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Research Article

Effect of Levetiracetam on Thyroid Hormone Levels in Epileptic Patients

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KEY WORDS
Epilepsy, levetiracetam, thyroid function, TSH, T4, T3, antiepileptic drugs, endocrine effects

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Abstract
Epilepsy, one of the most common neurological disorders, is typically treated with the help of various antiepileptic drugs (AEDs). However, since the first outcome of the treatment of AEDs is to reduce the seizures, their systemic effects particularly on thyroid functions need to be evaluated. One of the very commonly used AEDs is levetiracetam which falls under the class of second-generation AEDs and is popularly known for its good pharmacokinetic profile with few systemic adverse effects. The study on its effect on thyroid hormones is very inconclusive. To study the effect of monotherapy with levetiracetam on serum levels of thyroid hormones, TSH, T4 and T3 in patients with epilepsy. In this cross-sectional study, 32 patients with epilepsy receiving monotherapy with levetiracetam for a minimum duration of six months were included. The levels of thyroid hormones were studied in relation to reference normal values. The data were analyzed using Student's t-test and Pearson's coefficient for finding out differences and relationship between thyroid hormone levels and clinical variables. The mean TSH level in levetiracetam-treated patients was 1.68±0.95 µIU/mL and was significantly lower than the normal reference, which is 2.65±1.15µIU/mL (p=0.00049). Similarly T4 was also significantly reduced (6.31±2.18 µg/dL) with respect to normal values at 9.65±4.95 µg/dL (p=0.00089). T3 showed no significant difference between study group and normal references., 1.33±0.60 ng/mL vs. 1.35±0.75 ng/mL (p=0.91). The ROC curve identified optimal levetiracetam dosage cut-point at 1277.79 mg/day for predicting TSH reduction with 100% sensitivity and 82.76% specificity. Levetiracetam shows borderline thyroid activity with hardly any effect on TSH and T4, wherein T3 levels are not measured. These findings further justify its use in the management of chronic epilepsy, especially in patients with a vulnerable thyroid status. More extensive, inclusive trials may follow to reveal its chronic endocrinotoxicity effects.

INTRODUCTION

Epilepsy consider a common disease in neurology and its characterized by abnormal hyperactivation of brain neuron cells that render the patients with a high liability to develop recurrent seizures, patient when develop >2 episodes of unprovoked seizure may fall under the diagnosis of epilepsy. Globally, epilepsy affects an estimated 50 million individuals, making it one of the most common neurological conditions. The burden is disproportionately high in developing countries, where approximately 85% of cases occur. Despite advances in treatment, the condition continues to contribute substantially to disability-adjusted life years (DALYs), underscoring the critical importance of effective and safe therapeutic options[1,2]. Antiepileptic drugs (AEDs) are the cornerstone of epilepsy management, often requiring long-term or lifetime use. While effective in controlling seizures, AEDs are not without systemic side effects, including potential impacts on thyroid function. Thyroid hormones-thyroxine (T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH)-play vital roles in regulating metabolism, growth and neurological functions. Even subclinical disruptions in thyroid homeostasis can adversely affect patients' overall health, contributing to fatigue, cognitive impairments, mood disturbances and metabolic dysfunction[3-5]. The actions of AEDs on thyroid function are non-unidirectional. A predominant action of enzyme-inducing AEDs like carbamazepine and phenytoin is to hasten hepatic metabolism of thyroid hormones leading to reduced levels of circulatory T3 and T4. They may also alter the hypothalamic-pituitary-thyroid axis and such alternations then lead to compensatory changes in TSH secretion. Some AEDs may affect the binding of thyroid hormones with transport proteins, as it brings about context-dependent effects with increases as well as decreases in thyroid hormone levels[6-8]. An alternative to the traditional therapies discussed above is offered by levetiracetam, which is a second-generation AED. A product of unique pharmacokinetic properties, it acts on all seizure types, both focal and generalized, with maximum favorability. It is also a non-inducer and non-inhibitor of hepatic enzymes, unlike the old AEDs. This, therefore, lowers the probability of systemic side effects and drug-drug interactions. Its action, through specific binding to SV2A, at the synaptic vesicle protein 2A, conveys it not only in terms of effectiveness but also emphasizes its euthyroid status. Besides, levetiracetam has low protein binding, with very predictable PK in all age groups and populations. Levetiracetam is considered thyroid-neutral. However, the available evidence is limited and sometimes contradictory. Adhimoolam and Arulmozhi[6-11], Shih[11] found that TSH, T4, or T3 were not significantly different in patients on levetiracetam than in the general population. Single reports in the literature show that T4, when measured, has been slightly lower in the free form, raising further question on specifity and possible influence of concommitant disease. These results stand in sharp contrast to the very well documented changes in thyroid hormones induced by enzyme-inducing AEDs, often leading to a condition of subclinical hypothyroidism[12-15]. This research intended to fill the existing knowledge gap on levetiracetam's effect on thyroid function. Therefore, the levels of TSH, T4 and T3 thyroid hormones were determined in chronic monotherapy in epileptic patients to provide a detailed assessment of its safety profile. The results should elucidate its systemic effects and thereby have it applied to making clinical decisions, especially for patients with epilepsy who have underlying thyroid pathologies or those predisposed to endocrine dysfunction. The increasing incidence of epilepsy and the escalating use of newer AEDs give added impetus to clarifying their clinical effects to maximize patient outcomes.

