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Original article

# TO STUDY THE EFFECT OF ANTIEPILEPTIC DRUGS ON THYROID FUNCTION AND THYROID VOLUME IN CHILDREN 1-14 YEARS WITH SEIZURE DISORDER: A PROSPECTIVE STUDY.

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## ABSTRACT.

### Background:
The incidence of epilepsy (recurrent unprovoked seizures) in children and adolescents seems relatively constant across different populations studied, ranging from 50 to 100/l00,000 person-years. The prevalence of epilepsy as a major public health problem worldwide is estimated to be 0.5- 1% of the population in industrialized countries. Anti-epileptic drugs (AEDs) can impair thyroid hormone homeostasis by changing its biosynthesis, secretion, transport, metabolism, and excretion, which may cause growth and developmental disorders in children.

### Materials and methods:
This prospective study included children of 1 to 14 years with seizure disorder on AEDs over two years. Clinical and laboratory details were recorded in pre-designed proforma. Thyroid hormone levels were measured by ECLIA (Electro Chemiluminescent Immuno Assay). Ultrasound of the thyroid gland was performed for size measurement.

### Results:
A total of 50 children were included. The majority of the children were in the 7 to 10 years age group (48%). The mean (±SD) age was 7.36(±2.59) years, and there were 72% males. Forty-six (92%) children had TSH levels within the normal range, and 4(8%) had increased levels. The TSH level was progressively increasing while on monotherapy with all AEDs except levetiracetam. A significant increase in TSH level was found with valproic acid. There was no clinical hypothyroidism, and no significant change in thyroid gland size was noted. USG of the thyroid gland shows mild hypoechogenicity and increased vascularity in children with altered TSH levels.

### Conclusion:
Subclinical hypothyroidism with elevated TSH levels without any signs and symptoms of hypothyroidism was noted in children on all AEDs except levetiracetam, which had no effects on thyroid function.

### Recommendations:
Subclinical hypothyroidism has been found to affect cognition of the growing brains in children. Thus, periodic monitoring of Thyroid function and volume may be needed in children on anticonvulsants.

***Keywords:*** *Thyroid dysfunction, Epilepsy, Anti-epileptic drugs, Hypothyroidism*
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## INTRODUCTION.

Epilepsy is a neurological disorder characterized by recurrent seizures resulting from various factors, such as neurobiological, cognitive, psychological, and social factors (1,2). Epilepsy is the second most common and frequently encountered neurological condition that imposes a heavy burden on individuals, families, and healthcare systems. As per a recent study, 70 million people have epilepsy worldwide and nearly 90% of them are found in developing regions (3) Patients with epilepsy often experience cognitive dysfunction. Multiple factors can adversely affect cognition in epilepsy, including the etiology of the seizures, cerebral lesions acquired before the onset of seizures, seizure type, age at onset of epilepsy, seizure frequency, duration, and severity, intraictal and interictal physiologic dysfunction, structural cerebral damage caused by repetitive or prolonged seizures, hereditary factors, psychosocial factors, and sequelae of treatment for epilepsy, including antiepileptic drugs (AEDs) and epilepsy surgery. (4-9)

Some AEDs are associated with alterations in thyroid function. This was first shown in 1981 by Strandjord et al (10). In 42 patients on long-term CBZ treatment, thyroxine (T4), free T4-index (FT4), and triiodothyronine (T3) concentrations in serum were found to be significantly lower than in controls, while T3 uptake and thyrotropin (TSH) concentrations did not differ between patients and controls. A study of 90 men with epilepsy taking either CBZ, VPA, or OXC and 25 control men demonstrated that serum T4 and FT4 concentrations were low in men taking CBZ or OXC, with 45% and 24% falling below the reference range, respectively, but serum T3 and TSH levels were normal. In men taking VPA, the concentrations of thyroid hormones and TSH were normal (11).

Another study in children with new-onset epilepsy (12) was performed prospectively with baseline thyroid testing before drug administration, followed by testing at 3, 6, and 12 months after initiation of CBZ or VPA treatment. CBZ-treated patients demonstrated significantly lower serum T4 and FT4 levels than at baseline evaluation and compared with control subjects, but normal serum T3 and TSH response in a thyrotropin-releasing hormone (TRH) test. This difference could be identified after only 3 months of treatment. Some of the CBZ-treated children were withdrawn from CBZ for other reasons, and re-evaluation 6 months later revealed that their thyroid hormone values had normalized. All values remained normal in the VPA treatment group. The patients were found to be clinically euthyroid, also in the CBZ group. The authors conclude that thyroid hormone alterations are not associated with clinical or subclinical hypothyroidism.

