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## Assessment of Thyroid Hormones and Liver enzymes among Epileptic Adult Patients Treated with Carbamazepine Versus Levetiracetam

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### Abstract :

Aim of the study was to evaluate and compare the effect of carbamazepine and levetiracetam on thyroid hormones and liver enzymes in adult epileptic patients. Method: This Cross-Sectional study involved 105 subjects of them seventy patients having Primary Idiopathic Epilepsy with Normal Neurological Examination and Normal Brain imaging treated with either Carbamazepine or Levetiracetam monotherapy for more than 3 months enrolled and divided into two groups: first group included thirty five patients, treated with Carbamazepine monotherapy and Second group included thirty five patients, treated with Levetiracetam monotherapy, while the remaining thirty five healthy individuals' age and sex matched with the patients were considered as a control group. Thyroid function tests and Liver Function Test were measured for epileptic patients and control subjects. Result: A statistically significant low level of TT3 and TT4 with normal TSH level was observed in epileptic patients, who treated with carbamazepine when compared with control group, while there was no statistically significant difference in the level of TT3, TT4 and TSH in epileptic patients who treated with levetiracetam as compared with control group. A statistically significant high level of AST and ALT with normal ALP level was observed in epileptic patients who treated with carbamazepine when compared with control group, while those treated with levetiracetam showed a significantly high level of ALP as compared with control group. Conclusion: carbamazepine had the ability to decrease thyroid hormone levels and increase hepatic enzyme level while levetiracetam had no effect on thyroid hormone levels with ability to increase ALP liver enzyme level.

### المستخلص

الهدف من هذه الدراسة هو تقييم ومقارنة تأثير كاربامازيبين و ليفيتيراسيتام على مستوى هرمونات الغدة الدرقية و انزيمات الكبد لدى مرضى الصرع الكبار.

المنهجية: هذه الدراسة المقطعية تشمل مئة وخمسة اشخاص منهم سبعون مريضاً مشخصين بمرض الصرع الأساسي مجهول السبب مع الفحص العصبي الاعتيادي وتصوير الدماغ الطبيعي والمعالجين إما بالكاربامازيبين أو ليفيتيراسيتام كعلاج وحيد لأكثر من 3 أشهر وينقسمون إلى مجموعتين: المجموعة الأولى تشمل خمسة وثلاثون مريضاً ، تمت معالجتهم بالعلاج الأحادي كاربامازيبين و المجموعة الثانية تشمل خمسة وثلاثون مريضاً ، تمت

معالجتهم بالعلاج الأحادي ليفيتيراسيتام. وخمسة وثلاثون شخصاً آخر من الأصحاء يتطابقون بالجنس والعمر مع مرضى الصرع يعتبرون بمثابة سيطرة. تم قياس اختبارات وظائف الغدة الدرقية (TT3، TT4، و TSH) ، واختبار وظائف الكبد (ALT, AST, ALP) لمرضى الصرع والتحكم .

أظهرت النتائج الإحصائية انخفاض مستوى هرمون TT3 و TT4 مع مستوى طبيعي لهرمون TSH للمرضى المصابين بالصرع الذين تمت معالجتهم بالكاربامازيبين مقارنة مع مستوى هذه الهرمونات في مجموعة السيطرة، في حين لم يكن هناك فروق ذات دلالة إحصائية في مستوى TT3 و TT4 و TSH بين مرضى الصرع المعالجين بالفيتيراسيتام والسيطرة عليها. وان مستوى الإنزيم الكبدي AST و ALT إحصائياً عالي مع مستوى طبيعي للإنزيم الكبدي ALP للمرضى المصابين بالصرع والمعالجين بالكاربامازيبين مقارنة مع السيطرة، في حين المرضى المصابين بالصرع والمعالجين بالفيتيراسيتام اظهروا ارتفاع ذات دلالات إحصائية بمستوى الإنزيم الكبدي ALP مقارنة مع السيطرة .

استنتجت هذه الدراسة الحالية ان كاربامازيبين يسبب انخفاض مستوى هرمون الغدة الدرقية وزيادة مستوى انزيم الكبد في حين أن ليفيتيراسيتام ليس له أي تأثير على مستوى هرمون الغدة الدرقية لكنه سبب زيادة مستوى انزيم الكبدALP.

