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Research Paper

The Effect of Oxcarbazepine on Thyroid Hormone Levels in Epileptic Patients

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ABSTRACT:

BACKGROUND:

patients with epilepsy need long-term anti-seizure medication; several studies found that anti-seizure medication affects endocrine function, including the thyroid gland.

OBJECTIVE:

Assess the impact of Oxcarbazepine therapy on thyroid function test outcomes in epilepsy patients on Oxcarbazepine therapy.

PATIENTS AND METHOD:

A cross-sectional study was conducted at Baghdad Teaching Hospital, including 65 patients with epilepsy who used oxcarbazepine as a mono-antiepileptic drug. The epidemiological data include the type of epilepsy (focal), duration of the disease, duration of treatment, dosage of treatment, thyroid stimulating hormone (TSH), thyroxin (T4), and triiodothyronine (T3) levels were tested.

RESULTS:

The study group showed notable associations between the length and dosage of oxcarbazepine treatment and thyroid function level.

CONCLUSION:

There is a significant difference in TSH, T3, and T4 levels in patients receiving oxcarbazepine as monotherapy in correlation to its duration of use and to its dose; in the analysis, the correlation observed is in duration >5 years and dosage >600mg/day.

KEYWORDS: anti-seizure medication, epilepsy, thyroid hormones.

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INTRODUCTION:

Epilepsy is a medical condition that is marked by a long-lasting tendency to have seizures and is accompanied by neurological, cognitive, psychological, and social consequences. The criterion requires the presence of at least one epileptic seizure[1]. An epileptic seizure is a transient event characterized by aberrant and synchronized neuronal activity in the brain, manifesting signs and/or symptoms [1]. The probability of experiencing a solitary epileptic seizure over one's lifetime is approximately 10%. Although the likelihood of developing epilepsy after experiencing a single seizure is low, epilepsy is a prevalent neurological disorder that affects around 50 million individuals globally [2].

Epilepsy necessitates long-term treatment with anti-seizure medication (ASMs) [3]. Oxcarbazepine is a structural analog of carbamazepine, which came to the market in 2000. Oxcarbazepine is FDA-approved for the treatment of partial seizures in adults and children ages 4 to 16 [4]. This medication is useful as monotherapy or adjunctive to another drug [4]. Oxcarbazepine is a sodium channel blocker. It has good oral bioavailability. This medication gets metabolized by the liver and excreted by the kidneys[4]. The compound converts quickly into its monohydroxy derivative, which exists in two enantiomers. The S-licarbazepine enantiomer accounts for most (80%) of its anti-seizure efficacy, whereas the R-licarbazepine enantiomer is less active but contributes to its unfavorable effects [4,6]. Oxcarbazepine exhibits low potency as an inducer of CYP3A4 and has limited inhibitory effects on CYP2C19. Consequently, when administered in high doses, it can elevate the phenytoin concentration in the body. Unlike carbamazepine, it does not stimulate its metabolism and is not influenced by substances inhibiting CYP3A4 enzymes [7].

Oxcarbazepine can induce somnolence, cephalalgia, and lethargy. Elevated doses may result in dizziness, blurred vision, double vision, nausea, vomiting, and ataxia. Approximately 2% to 4% of persons may experience a rash, and

oxcarbazepine has a 25% cross-reactivity with carbamazepine. Oxcarbazepine has a higher likelihood of causing hyponatremia compared to carbamazepine. Symptomatic hyponatremia is more common in older adults and those who are taking a diuretic [8].

The thyroid gland is an endocrine gland that controls various bodily activities, including energy expenditure, metabolic rate, and the functioning of organs such as the heart and brain. The thyroid gland mostly consists of thyroid follicles. The follicles consist of a core chamber that contains colloid, a fluid responsible for the generation of thyroid hormones. Levothyroxine (T4) and triiodothyronine (T3) are the primary substances produced by the thyroid gland [9, 10].

The objective of this study was to assess the impact of Oxcarbazepine treatment on thyroid function test outcomes in epilepsy patients who are undergoing Oxcarbazepine therapy.

PATIENTS AND METHOD:

Study design and settings

This study is a cross-sectional observational study that included a total of 65 patients. Among these patients, there were 33 males and 32 females. The age range of the patients was from 10 to 71 years. All patients were diagnosed with focal epilepsy based on clinical and electroencephalography findings. The study was conducted at the epilepsy outpatient clinic of Baghdad Teaching Hospital from October 2022 to December 2022.

Inclusion and exclusion criteria

Epileptic patients who use oxcarbazepine as a mono-antiepileptic drug, epileptic patients on other anti-seizure medication, and those with a history of thyroid problems were excluded.

