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Thyroid Gland Volume in Adults with Epilepsy: Relationship to Thyroid hormonal function

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Abstract

Several studies were done investigating thyroid function in patients with epilepsy. However the results of different studies were conflicting or controversial. This study aimed to evaluate thyroid hormonal changes and their relationship to thyroid volume in epileptic adults on long-term treatment with antiepileptic drugs (AEDs). This study included 135 adults with idiopathic epilepsy with mean age of 32.32±4.34years, duration of illness of 10.52±5.08 years and on treatment with carbamazepine (CBZ), valproate (VPA) or CBZ+VPA for a mean duration of 8.66±3.32years. The serum levels of free thyroxine (fT4), triiodothyronine (fT3), and thyroid-stimulating hormone (TSH) were assessed. Thyroid volume was measured using ultrasonography. Compared to control subjects, patients had significant lower fT4 (p<0.01) and fT3 (p<0.01) and higher levels of TSH (p<0.0001). The majority of patients with reduced fT4 also had reduced fT3 and increased TSH levels. Nearly 26% of the patients had enlargement of the thyroid gland (p<0.001). Patients on polytherapy had more thyroid volume compared to patients on monotherapy (p<0.05) and patients on VPA had more thyroid volume compared to patients on CBZ (p<0.03). All patients were clinically euthyroid. Significant correlations were identified between fT4 concentrations and duration of illness, dose, serum level and duration of AEDs treatment, fT3 and TSH concentrations and between thyroid volume and fT4, fT3 and TSH concentrations. In conclusion, CBZ and VPA as mono- or polytherapies may cause thyroid hormonal and structural abnormalities. Thyroid enlargement is due to associated subclinical hypothyroidsm. This data have implications suggesting prevention strategies.

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Key words: Epilepsy; antiepileptic drugs; subclinical hypothyroidism, thyroid volume

Abbreviations: AEDs, Antiepileptic drugs; CBZ, carbamazepine; VPA, valproate; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid stimulating hormone; SCH, subclinical hypothyroidism

Introduction

Epilepsy is a common chronic medical problem and often requires long-term therapy, which may even continue throughout life (1). Disturbances in endocrine hormones have been reported in patients with epilepsy and with some antiepileptic drugs (AEDs), among are thyroid hormones. The majority of the studies suggested that the changes of thyroid hormones in epileptics were due to the effect of some AEDs and not the due to the disease itself (2,3). Earlier studies frequently reported abnormal thyroid hormonal levels with enzyme inducing AEDs [carbamazepine (CBZ), phenytoin (PHT) and phenobarbital (PB)]. These abnormalities included reduced serum concentrations of total thyroxine (T4), free T4 (fT4), tri-iodothyronine (T3), free T3 (fT3), free T4-index (fT4I), free T3-index (fT3I), thyroxine binding globulin (TBG) and increased concentrations of thyroid stimulating hormone (TSH) (2-6). Also earlier studies reported normal thyroid hormonal levels with non-enzyme inducing AED (valproate or VPA) which included normal concentrations of T4 (7-9), T3, T3 uptake (T3U) and thyrotropin (TSH) and thyrotropin releasing hormone (TRH) stimulation (4,7,10-16). Further studies reported that non-enzyme inducing AED (valproate or VPA) is also associated with thyroid hormonal dysfunction (17-25). None of these studies reported overt manifestations of thyroid abnormalities. Reduction in fT4 and increase in TSH levels were reported as early as one to three months after starting treatment with CBZ, PB or VPA (20, 25). Also, previous studies demonstrated that the changes induced by these drugs are transient (4,16). Studies reported increase in serum concentrations of fT4, fT3 and reduction of TSH and restoration of euthyroid state several months following AED withdrawal even after years of treatment (26,27) or with L-thyroxine substitutive supplement (28).

Few studies were done to assess thyroid volume in patients with epilepsy and on AEDs. Some studies reported ultrsongraphic evidence of thyroid enlargement (goiter). Also, these studies reported significant correlation between thyroid volume and thyroid hormonal abnormalities (5,29).