## Introduction

Epilepsy is a common chronic neuronal disorder or group of disorders, which is characterized by the recurrent (two or more) epileptic seizures. It affects approximately 70 million people of all ages throughout the world <sup>(1)</sup> with higher prevalence rate for developing countries <sup>(2)</sup>.

Epilepsy is a clinical presentation that linked to an abnormal and excessive discharge from a set of neurons in a specific locus of the brain <sup>(1)</sup>.

Therefore, the goal of treatment is to control rapid firing of population of neurons with antiepileptic drugs (AEDs) either as monotherapy or as combination therapy <sup>(3)</sup>. Commonly used drugs are conventional AEDs

such as phenytoin, phenobarbitone, carbamazepine, and valproate which have different adverse drug reactions due to their complex pharmacological properties and narrow therapeutic index that often dictate the choice of AEDs and subsequent adjustment of therapy <sup>(2,4)</sup>. Newer AEDs are more efficacious and less adverse effect as compared to conventional AEDs <sup>(5)</sup>, that can be used as an alternative or add-on therapy such as lamotrigine, gabapentin, levetiracetam, and topiramate <sup>(4)</sup>.

However, use of AEDs for long period linked to adverse effects such as metabolic and organ toxicity, cardiovascular toxicity, endocrine disturbance, negative cognitive effects, psychiatric problems, and cancer <sup>(6,7)</sup>,

especially change in thyroid function in patients with epilepsy<sup>(8)</sup>, which lead to growth and development failure in children and disturbances of endocrine homeostasis in adults because thyroid hormones are essential for the development and regulation of the metabolic state of many tissues<sup>(7)</sup>. The effects of AEDs on thyroid gland are first studied in 1961 by Oppenheimer *et al.*<sup>(9)</sup>. Then many different studies, showed different results had been achieved depending on the effect of antiepileptic medications on thyroid function tests<sup>(10-13)</sup> some studies reported that carbamazepine causes reduction of free thyroxin (fT4) levels, but has variable effects on levels of thyroid stimulating hormone (TSH)<sup>(9-11, 13-16)</sup>, while Levetiracetam-treated epileptic children's showed no effects on thyroid hormone levels in compared to other conventional AEDs<sup>(17)</sup>. Although many studies report the effect of conventional AEDs on thyroid function, fewer studies demonstrate the effect of newer AEDs on thyroid function so the aim of the this study is to assess thyroid hormone and hepatic enzyme level among adult epileptic patients treated with carbamazepine versus levetiracetam.

## **Materials and Methods**

### **Study design**

This Cross-Sectional study carried out in Azadi Teaching Hospital after getting approval of informed consent in Neurology Clinic and Outpatient Neurology department starting from September 2017 ending at March 2018.

### **Subjects**

One hundred and five subjects enrolled in this study. Of them seventy patients whose age between (15-40) years, have Primary Idiopathic Epilepsy with Normal Neurological Examination and Normal Brain imaging treated with either Carbamazepine or Levetiracetam monotherapy for more than 3 months enrolled in this study. The main criteria for exclusion from the study were: patients have Abnormal Brain imaging or Abnormal Neurological examination, Systemic or Psychiatric diseases, chronic drug users rather than Carbamazepine and Levetiracetam and Pregnant or Lactating mothers. The patients divided into two groups: first group included thirty five patients, treated with Carbamazepine monotherapy for more than 3 months. Second group included thirty five patients, treated with Levetiracetam monotherapy for more than 3 months.

The remaining thirty five healthy individuals' age and sex matched with the patients considered as a control group. After grouping of epileptic patient they classified according to Age, Sex, Duration of Epilepsy, Types and Dose of drugs that controlled their epilepsy.

### **Measurement of hormones and enzymes**

Thyroid function tests, Total Triiodothyronine(TT3) , Total Thyroxin (TT4) and TSH were measured by using (VIDAS<sup>®</sup>, France) kits and analyzed by using Vidas machine model 2010 with normal value for TT3 is 0.95-2.5 nmol/l, TT4 is 60-120 nmol/l, and TSH is 0.25-5 uIU/mL, and Liver Function Test, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and Alkaline Phosphatase (ALP) were measured. AST and ALT assessed by using Beckman Coulter Synchron LX20 autoanalyzer with normal value AST (10-50 IU/L), ALT ( 5-60 IU/L), while ALP assessed by Biolis 24 Model 2014 with normal value for Male (40-129) U/L and for Female (35-104)U/L.