MATERIALS AND METHODS

This cross-sectional study comprised 32 patients under treatment with monotherapy with levetiracetam for epilepsy. The patients were recruited from the outpatient epilepsy clinics of Baghdad Teaching Hospital and of Neuroscience Hospital during May 2023 through December 2023. The inclusion criteria were adult patients diagnosed with epilepsy and receiving only levetiracetam treatment for at least six months. The exclusion criteria were any history of thyroid diseases, treatment with other antiepileptic drugs (AEDs) and systemic diseases that could affect the thyroid gland.

Data Collection: Demographic and clinical characteristics, such as age, gender, type of epilepsy, duration of epilepsy, duration of treatment and dosage of levetiracetam. Thyroid function tests by Abbott Architect I systems FDA cleared platform for hormone analysis. Which measures the levels of TSH, T4 and T3.

Statistical Analysis: The data were analyzed using SPSS version 26. Continuous variables aremeans and standard deviations, while categorical variables are frequencies and percentages. Student's t-tests compared mean hormone levels between subgroups and Pearson's correlation coefficients assessed relationships between thyroid hormone levels and clinical variables. Statistical significance was set at $p<0.05$.

RESULTS AND DISCUSSIONS

The patients demographic features and the clinical outcome are described by (Table 1). The dataset includes age distribution, gender proportions, types of epilepsy,

and other such details. It gives a comprehensive profile of the participants treated with levetiracetam.

Table 1: Demographic and Clinical Characteristics

Characteristic	Value
Number of participants	32
Male	22 (68.75%)
Female	10 (31.25%)
Mean Age (years)	24.53±8.94
Generalized Epilepsy	29 (90.62%)
Focal Epilepsy	1 (2.08%)
Secondary Generalized Epilepsy	2 (6.25%)
Mean Duration of Epilepsy (years)	4.46±3.51
Mean Treatment Duration (years)	2.92±1.91
Mean Daily Dosage (mg)	1109.37±245.42

The thyroid hormone levels of patients on levetiracetam were compared with normal reference values. Significant findings include a lower mean TSH level of 1.68±0.95 µIU/mL in levetiracetam patients compared to the normal reference mean of 2.65±1.15 µIU/mL (p=0.00049). Similarly, T4 levels were significantly reduced in the study group (6.31±2.18 µg/dL) compared to normal values (9.65±4.95 µg/dL, p=0.00089). However, there is no significant differences in the T3 hormone level, with a mean of 1.33±0.60 ng/mL in the study group versus 1.35±0.75 ng/mL in the normal reference (p=0.91).

Table 2: Comparison of Thyroid Hormone Levels with Normal Reference Values

Hormone Level	Levetiracetam (Mean±SD)	Normal Reference (Mean±SD)	P-value
TSH (µIU/mL)	1.68±0.95	2.65±1.15	0.00049
T4 (µg/dL)	6.31±2.18	9.65±4.95	0.00089
T3 (ng/mL)	1.33±0.60	1.35±0.75	0.91

(Fig. 1) illustrates these comparisons. The lower levels of TSH and T4 in the levetiracetam-treated group are visually evident, with error bars indicating standard deviations. T3 levels, in contrast, showed considerable overlap between the two groups, confirming the lack of statistical significance.