Another study of 35 patients on long-term PHT or CBZ treatment (13) reported that the mean concentrations of T4, FT4, FT3, and reverse triiodothyronine (rT3), but not T3, of these patients were significantly lower than those of 19 controls. Clinical examination of these patients did not reveal clinical signs of functional hypothyroidism. The authors also assessed response to thyroxine treatment in a smaller subset of patients, and the clinical parameters they examined were found to be unchanged after treatment. Based on the data from the cross-sectional and thyroxine treatment studies, the authors concluded that patients receiving AEDs chronically are metabolic and do not need thyroxine supplementation.

A recent prospective study on 23 children receiving OXC (14) showed that FT4, but not FT3, was significantly reduced after 8 and 18 months of treatment, while TSH was significantly increased.

Alterations in thyroid function seem to be reversible after withdrawal of medication. Lossius et al (15) showed significant increases in FT4 serum concentrations 4 months after CBZ withdrawal, in both men and women.

## NOVELTY OF THE STUDY.

There have been only a few studies on the effect of antiepileptic drugs on thyroid function tests and two studies on the effect of antiepileptic drugs on thyroid function and thyroid volume so far. To validate this study, there need to be further multicentric studies evaluating their sensitivity and specificity to use this study during follow-up of patients with a seizure disorder for evaluating for AED's AED-induced hypothyroidism. Doing this study in our institute will also help identify the parameters i.e. thyroid function and thyroid volume which will help us to know the adverse effects of AEDs on prolonged use. In this study, we will be comparing the patients on different AEDs and will find the AEDs that have the least effect on thyroid function and thyroid volume as hypothyroidism can lead to various neurologic and other abnormalities hampering proper growth and development of the children.

## OBJECTIVES.

To evaluate the thyroid function and thyroid volume in children diagnosed with seizure disorder aged 1-14 years on antiepileptic drugs at 0, 3, and 6 months.

## MATERIALS AND METHODS.

This prospective study was conducted in a tertiary care teaching hospital in the Eastern part of India. Children of 1 to 14 years with seizure disorder on AED therapy attending the outpatient and inpatient were included over two years from December 2020 to 2022. Children with gross developmental delay, thyroid, liver, or kidney disease, endocrinopathies, chromosomal abnormalities, and any neurological abnormalities were excluded.

The study was approved by the Hospital ethics committee (1103/25/08/2022). After getting informed consent, patients were subjected to detailed history and clinical examination. A pre-designed proforma was used to collect data regarding age, sex, socio-demographic profile, presenting complaints, seizure semiology, developmental milestones, and relevant peri-natal, past & family history. Clinical examinations including general physical examination, and systemic examinations were done. In the case of inpatients, hospitalization details including indication, duration of stay, development of any complications, treatment given, and outcome were recorded in the proforma.

Routine hemogram like complete blood count, liver function test, and renal function test was done in every case. In a case of convulsive disorder electroencephalogram, Magnetic resonance imaging of the brain was done to rule out any structural deformity.

For thyroid hormone level measurement, 2ml of blood was collected into test tubes through venipuncture under strict aseptic precautions. The serum was separated from cells by centrifugation. The sample was then subjected to ECLIA (Electro Chemiluminescent Immuno Assay) to measure free T3 (FT3), free T4 (FT4), and TSH levels. Thyroid USG was performed to calculate the thyroid volume using the length, width, and A-P diameter of each gland, and summing up both after excluding the isthmus. Thyroid hormone profile and thyroid volume were evaluated at baseline, at third and sixth months in all patients. To reduce the bias, it was compared with the controls and exclusion criteria were followed strictly.

## Study size.

After getting informed consent from the parents of cases and controls, they are subjected to detailed history and clinical examination and the findings are entered in the proforma. The cases who qualified (inclusion & exclusion as mentioned above) for the study were enrolled in the study. A total of 67 cases were included in the study. 8 cases did not give consent for the study, and 9 were lost to follow-up. The remaining 50 cases were included in our study.

## Statistical analysis.

Data was collected and entered into an Excel spreadsheet. Data were analyzed using SPSS Statistical software for Windows, version 25.0 (IBM Corporation, USA). Categorical variables were expressed as numbers and percentages. Continuous variables were expressed as minimum, maximum, mean, and standard deviation, as appropriate. The Chi-square test for categorical variables and t-test for quantitative variables were used to determine the association of different parameters of each score. Analysis of variance (ANOVA) was used to see any difference among the means of different groups by examining the amount of variation within each sample. A p-value of <0.05 was considered as significant.