Induction of metabolism of thyroid hormones by the hepatic microsomal enzyme system has been suggested as the main mechanism for decreased serum T4, fT4, T3 and fT3 concentrations with enzyme inducing AEDs. The reduction in thyroid hormone concentrations in the periphery is associated with compensatory increase in the serum TSH enhancement. Some suggested that interference with hypothalamic regulation of thyroid function by AEDs seems a possible mechanism for thyroid hormonal abnormalities with AEDs (30). The development of high levels of TSH more than 5mIU/mL is known as subclinical hypothyroidism (SCH). However, the mechanism of thyroid hormonal with non-enzyme inducing VPA is unclear. The increase in the concen-

tration of T3 reported by some authors with AEDs (13) could be explained as a mechanism of the body to counteract the impact of diminishing production of T4 through a preferential thyroidal secretion of T3 and enhanced conversion of T4 into T3 particularly in the early stage of development of hypothyroidism. Some suggested that increased T3 may result from augmented T4 to T3 conversion rate due to accelerated T4 metabolic clearance (31).

Aim of work

Although thyroid function has been frequently investigated in patients with epilepsy, however conflicting data exist for the influence and mechanisms of AEDs on thyroid function. In addition, data regarding the predictors for thyroid enlargement (goiter) with epilepsy are still unknown. This study aimed to investigate the functional and volume changes of the thyroid gland in adults with epilepsy and on long-term AEDs.

Materials and Methods

Subjects

This is a cross-sectional study. It included 135 adult patients with idiopathic epilepsy (male = 88, females = 47) with age ranged between 20 to 50 years (mean: 32.32 ± 4.34), duration of illness of 5 to 20 years (mean: 10.52 ± 5.08) and on chronic treatment with CBZ (n = 65), VPA (n = 30) or CBZ+VPA (n = 40) for a duration ranged between 6 to 15 years (mean: 8.66 ± 3.32). **Table (1)** showed the demographic, clinical and laboratory features of the studied patients. Epilepsy type was classified according to the recommendations of the International League Against Epilepsy (32). Patients were recruited from the out-patient epilepsy clinic of Assiut and Al-Azhar University Hospitals, Assiut, Egypt. Sixty normal healthy subjects matched for age, sex and socioeconomic status were chosen as control subjects for statistical comparisons. Control subjects were recruited from the general population. The protocol of the study was reviewed and approved by the ethical committee of Assiut and Al-Azhar University Hospitals and all subjects in this study gave their informed consent before participation.

All participants were subjected to full medical, endocrinological and neurological histories and examinations. Biological variables collected included: age, gender and body mass index (BMI). Seizures were analyzed determining seizure type, duration of illness, duration of treatment with AEDs and the degree of response to AEDs. Patients were considered controlled on AEDs when seizure free for ≥ 1 year. Patients with diseases other than epilepsy, iodine deficiency conditions, family history of thyroid disease, history of thyroid surgery, manifestations of a pituitary mass or of hypopituitarism (which suggest the presence of central hypothyroidism) or taking regular medication(s) beside AEDs, were excluded.

Specimen collection and analysis

After an overnight fast and patients were seizure free for at least 72 hours [as any postictal central hormonal dysfunction is recognized to reverse within hours], blood samples were drawn at (8.00-10.00 a.m.) for routine testing as complete blood count (CBC), fasting blood glucose (FBG), and serum levels of creatinine, aspartat amino transferase (AST), alanine amino transferase (ALT) and gamma glutamyl transferase (GGT). The rest of serum sample was kept frozen at -70°C in aliquots for the assay of serum levels of AEDs, fT3, fT4 and TSH. Hormonal concentrations and serum drug levels were measured as part of the investigation in batched assays. For all patient and control subjects, the serum concentrations of fT4, fT3 and TSH were measured by immunoenzymetric assay kits (IMMULITE reproductive hormone assays by kits obtained from DPC

or Diagnostic Products Corporation, Los Angeles, USA as described by the manufacturer (33-35). The serum level of AED(s) were determined in the therapeutic drug monitoring (TDM) lab, Assiut University Hospital, Assiut Egypt, by fluorescence polarization immunoassay system of Abbott (EPIA) using TDxFLX apparatus (Abbott Lab, Wiesbaden, Germany) (17).