Data collection

The thyroid-stimulating hormone (TSH), T3, and T4 levels were assessed using the Abbott Architect I system, which the US FDA cleared. The study examined the levels of thyroid hormones, and the length of time anti-seizure medications (ASMs) were used. The clinical data was acquired by a meticulous examination of medical records conducted by a proficient specialist in epilepsy. The researcher documented the demographic information, which encompassed age, gender, type and duration of epilepsy, dosage, and length of treatment, as well as the average frequency of seizures during the past 12 months. The classification of clinical seizure and epileptic syndromes was determined based on the seizure type classification established by the International League against Epilepsy in 2017 [11].

Assessment of thyroid function:

ARCHITECT performed the tests in the ABBOTT system (US FDA cleared). A T4 level of 4.7-14.6 ug /dl, a T3 level of 0.6- 2.1 ng/dl, and a TSH level of 0.5-4.8 IU/L were considered normal.

Statistical Analyses

The data was inputted into Microsoft Excel sheet 2019 and imported into SPSS (Statistical Package for Social Sciences) version 24. The parametric data is displayed as the mean value plus or minus the standard deviation, while the categorical data is provided as numerical values and percentages. Fisher's exact tests were employed to assess homogeneity, while the independent t-test and one-way ANOVA were utilized to quantify the disparity between groups for parametric variables. The Kolmogorov-Smirnov test assessed the normal distribution of the study-dependent variables. A P-value of ≤ 0.05 was deemed to indicate statistical significance.

RESULTS:

The highest proportion, 44.6% (29 cases), were within the age group 21 – 40 years old. Males and females were almost equal (33 (50.8%) and 32 (49.2%) respectively). In most of the cases, 20 (30.8%) were diagnosed with epilepsy at age (11-20 years); as shown in table 1.

In most study cases, 46 (70.8%) had an epilepsy duration of ≤ 5 years. Also, 48 (73.8%) received treatment for ≤ 5 years in most study cases. In almost half of the study cases, 32 (49.2%) had an epilepsy duration of 1 - 3 years. Also, 35 (53.8%) of more than half of the study cases were under treatment for 1-3 years, as shown in Table 1.

Table 1: Demographic and epileptic characteristics.

Parameters	Number	Percentage
Age group		
≤ 20 years	20	30.8
21-40 years	29	44.6
41-60 years	14	21.5
> 60 years	2	3.1
Sex		
Male	33	50.8
Female	32	49.2

Age at diagnosis		
≤ 10 years	9	13.8
11 - 20 years	20	30.8
21 - 30 years	14	21.5
31 - 40 years	14	21.5
41 - 50 years	4	6.2
51 - 60 years	4	6.2
Duration of epilepsy		
≤ 5 years	46	70.8
> 5 years	19	29.2
Duration of Oxcarbazepine Treatment		
≤ 5 years	48	73.8
> 5 years	17	26.2
Duration of epilepsy		
1 - 3 years	32	49.2
4 - 6 years	19	29.2
7 - 9 years	10	15.4
10 - 12 years	4	6.2
Duration of Oxcarbazepine treatment		
1 - 3 years	35	53.8
4 - 6 years	18	27.7
7 - 9 years	9	13.8
10 - 12 years	3	4.6

Five patients had a positive medical history of migraine. Four cases were having hypertension. Two cases were with psychomotor delay. Also, there was one case of each of the following (depression, SLE, arthritis, TB, stroke, and psychosis). Most of the study cases (20 cases) were treated with Oxcarbazepine 300 mg twice daily, 16 cases were treated with Oxcarbazepine 450 mg twice daily, and 11 cases were treated with Oxcarbazepine 600 mg twice daily. The highest proportion of study cases, 68% (44 cases), had not experienced any seizure in the last 12 months. While approximately 21% (14 cases) experienced seizure for once, 8% (5 cases) for twice, and 3% (2 cases) for thrice.

Table 2 and Figure 1 show that epileptic cases with Oxcarbazepine treatment duration of> 5 years had higher TSH levels (3.84 ± 3.651 ng/ml) than epileptic cases with treatment duration ≤ 5 years were TSH levels (1.87 ± 1.894 ng/ml), and this difference in TSH levels according to Oxcarbazepine treatment duration was significant (P=0.047). There was a statistical difference (P=0.032) in T4 levels (5.70 ± 1.423 ng/ml) among epileptic cases with Oxcarbazepine treatment duration of > 5 years and T4 levels (6.66 ± 1.579 ng/ml) of epileptic cases with Oxcarbazepine treatment duration ≤ 5 years. Additionally, epileptic cases with Oxcarbazepine treatment duration for ≤ 5 years had higher T3 levels (1.18 ± 0.787 ng/ml) than epileptic cases with treatment duration > 5 years were T3 levels (0.77 ± 0.215 ng/ml), and this difference in T3 levels according to Oxcarbazepine treatment duration was significance (P=0.042).