## RESULTS.

In this study, a total of 50 cases were included. The distribution of age groups was: 1-3 years (8%), 4-6 years (30%), 7-10 years (48%), and 11-14 years (14%). The mean (±SD) age was 7.36(±2.59) years, and there were 72% males. The distribution of seizures among the cases was: generalized tonic-clonic seizure (92%), focal seizure (6%), and focal with secondary generalization (2%). No cases were found with absence or myoclonic seizures. The age of onset of seizure disorders was: 48% during 6-10 years of age, 38% during 3-6 years of age, and 14% during 1-3 years of age. No seizure had an onset in the age group of 10-14 years. Regarding the AEDs; 47(94%) children were on monotherapy, and 3(6%) were on polytherapy.

Among the monotherapy group, 62% were on VPA, 18% on phenytoin, 12% on levetiracetam, and 2% on carbamazepine. Among the polytherapy group, all the 3 cases were on VPA and levetiracetam. Regarding the duration of AEDs, 28%children were taking it for <6 months, 44% for 6-12 months, 22% for 12-24 months, and 6% for 24-36 months.

Regarding thyroid functions, 46(92%) had TSH levels within the normal range, and 4(8%) had levels in the higher limit (>4.2mIU/L). Out of 4 cases with high TSH levels, the mean(±SD) level of TSH at 0 months was 2.86(±1.18) mIU/L with the minimum being 1.07mIU/L and the maximum being 6.42mIU/L. At 3 months, the TSH level was2.96(±1.22) mIU/L with the minimum being 1.07 mIU/L, and the maximum being 6.91 mIU/L. At 6 months, the TSH level was 3.04(±1.24) mIU/L with the minimum being 1.15 mIU/L, and the maximum being 7.12 mIU/L. There was a significant difference in the TSH level between the groups at different time points (p<0.001).

FT4 levels were found within the normal range (12-22 mcg/dl) at 0 months, 3 months, and 6 months. The mean(±SD) level of FT4 at month was 15.13(±1.72) mcg/dl with the minimum being 12.03 mcg/dl, and the maximum being 18.76 mcg/dl. At 3 months, the FT4 level was 15.01 (±1.52) mcg/dl with the minimum being 12.11 mcg/dl, and the maximum being 18.25 mcg/dl. At 6 months, the FT4 level was 14.79(±1.41) mcg/dl with the minimum being 1.15 mcg/dl, and the maximum being 7.12 mcg/dl. There was no significant difference in the FT4 level between the groups at different time points (p = 0.09).

FT3 levels were found within the normal range (3.2-6.8 mcg/dl) at 0 months, 3 months, and 6 months. The mean(±SD) level of FT3 at 0 months was 4.65(±0.69) mcg/dl with the minimum being 3.27 mcg/dl, and the maximum being 6.22 mcg/dl. At 3 months, the FT3 level was 4.7 (±0.69) mcg/dl with the minimum being 3.29 mcg/dl, and the maximum being 6.19 mcg/dl. At 6 months, the FT3 level was 4.79(±0.74) mcg/dl with the minimum being 3.33 mcg/dl, and the maximum being 6.24 mcg/dl. There was no significant difference in the FT3 level between the groups at different time points (p = 0.79).

The levels of TSH, FT4, and FT3 at different time points with various AEDs have been shown in Tables **1** to **4**. The TSH level was progressively increasing while on monotherapy with all AEDs except levetiracetam. The significant increase in TSH level was found with VPA (**Tables 1** to **3**). A similar trend was found with VPA plus levetiracetam polytherapy (**Table 4**).

**Table 1: TSH levels at 0,3, and 6 months with various AED (monotherapy).**

| AEDs taken | TSH (Mean±SD) | | | P-value |
|---|---|---|---|---|
| | 0 month | 3 months | 6 months | |
| Valproic acid | 3.03±1.31 | 3.13±1.39 | 3.20±1.44 | 0.001 |
| Phenytoin | 2.69±0.81 | 2.81±0.81 | 2.88±0.79 | 0.061 |
| Levetiracetam | 2.59±0.95 | 2.6±0.93 | 2.58±0.9 | 0.095 |
| Carbamazepine (n = 1) | 1.54 | 1.59 | 1.64 | N/A |

**Table 2: Free T4 levels at 0,3, and 6 months with various AED (monotherapy)**

| AEDs taken | Free T4 (Mean±SD) | | | P-value |
|---|---|---|---|---|
| | 0 month | 3 months | 6 months | |
| Valproic acid | 15.20±1.74 | 15.11±1.54 | 14.73±1.37 | 0.313 |
| Phenytoin | 14.91±1.74 | 14.81±1.56 | 14.75±1.57 | 0.443 |
| Levetiracetam | 15.97±1.47 | 15.61±1.20 | 15.74±1.1 | 0.438 |
| Carbamazepine (n = 1) | 15.16 | 14.66 | 15.72 | N/A |