Ultrasonography (US) of the thyroid

Ultrasonography was done by the same radiologist using a real time ultrasound equipment capable of B-mode imaging, pulsed wave duplex scanning, color Doppler flow imaging and power Doppler imaging (GE, LOGIQ 3 Color Doppler Machine, Korea). A 7.5-MHz linear transducer B-mode was used for measurement. The volume of each lobe was calculated using the formula for a prolate ellipse: (Volume = 0.5 [length (L) x anterior-posterior depth (D) x transverse width (W)]. Longitudinal and transverse images of the right and left thyroid lobes were obtained to show their maximal linear dimensions. All measurements were performed with electronic calipers on the frozen B-scan image (36).

Statistical analysis

Data were expressed as means ± SD. Calculations were done with the statistical package SPSS for windows, version 12.0 (SPSS Inc., Chicago, IL, USA). Student's *t*-test was used to compare between means. Pearson's correlation coefficient was used to look for association between different metabolic variables. For all tests, values of P<0.05 (two-tailed) were considered statistically significant.

Table 1. Demographic and clinical features of the studied patients

Age; years	20 - 50 (32.32 ± 4.34)
Gender (Male/Female)	88/47
Body mass index (BMI); kg/m^2	16 - 40 (25.89 ± 2.69)
Duration of illness; years	5 - 20 (10.52 ± 5.08)
Type of epilepsy:	
Generalized tonic-clonic epilepsy	58 (42.96%)
Complex partial/Partial epilepsy with secondary generalization	77 (57.04%)
Antiepileptic drugs (AEDs) utilized:	
Carbamazepine (CBZ)	65 (48.15%)
Valproate (VPA)	30 (22.22%)
CBZ+VPA	40 (29.63%)
Dose of AED; mg/day	
CBZ	400 - 1200 (650.55 ± 289.83)
VPA	1000 – 2250 (1250.00 ± 250.00)
Duration of treatment; years	6 - 15 (8.66 ± 3.32)
Serum drug level; µg/ml	
CBZ	4.5 - 11.0 (8.02 ± 3.05)
VPA	70.04 - 105.50 (90.55 ± 25.50)
Degree of control on AED(s)	
Controlled (seizure free for ≥ 1 year)	85 (62.96%)
Uncontrolled	50 (37.04%)

Values are expressed as mean ± SD and number (%).

Results

Patients had normal ALT and AST and GGT. Compared to control subjects, patients had significant lower serum levels of fT4 (p<0.01) and fT3 (p<0.01) and higher levels of TSH (p<0.0001). Marked abnormalities were observed in patients on polytherapy (CBZ+VPA) compared to patients on monotherapy

(CBZ or VPA). The majority of patients with reduced serum levels of fT4 had also reduced levels of fT3 and increased levels of TSH. Nearly 26% of the patients had increase in the thyroid gland volume (p<0.001) (versus 6.7% for control subjects). Patients on polytherapy had more thyroid gland volume compared to patients on monotherapy (p<0.05) and patients on VPA had more thyroid gland volume compared to patients on CBZ (p<0.03) **(table 2)**. All patients were clinically euthyroid. Compared to patients without SCH (n = 59), patients with SCH (n = 76) were older, had longer duration of illness, higher doses of AEDs, higher serum levels of AEDs and longer duration of treatment on AEDs **(table 3)**. No significant differences were identified in the serum levels of fT4, fT3, TSH or thyroid volume between patients who were controlled or those who were uncontrolled on AEDs. Correlations between demo-