### **Statistical Analysis**

Data were analyzed using the statistical package for social sciences (SPSS version 18); Chi-square test was applied to identify the relationship between two variables. P-Value <0.05 was considered to be significant.

### **Results**

For the 70 epileptic patients participate in this study who received antiepileptic drugs for more than 3 months, 36 cases were males (51.42%) and 34 cases were females (48.57%).

Thirty five patients (18 Female & 17 Male) whose age ( $27.629 \pm 6.357$ ) years received Carbamazepine monotherapy for ( $9.571 \pm 4.111$ ) months and thirty five patients (16 Female & 19 Male) whose age ( $28.57 \pm 6.908$ ) years treated with Levetiracetam monotherapy for ( $10.171 \pm 3.815$ ) months enrolled in this study. Also other 35 healthy individuals (19 Female & 16 Male) whose age ( $27.886 \pm 6.846$ ) consider as control.

All studied groups were compared according to age and sex that reported no statistical significance with P-Value > 0.05, (Table 1).

**Table (1): Classification of Studied groups according to Ages and Sex**

Studied Groups	Age Groups (year)			Sex	
	(15-20)	(21-30)	(31-40)	Male	Female
<b>Carbamazepine group( n=35)</b>	4	20	11	17	18
<b>Levetiracetam group(n=35)</b>	3	22	10	19	16
<b>Control group(n=35)</b>	4	19	12	16	19
<b>P- value</b>	0.964			0.766	

\*Chi-square test applied for correlation between age versus sex with three groups (Carbamazepine, Levetiracetam and Control) shows no statistical significance with P-Value > 0.05.

The current study recorded no who are treated with different doses as significant difference in studied groups shown in (Table 2).

**Table (2): Distribution of Patients groups therapy according to daily dosage**

Studied Groups	Daily Dose (mg/day)			P- value
	(<500)	(500-1500)	(>1500)	
<b>Carbamazepine group(n=35)</b>	4	25	6	0.936
<b>Levetiracetam group(n=35)</b>	5	24	6	

\*Chi-square test applied for correlation between different daily doses with studied groups (Carbamazepine and Levetiracetam) shows no statistical significance with P-Value > 0.05.

This study reported that the differences effect with P-Value > 0.05 as shown in in the duration of disease between (Table 3). studied groups have no significant

**Table (3): Distribution of Patients groups therapy according to disease duration**

Studied Groups	Disease Duration (months)			P- value
	(<6)	(6-12)	(>12)	

<b>Carbamazepine group(n=35)</b>	5	23	7	0.747
<b>Levetiracetam group(n=35)</b>	3	25	7	

\*Chi-square test applied for correlation between different disease duration with studied groups (Carbamazepine and Levetiracetam) shows no statistical significance with P-Value >0.05.

Table 4. Shows that the level of TT3and TT4 in epileptic patients using Carbamazepine was significantly lower than the control group with P-Value <0.001, and no statistically significant differences in the level of TT3and TT4

between epileptic patients using Levetiracetam and control group. No statistically differences in TSH level between all patients groups and control group.

**Table (4):Classification of Study groups according to Results of Thyroid Function Tests**

Studied Groups	TT3			TT4			TSH		
	L	N	H	L	N	H	L	N	H
<b>Carbamazepine group(n=35)</b>	28	5	2	26	6	3	1	31	3
<b>Levetiracetam group(n=35)</b>	1	33	1	-	34	1	2	33	-
<b>Control group(n=35)</b>	1	34	-	-	34	1	1	33	1

N=Normal, L= Low, H=High,TT3= Total Triiodothyronine,TT4= Total Thyroxin, TSH= Thyroid-stimulating hormone.

\*Chi-square test applied for correlation between TT3 (Carbamazepine with Control) P-Value <0.001, TT3 (Levetiracetam with Control) P-Value >0.05, TT4 (Carbamazepine with Control) P-Value <0.001, TT4 (Levetiracetam with Control) P-Value >0.05, TSH (Carbamazepine versus Levetiracetam with Control) P-Value >0.05.

Table 5. Shows that the level of AST and ALT in epileptic patients using Carbamazepine was significantly higher than the control group while no statistically significant differences in

ALP level with P-Value >0.05. No difference in AST and ALT between epileptic patients using Levetiracetam and control group with p-Value >0.05,

while statistically significant higher level of ALP with P-Value <0.001.