Further categorization of epilepsy duration and treatment duration found that epileptic cases with Oxcarbazepine treatment duration of 10-12 years and 7-9 years had higher TSH levels than epileptic cases with treatment duration of 1-3 years and 4-6 years. This difference in TSH levels, according to Oxcarbazepine treatment duration, was significant (P=0.003), a statistical difference (P=0.047) in T4 levels among epileptic cases according to different duration Oxcarbazepine treatment. Epileptic cases with Oxcarbazepine treatment duration of 1-3 years and 4-6 years had higher T3 levels than epileptic cases with treatment duration 7-9years and 10-12 years; also, this difference in T3 levels according to Oxcarbazepine treatment duration was significant (P=0.049), as shown in Figure 2.

Table 2: The differences in thyroid hormone levels according to the duration of epilepsy treatment with oxcarbazepine.

Parameters	Mean ± SD	p-value
TSH		
≤ 5 years	1.87 ± 1.894 ng/ml	0.047
> 5 years	3.84 ± 3.651 ng/ml	
T4		
≤ 5 years	6.66 ± 1.579 ng/ml	0.032
> 5 years	5.70 ± 1.423 ng/ml	
T3		
≤ 5 years	1.18 ± 0.787 ng/ml	0.042
> 5 years	0.77 ± 0.215 ng/ml	
TSH		
1 - 3 years	1.75 ± 1.45 ng/ml	0.003
4 - 6 years	2.12 ± 2.39 ng/ml	
7 - 9 years	4.13 ± 4.04 ng/ml	
10 - 12 years	6.31 ± 4.61 ng/ml	
T4		
1 - 3 years	6.67 ± 1.66 ng/ml	0.047
4 - 6 years	6.51 ± 1.61 ng/ml	
7 - 9 years	5.77 ± 1.43 ng/ml	
10 - 12 years	4.87 ± 0.23 ng/ml	
T3		
1 - 3 years	1.05 ± 0.57 ng/ml	0.049
4 - 6 years	0.91 ± 0.04 ng/ml	
7 - 9 years	0.82 ± 0.26 ng/ml	
10 - 12 years	0.79 ± 0.10 ng/ml	

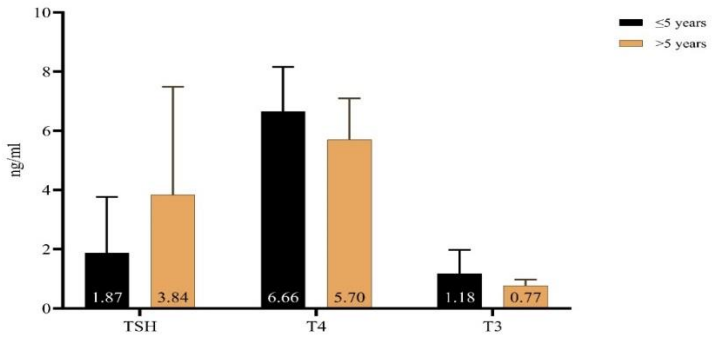

Figure 1: Thyroid hormone levels according to the duration of epilepsy treatment with oxcarbazepine (two age groups).

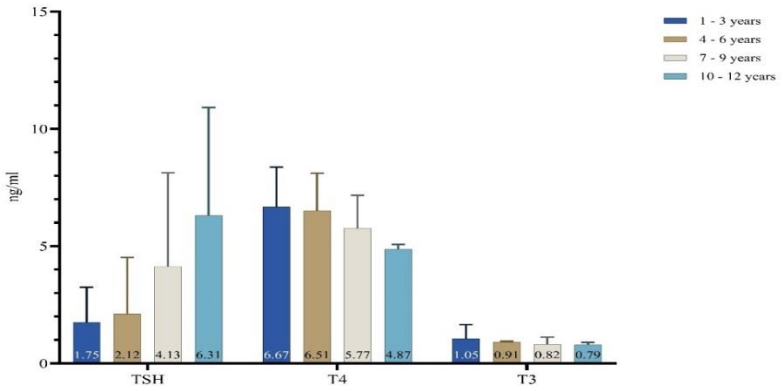

Figure 2: Thyroid hormone levels according to the duration of epilepsy treatment with oxcarbazepine (four age groups).