Table 2. Thyroid hormonal and volume results of the studied groups

Variable	Patients (n = 135)	Patients on CBZ (n = 65)	Patients on VPA (n = 30)	Patients on CBZ+VPA (n = 40)	Controls (n = 60)
fT4; ng/ml	76 (56.30%) 1.06-4.63 1.98±±0.38	31 (47.69%) 1.26-3.37 1.44±±0.50	18 (60%) 1.06-4.63 1.84±±0.30	26 (65%) 0.26-2.86 0.96±±0.30	5 (8.33%) 1.75-3.85 2.39±±0.45
P1 P2 P3	**0.010** **-** **-**	**0.010** >0.05 **0.045**	**0.010** - **0.036**	**0.001** **-** **-**	- - -
fT3; pg/ml	52 (38.52%) 1.52-4.64 1.90±±0.22	23 (35.38%) 2.23-4.43 2.56±±0.32	11 (36.67%) 1.67-4.64 2.05±±0.66	18 (45%) 1.52-3.86 1.85±±0.72	2 (3.33%) 1.73-4.95 3.86±±0.53
P1 P2 P3	**0.010** **-** **-**	**0.010** >0.05 >0.05	**0.010** - >0.05	**0.010** **-** **-**	- - -
TSH; mIU/L	56 (41.48%) 3.37-12.00 7.68±±0.42	24 (36.92%) 3.37-10.52 6.42±±0.34	10 (33.33%) 2.76-11.43 6.88±±0.64	22 (55%) 4.22-12.00 8.06±±0.38	7 (11.67%) 2.85-4.60 2.54±±0.67
P1 P2 P3	**0.0001** **-** **-**	**0.0001** >0.05 **0.010**	**0.0001** - **0.010**	**0.0001** **-** **-**	- - -
Thyroid volume; ml	35* (25.93%) 10.54-58.40 24.64±±3.30	8* (12.31%) 10.54-47.84 22.55±±3.62	9* (30%) 12.54-48.45 25.08±±2.32	18* (45%) 14.08-58.40 28.96±±2.08	4* (6.67%) 9.75-42.82 14.53±±2.64
P1 P2 P3	**0.001** **-** **-**	**0.001** **0.030** **0.010**	**0.001** - **0.043**	**0.001** **-** **-**	- - -

Data are expressed as means ± SD, number (%) of patients with abnormal results.
fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyroid stimulating hormone
P1: significance versus controls, P2: significance versus VPA, P3: significance versus CBZ+VPA
*: Number of patients with thyroid enlargement (goiter)

Table 3. Demographic and clinical features and thyroid volume in relationship to the presence or absence of subclinical hypothyroidism

Demographic and clinical features	Patients with subclinical hypothyroidism (n = 76)	Patients without subclinical hypothyroidism (n = 59)	P-value
Age	38.53 ± 2.66	30.02 ± 3.82	**0.010**
Gender (Male/Female)	45/31	43/16	-
Body mass index (BMI)	22.54 ± 2.40	26.64 ± 3.66	0.089
Duration of illness	15.63 ± 3.53	8.86 ± 2.45	**0.001**
Type of epilepsy:			
Generalized tonic-clonic epilepsy	22 (28.95%)	36 (61.02%)	-
Complex partial/Partial epilepsy with secondary generalization	54 (71.05%)	23 (38.98%)	-
Antiepileptic drugs (AEDs) utilized			
CBZ	32 (42.11%)	33 (55.93%)	-
VPA	18 (23.68%)	12 (20.34%)	-
CBZ+VPA	26 (34.21%)	14 (23.73%)	-
Dose of AED			
CBZ	850.00 ± 200.50	400.50 ± 150.00	**0.001**
VPA	1400.00 ± 250.00	1000.00 ± 350.80	**0.010**
Duration of treatment	13.45 ± 4.46	6.47 ± 2.82	**0.001**
Serum drug level			
CBZ	10.45 ± 1.62	6.88 ± 1.45	**0.010**
VPA	100.40 ± 25.35	70.65 ± 15.25	**0.001**
Degree of control on AED(s)			
Controlled (seizure free for ≥ 1 year)	54 (71.05%)	31 (52.54%)	-
Uncontrolled	22 (28.95%)	28 (47.46%)	-
Thyroid volume	35* (46.05%)	59 (0%)	-
	24.64±±3.30	15.64 ±± 3.53	**0.001**