**Table (5): Classification of study groups therapy according to Results of Liver Function Tests**

Studied Groups	AST			ALT			ALP		
	L	N	H	L	N	H	L	N	H
<b>Carbmazepine group(n=35)</b>	2	8	25	1	7	27	1	31	3
<b>Levetiracetam group(n=35)</b>	1	32	2	-	34	1	1	2	32
<b>Control group(n=35)</b>	1	34	-	1	33	1	2	33	-

(Levetiracetam with Control) P-Value >0.05, ALT (Carbmazepine with Control) P-Value <0.001, ALT (Levetiracetam with Control) P-Value >0.05, ALP (Carbmazepine with Control) P-Value >0.05, ALP (Levetiracetam with Control) P-Value <0.001.

N=Normal, L= Low, H=High, AST= Aspartate Aminotransferase, ALT= Alanine Aminotransferase, ALP= Alkaline Phosphatase.

\*Chi-square test applied for correlation between AST (Carbmazepine with Control) P-Value <0.05, AST

## Discussion

There were a lot of studies documented that some AEDs affect on thyroid function test, many of these drugs increase hepatic microsomal enzyme systems, that accelerate clearance of thyroid hormone, while others interfere with the hypothalamic–pituitary axis<sup>(18, 19)</sup>. The current study involved 105 subjects divided into three groups, consists of 35 subjects for each carbamazepine, Levetiracetam and control groups. The groups were matched concerning to their ages as well as the number of males and females as confirmed statistically by the absence of significant differences between the studied groups (Table 1). This matching of age and gender, may exclude any effect of these parameters on the results of the study.

The present study found that most of epileptic patients who are treated with Carbamazepine had low level of TT3 and TT4 while normal level of TT3 and TT4 for those treated with Levetiracetam as compared to control group (Table 4). These results are agreed with the results of several previous studies<sup>(20-23)</sup>. Although the exact mechanism is unknown, it has been postulated in previous studies that thyroid hormone levels alteration caused by

antiepileptic therapy through several mechanisms, one possible mechanism is attributed to hepatic CYP450 enzyme induction by carbamazepine with consequent accelerated thyroid hormone metabolism, thereby decreasing its serum concentration and by interfering with thyroid hormone competitive binding to thyroid binding globulin<sup>(17, 19)</sup>.

In addition, study done by Villa and Alexander also suggested that iodine uptake inhibition by the thyroid gland might be one of the other mechanism by which carbamazepine can induce thyroid dysfunction<sup>(24)</sup>.

Although there was a reduction in the level of both TT3 and TT4 in patients who are treated with carbamazepine and normal for those on levetiracetam therapy, there was statistically significant normal TSH level in both patients groups that treated with carbamazepine and levetiracetam as compared to control group (Table 4) that is comparable to study of Apak I<sup>(25)</sup>.

This effect can be explained by the intact Hypothalamic-Thyroid axis that stimulated secretion of more TSH and this is Comparable to what's mentioned by Tiihonen M<sup>(10)</sup>.

In accordance with the results, there was statistical significance of high level of liver



enzymes (AST, ALT) in those who were treated with Carbamazepine while normal in patients were treated with levetiracetam as compared to control group (Table 5) this is mostly can be explained as Carbamazepine was hepatic microsomal enzyme inducer which had mode of action differ from Levetiracetam that is metabolized by kidneys <sup>(26)</sup>.

In addition the results of the current study, demonstrated that there was a statistically significant high level of serum Alkaline Phosphatase (ALP) in Patients treated with Levetiracetam therapy as compared to patients treated with carbamazepine therapy and control groups. ALP level increase when there were liver injury and active bone formation (osteoblast activity) <sup>(27, 28)</sup>.

Levetiracetam was associated with hepatic failure and liver cell damage due to induction of oxidative stress <sup>(29)</sup>, and also had osteoblast activity on bone that increases level of ALP in the blood <sup>(30)</sup>.

## Conclusion

It is cleared from this study that carbamazepine had the ability to decrease level of TT3 and TT4 without affecting TSH level, while levetiracetam had no effect on

thyroid hormone level. Hepatic enzyme level of AST and ALT were elevated in epileptic patients treated with carbamazepine monotherapy, while levetiracetam had the ability to increase level of ALP only.

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