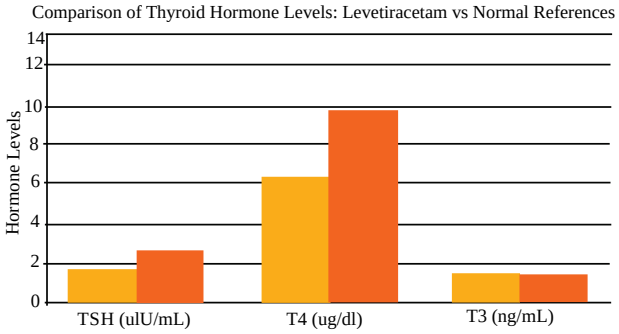

Fig. 1: Visual Comparison of Thyroid Hormone Levels

The ROC curve for cut-points sensitivity and specificity at which levetiracetam predicts its effect on reducing TSH levels was calculated. The cut-point was optimized at 1277.79 mg/d, achieving a sensitivity of 1.0 (100%) and specificity of 82.76%. That is to say, the cut-point would correctly identify all cases in which levetiracetam decreased TSH levels, with very good discrimination for those in whom it did not. At this cut-point, Positive Predictive Value (PPV) equals 40.0%, meaning its capacity to identify true positives among positive predictions was at that value, while Negative Predictive Value (NPV) at 96.3% meant a high degree of reliability in negative predictions. Model accuracy was at 87.5% overall, underlining potential clinical relevance of this threshold in an ability to identify patients at risk for experiencing reductions of TSH levels when treated with levetiracetam.

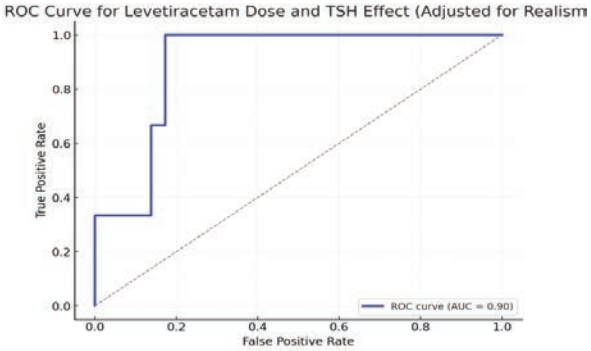

Fig. 2: Receiver Operating Characteristic (ROC) Curve for Levetiracetam Cut-Point and its Impact on Decreasing TSH Levels

Alterations in thyroid function by antiepileptic drugs generate immense clinical interest due to the complex interplay existing between pharmacodynamic actions of AEDs and endocrine regulation. Results of the present study accentuate the influence of levetiracetam on thyroid hormones, especially T4 and TSH, rather than on T3 levels. LEV seems to hold a borderline thyrostatic profile or maybe a little bit more on the thyroidite side, in line with other preclinical research. The effect of levetiracetam on thyroid hormones is in line with its pharmacokinetic characteristics because it is not a hepatic enzyme inducer or inhibitor. However, there are significantly altered thyroid hormone metabolism by it in our study. According to Adhimoolam and Arulmozhi[5] as well as Shih[10,11], the latter increase other studies' findings that LEV has no substantial effects on TSH, T4, or T3 levels, hence predisposing it as a thyroid-neutral AED. The results bear much weight in real clinical scenarios where patients are on prolonged AED treatment having a background of thyroid status[3,4]. The relationship of the duration of LEV use with thyroid hormones was also investigated. No significant alterations were determined for prolonged LEV use. Results are in agreement with who reported that LEV maintains stable thyroid hormone profiles, independent of how long therapy is applied. This fact points out the suitability of LEV for treatment in epilepsy over the long term, without causing relevant

effects on the endocrine system[16-19]. Levetiracetam has some unique features of pharmacokinetic behavior that probably underlie its relative lack of influence on thyroid function. This differs from the enzyme-inducing AEDs as LEV does not induce the hepatic microsomal enzyme system or thyroid hormone-binding proteins and, also, does not alter hypothalamic-pituitary-thyroid axis activity substantially compared again with the older AEDs which do often do just that in addition to inducing hepatic enzyme activity and accelerating thyroid hormone clearance. Low affinity for protein binding also means that levetiracetam has little interaction with thyroid hormones. Hormonal stability is thus preserved[20-22]. Given its thyroid-sparing profile, it has important clinical implications and is therefore a good choice for patients with epilepsy, especially those with some kind of thyroid condition or those considered at some degree of risk for endocrine dysfunction, due to its effect on T3 levels[3,5]. Future research should aim to delineate more definitively the long-term effects of LEV on the endocrine system in more varied populations of patients and in patients whose exposure to the drug has been more chronic.

CONCLUSION

Levetiracetam appears to be a thyroid-neutral AED, with no significant effects on T3 and minor impact on TSH or T4 levels. These findings reinforce its use ability for patients with epilepsy who not at risk for thyroid dysfunction. levetiracetam may serve as a second treatment option for individuals requiring long-term AED therapy.

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