Study cases reported elevated TSH levels in seven cases; one of them was on Oxcarbazepine 150 mg×2, one case was on Oxcarbazepine 300 mg×2, and two cases were on Oxcarbazepine 600 mg×2. Only one case reported a reduction in TSH level to the normally accepted values on Oxcarbazepine 150+300 mg. When grouping study cases according to Oxcarbazepine doses/day as ≤ 300mg×2 and >300 mg×2, results showed that 5 cases out of the seven cases with elevated TSH levels were on Oxcarbazepine > 300 mg×2. The case with reduced TSH level was on Oxcarbazepine ≤ 300 mg×2.

Table 3 clarifies that there were 5 (71.4%) study cases of Oxcarbazepine dose > 300mg×2 and 2 (28.6%) cases of Oxcarbazepine dose ≤ 300mg×2 with elevated TSH level and this difference was significant (P=0.049). The highest proportion of study cases, 66.7% (4 cases) with reduced T4 levels were Oxcarbazepine dose > 300mg×2, while only 2 (33.3%) with reduced T4 were with ≤ 300mg × 2, and this difference was significant (P=0.038). Seven cases (87.5%) with elevated T3 were on Oxcarbazepine dose > 300mg×2, and one case (12.5%) was on Oxcarbazepine dose ≤ 300mg×2 (P=0.022).

Table 3: The distribution of thyroid hormonal assay according to the Oxcarbazepine dose.

Parameters	Total	Oxcarbazepine dose/day				P-value
		≤ 300mg×2		> 300mg×2		
		No	%	No	%	
TSH						
Normal (0.27-4.78 ng/ml)	57	31	54.3	26	45.6	0.049
Elevated (> 4.78 ng/ml)	7	2	28.5	5	71.4	
Reduced (<0.27 ng/ml)	1	1	100.0	0	0.0	
T4						
Normal (4.5-11.9 ng/ml)	57	32	54.2	27	45.8	0.038
Reduced (<4.5 ng/ml)	8	2	33.3	4	66.7	
T3						
Normal (0.60-1.81ng/ml)	57	33	57.9	24	42.1	0.022
Reduced (<0.60 ng/ml)	8	1	12.5	7	87.5	
Fisher exact test						

Table 4 and Figure 3 show that epileptic cases on Oxcarbazepine dose >300mg×2 had higher TSH levels (3.97 ± 2.651 ng/ml) than epileptic cases on Oxcarbazepine dose ≤300mg×2 TSH levels (1.77 ± 0.894 ng/ml), and this difference in TSH levels according to Oxcarbazepine dose was significant (P<0.001). There was a statistical difference (P=0.007) in T4 levels (6.68 ± 2.579 ng/ml) among epileptic cases on oxcarbazepine ≤300mg/day and T4 levels (4.81 ± 1.423 ng/ml) of epileptic cases on oxcarbazepine>300mg×2. Epileptic cases on Oxcarbazepine >300mg×2 had lower T3 levels (0.98 ± 0.135 ng/ml) than epileptic cases on oxcarbazepine ≤300mg×2 were T3 levels (1.18 ± 0.787 ng/ml), and this difference was statistically not significant (P=0.288) .

Table 4: The differences in thyroid hormone levels according to the dose of Oxcarbazepine/day.

Parameters	≤ 300 mg×2	> 300 mg×2	p-value
Number	34	31	
TSH (ng/ml)	1.77 ± 0.894	3.97 ± 2.651	<0.001
T4 (ng/ml)	6.68 ± 2.579	4.81 ± 1.423	0.007
T3 (ng/ml)	1.18 ± 0.787	0.98 ± 0.135	0.049
Independent t-test			

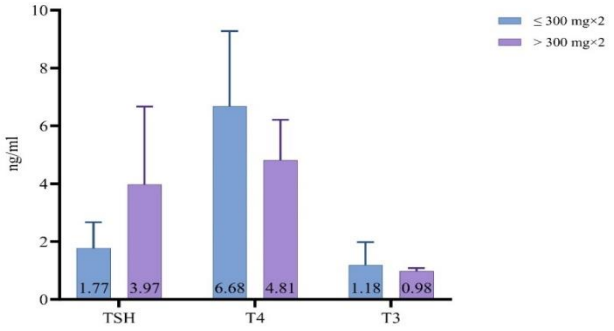

Figure 3: Thyroid hormone levels according to the dose of Oxcarbazepine/day.