Values are expressed as mean ± SD and number (%)
*: Number of patients with thyroid gland enlargement (goiter)

graphic, clinical, laboratory and US characteristics of the studied group revealed significant correlations between the followings: **1)** fT4 concentrations and duration of illness (r = -0.362, *p* = 0.043), dose of AED (CBZ: r = -0.508, *p* = 0.001; VPA: r = -0.638, *p* = 0.001), serum level of AED (CBZ: r = -0.742, *p* = 0.001; VPA: r = -0.570, *p* = 0.001), duration of treatment (r = -0.456, *p* = 0.01), fT3 concentrations (r = 0.456, *p* = 0.01), TSH concentrations (r = -0.854, *p* = 0.0001) and thyroid volume (r = -0.576, *p* = 0.001), **2)** fT3 concentrations and fT4 concentrations (r = 0.456, *p* = 0.01), TSH concentrations (r = -0.632, *p* = 0.001) and thyroid volume (r = -0.388, *p* = 0.042), **3)** TSH concentrations and dose of AED (CBZ: r = 0.623, *p* = 0.001; VPA: r = 0.568, *p* = 0.007), duration of treatment (r = 0.577, *p* = 0.006), fT4 concentrations (r = -0.854, *p* = 0.0001), fT3 concentrations (r = -0.632, *p* = 0.001) and thyroid volume (r = 0.680, *p* = 0.001), and **4)** No significant correlations were found between serum levels of fT4, fT3 or TSH and GGT concentrations.

Discussion

The results of this study indicate that adults with epilepsy and on long-term treatment with enzyme-inducing and non-enzyme inducing old AEDs experience the followings: **1)** high frequency of subclinical hypothyroidism (SCH) as evidenced by lower serum concentrations of fT4 and fT3 and higher concentrations of TSH. These changes occurred regardless to the type of epilepsy or the degree of control on AEDs, **2)** a significant frequency of patients with SCH had ultrasonographic evidence of thyroid enlargement (goiter), **3)** patients on polytherapy showed marked abnormalities and more increase in thyroid volume compared to those on monotherapy, **4)** age, duration of illness, duration of treatment and dose and serum level of AEDs are risk factors for SCH. The latter is a risk factor for thyroid enlargement, and **5)** The presence of abnormalities of thyroid hormones and volume with CBZ and VPA and normal GGT (a marker of liver enzyme induction), highly suggest the presence of mechanisms other that enzyme induction that may contribute to thyroid hormonal and structural abnormalities among patients with epilepsy.

In this study, SCH was reported in approximately half of the epileptic patients (i.e. reduced fT4 and fT3 and increased TSH in 56.30%, 38.52% and 41.48% versus 8.33%, 3.33% and 11.67% of control subjects, respectively). With CBZ, we reported SCH in 1/3-1/2 of patients (i.e. reduced fT4 and fT3 and increased TSH in 47.69%, 35.38% and 36.92%). With CBZ, Yılmaz et al. (25) reported SCH in 13.9%, Isojarvi et al. (8) reported reduced levels of T4 in 53.3%, fT4 in 28.9% and Eiris-Punal et al. (15) reported increased levels of TSH in 8.2% (versus 3.6% for controls). With VPA, we reported SCH in 1/3-2/3 of patients (i.e. reduced fT4 and fT3 and increased TSH in 47.69%, 35.38% and 36.92%). Previous studies reported SCH in 25.2% (19), 19.6% (22), 52.4 (23), 26% (24) and 28% (25) with VPA. We reported SCH in more than 1/3-1/2 of patients on combined therapy (CBZ + VPA) (fT4 = 65%; fT3 = 45%; TSH = 55%). Isojarvi et al. (8) reported reduced levels of fT4 in 50-100% of patients on CBZ-VPA. Previous studies reported that polytherapy was associated with SCH (19,23). The altered thyroid function during CBZ medication and been attributed to induction of the hepatic P-450 enzyme system and the consequent increase in the metabolism of thyroid hormones (3-6,11,37). The presence of normal GGT and the presence of thyroid abnormalities with VPA highly suggest that there are other mechanisms which induce thyroid hormonal abnormalities in patients with epilepsy and on AEDs. Hypothalamic interference of regulation of thyroid hormone production by AEDs seems possible. In addition, some authors suggested that there are other mechanisms which may result in thyroid abnormalities with CBZ other than enzyme

