine, or valproate monotherapy and after withdrawal of medication. Epilepsia 2004;45:197-203.
23. Shih FY, Chuang YC, Chuang MJ, Lu YT, Tsai WC, Fu TY, Tsai MH. Effects of antiepileptic drugs on thyroid hormone function in epilepsy patients. Seizure 2017;48:7-10.
24. Chakova L, Karakhanian E, Dimitrov H, Lutakova E. Effect of antiepileptic drugs on the thyroid gland in children with epilepsy (preliminary report). Folia Med (Plovdiv) 1998;40:80-3.
25. Wang P, Gao YJ, Cheng J, Kong GL, Wang Y, Wu XY, Zhao ZG, Yuan HJ. Serum thyroid hormone reference intervals in the apparently healthy individuals of Zhengzhou area of China. Genet Mol Res. 2014;13:7275-81.
26. Yılmaz U, Yılmaz TS, Akıncı G, Korkmaz HA, Tekgül H. The effect of antiepileptic drugs on thyroid function in children. Seizure 2014;23:29-35.
27. Aparicio-Claure AL, Rayo-Mares JD, Nishimura-Meguro E, Herrera-Márquez JR, Muñoz-Montúfar JP, Núñez-Enríquez JC. Prevalence of subclinical hypothyroidism in pediatric patients with drug-resistant epilepsy. Rev Med Inst Mex Seguro Soc 2017;55:579-86.
28. Hamed SA. The effect of antiepileptic drugs on thyroid hormonal function: causes and implications. Expert Rev Clin Pharmacol 2015;8:741-50.
29. Jensovsky J, Ruzicka E, Spackova N, Hejdukova B. Changes of event related potential and cognitive processes in patients with subclinical hypothyroidism after thyroxine treatment. Endocr Regul 2002;36:115-22.