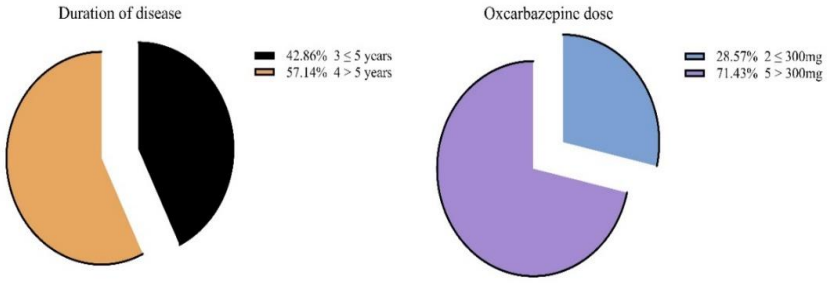

Figure 4: The distribution of the cases with elevated thyroid stimulating hormone according to the Oxcarbazepine dose and duration of disease treatment.

DISCUSSION:

Epilepsy has a global impact on over 50 million individuals, resulting in a substantial detriment to their quality of life and that of their families. Approximately 70% of individuals diagnosed with epilepsy can live a typical lifestyle if they receive appropriate medical intervention. As previously stated, the prolonged use of ASMs may impact thyroid function [12,16]. Although most individuals with subclinical hypothyroidism linked with ASMs have normal levels of thyroid hormones, they may nonetheless develop a hypometabolic state [17]. Nevertheless, the overall prognosis and necessity of L-thyroxin therapy for this clinical condition are still uncertain [18].

Antiepileptic medications can cause alterations in thyroid function through multiple routes [19, 20]. Multiple research investigations have reported the effects of oxycarbazepine on thyroid function test values. The precise method by which oxycarbazepine affects thyroid function remains incompletely understood. One potential mechanism involves the disturbance of the hypothalamic-pituitary axis. Several case studies have indicated that central hypothyroidism may be the primary etiology of hypothyroidism with oxcarbazepine therapy [20]. Another potential rationale is that oxcarbazepine may enhance the metabolic activity of thyroid hormones.

While oxcarbazepine has a limited ability to induce

hepatic CYP enzyme, it can nevertheless induce this enzyme at large doses [21,22]. The impact of oxcarbazepine on thyroid function is likely due to its ability to compete with thyroid hormones for binding to their associated proteins, resulting in reduced binding [12].

This study is a cross-sectional investigation that examines the impact of oxcarbazepine on thyroid function in 65 epileptic patients who are solely taking this medication. The patients are divided into various age groups and have been using varying dosages and durations of the drug. Prior research has indicated that the levels of T4 and T3 fell in patients who were on oxcarbazepine, even if there was no change in their TSH levels [12,14,23]; our study reported that epileptic patients with Oxcarbazepine treatment duration for > 5 years had higher TSH levels than epileptic cases with treatment duration ≤ 5 years with statistically significant P value (0.047). Significant differences exist in T4 and T3 levels for patients on treatment for >5 years than ≤5 years with P values (0.032, 0.042), respectively. Our study also showed that epileptic cases on Oxcarbazepine dose >300mg×2 had higher TSH levels than epileptic cases on Oxcarbazepine dose ≤300mg×2 and this difference in TSH levels according to Oxcarbazepine dose was significant (P<0.001). There was also a statistical difference (P=0.007, P=0.288) in T4 and T3 levels among epileptic patients on oxcarbazepine ≤300mg/day and epileptic patients on oxcarbazepine>300mg×2; this indicates that there is a direct relation between the dosage and duration of treatment and thyroid gland dysfunction.

Although previous studies revealed no change in TSH levels, in our study, seven patients showed elevated TSH levels; when grouping them according to Oxcarbazepine doses/day as ≤ 300mg×2 and >300mg×2, results showed that 5 cases out of the total seven cases with TSH levels were on oxcarbazepine> 300mg×2, and 2 cases with elevated TSH level was on oxcarbazepine ≤ 300mg×2. When grouping them according to treatment duration as for > 5 years and ≤5 years, four out of the total seven cases were with > 5 years duration, and 3 cases were with ≤5 years duration; this can be explained by the nature of our study that included patients with different drug dosage and duration.

Study limitations

The short duration of the study was only three months. The study has a small sample size of 65 patients. The study includes patients from one epilepsy clinic (Baghdad Teaching Hospital).

CONCLUSION:

Overall, the levels of blood T3, T4, and TSH in epileptic patients were found to undergo considerable changes in response to oxcarbazepine treatment, depending on the dosage and duration of the treatment. Thyroid function testing is not obligatory for individuals who are using oxcarbazepine now. We recommend conducting regular thyroid function tests, measuring TSH and T4 levels from the beginning of oxcarbazepine medication and at regular intervals. It is advisable to perform these tests every three months for the first two years and then annually afterward.

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