induction. Villa et al. (38) suggested that inhibition of iodine uptake by the thyroid gland might be one of the mechanisms by which CBZ can induce thyroid dysfunction. Surks and DeFesi (39) showed that patients taking CBZ medication had low fT4 and fT3 levels when serum samples were analyzed by a commercial procedure from diluted serum, but not when an ultrafiltration method from undiluted serum was used. The authors concluded that their results further support the view that hepatic P-450 enzyme induction is not the main or the only reason for decreased thyroid hormone concentrations during CBZ treatment. However, the mechanism of thyroid dysfunction with VPA is still unknown.

In this study, thyroid enlargement was reported in one fourth of patients (26% versus 6.67% controls) which represents 46.05% of patients with lab evidence of SCH. The higher frequency of patients with thyroid enlargement were on combined therapy (CBZ + VPA) (45%) followed by those on VPA (30%). Previous studies reported thyroid enlargement with enzyme-inducing and non-enzyme inducing AEDs (5,29,40). Hegedüs et al. (5) reported increased thyroid volume with CBZ (range: 13-66 ml, mean: 25 ml; versus range: 9-44 ml, mean: 16 ml for controls; $p<0.010$). The authors reported an associated between the thyroid volume and reduced serum levels of T4, fT4I and fT3I and increased serum level of thyroglobulin but normal serum levels of T3, T3RU and TSH. Chakova et al. (29) reported thyroid enlargement in 18.2% of the children on long-term treatment with AEDs. Clinical signs of initial hyperplasia of the thyroid gland were observed in 13.64%. The ultrasound examination revealed slight structural changes, decreased colloid uptake, and strip-like sprouts in 63.6% particularly with combined AEDs (polytherapy) (54.55%). The authors reported associated between thyroid enlargement and abnormalities in the thyroid hormones and thyrotropin serum concentration (22.73%). However in contrast, normal thyroid volume was reported despite lower levels of T4, fT4 and T3. with CBZ and VPA (41). The identified significant correlations between thyroid volume and thyroid hormones abnormalities found in this and other studies highly suggest that the increase in thyroid volume is probably a compensatory mechanism due to the low serum concentrations of fT4 and compensatory reduced concentrations of fT3 and enhanced concentrations of TSH regardless of the type of AEDs (enzyme-inducing versus non-enzyme inducing AEDs).

Despite the strength of this study, it has some limitations: **1)** the recruitment of the study group from a tertiary care center (a University hospital) with more severe cases and this explains the high percentage of thyroid hormonal and volume abnormalities. However, it should be kept in mind that SCH is a relatively common condition with incidence between 3 to 7% in the general population (42)**.** The prevalence of the disease is approximately 20% (43). Hence probably, such frequency rates for developing SCH might be increased among the patients with epilepsy group of population, which is also common, and **2)** because of the cross-sectional nature of the present study, it was not possible to know temporal relationship between thyroid dysfunction to the use of AEDs. However, such limitations could only be overcomed through a longitudinal and multi-center study design.

Conclusions

CBZ and VPA as mono- or poly- therapies may cause thyroid hormonal and structural abnormalities. The increased thyroid volume is probably due to associated subclinical hypothyroidism (SCH). This data indicates the importance of monitoring thyroid function in patients with epilepsy and on treatment with AEDs. This data also may have implications suggesting prevention strategies.

Conflict of interests

The authors declare that they have no competing interests. Authors did not receive fund for this work and all were authors' responsibility.

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