**Table 3: Free T3 levels at 0,3, and 6 months with various AED (monotherapy)**

| AEDs taken | Free T3 (Mean±SD) | | | P-value |
|---|---|---|---|---|
| | 0 month | 3 months | 6 months | |
| Valproic acid | 4.62±0.72 | 4.68±0.69 | 4.78±0.74 | 0.063 |
| Phenytoin | 4.48±0.43 | 4.56±0.46 | 4.86±0.81 | 0.097 |
| Levetiracetam | 5.17±0.80 | 5.24±0.84 | 5.02±0.69 | 0.42 |
| Carbamazepine (n = 1) | 4.92 | 4.13 | 4.16 | N/A |

**Table 4: Thyroid profile at 0,3, and 6 months with polytherapy (valproic acid + leviteracetam).**

| Thyroid profile | TSH (Mean±SD) | | | P-value |
|---|---|---|---|---|
| | 0 month | 3 months | 6 months | |
| TSH | 2.56±1.17 | 2.66±0.93 | 2.88±0.98 | 0.05 |
| FT4 | 13.33±1.54 | 13.41±1.56 | 13.36±1.54 | 0.368 |
| FT3 | 4.40±0.73 | 4.46±0.72 | 4.48±0.74 | 0.067 |

**Tables 5** and **6** show the thyroid gland volumes at different time points as well with monotherapy vs polytherapy. The differences were not statistically significant.

**Table 5: Thyroid volume (ml) at 0, 3, and 6 months.**

| Thyroid volume | Minimum | Maximum | Mean±SD | P-value |
|---|---|---|---|---|
| At 0 months | 1.25 | 8.80 | 3.10±1.54 | 0.084 |
| At 3 months | 1.25 | 8.80 | 3.15±1.54 | |
| At 6 months | 1.25 | 9.00 | 3.18±1.57 | |

**Table 6: Thyroid volume (ml) at 0, 3, and 6 months in monotherapy vs polytherapy.**

| Thyroid volume | 0 months | 3 months | 6 months |
|---|---|---|---|
| Monotherapy | 3.10±1.56 | 3.15±1.56 | 3.18±1.59 |
| Polytherapy | 3.10±1.41 | 3.14±1.46 | 3.15±1.46 |
| P-value* | 0.87 | 0.84 | 0.88 |

**Mann-Whitney U test*

## DISCUSSION.

The effect of antiepileptic drugs on thyroid function and thyroid volume has been known for a long time. There seems to be considerable individual variability of response to AEDs, probably depending on peripheral changes in the hormone metabolism. In children, thyroid hormones are important for normal mental and physical growth, so the study of the effect of AEDs on thyroid function is important.

In this study, a total of 50 cases were included. Children in the age group of 7-10 years (48%) dominated the study population, and the male-to-female ratio was 2.57. Generalized tonic-clonic seizure was the most common type (92%), and the majority (62%) were on VPA. The majority (44%) of the children were taking the AEDs for 6-12 months. The TSH values were elevated in 8% of the

cases (VPA monotherapy = 62%). All children on levetiracetam had normal TSH values.

Aggarwal *et al* found that TSH level increased with both VPA and carbamazepine compared to control but was significant with VPA (P <0.001). The authors concluded that carbamazepine and VPA alter thyroid functions by decreasing FT4 levels. Compensation by increase in TSH is better with VPA (16). Verrott et *al* found that children treated with carbamazepine may have subclinical signs of hypothyroidism, with the changes in thyroid function being more evident if VPA was added as there was no alteration in thyroid hormones with VPA monotherapy (12). Based on these findings, the authors concluded that TSH and thyrotropin-releasing hormone (TRH) levels do not seem to be affected by these drugs, suggesting that hypothalamic function is not affected in these children which was also noted by Verrotti*et al* with two co-authors in different point of time (16,12).

Elshorbagy *et al* studied the effect of old or traditional (VPA, carbamazepine, and phenobarbitone) AEDs versus the newer AEDs (levetiracetam, oxcarbazepine, and topiramate) (17). They found subclinical hypothyroidism in 20% of children treated with traditional AEDs and 5% of children treated with newer AEDs. There was a significant decrease in the serum FT4 level along with an increase in the TSH level in children on old or traditional AEDs, but the serum FT3 level was not affected. T3 is derived from T4 in peripheral tissues. Nandi-Munshi et al studied that the serum T3 and FT3 levels may remain unaffected even in severe cases of hypothyroidism, which is why not useful for hypothyroidism diagnosis (18). This might explain our observation of no change in the serum FT3 level in our study.
Hirfanoglu et al and Hegedüs L et al found that Carbamazepine may induce a state of reversible hypothyroidism as seen in some of the previously published studies (19,20). This is because of competitive inhibition of binding of thyroid hormones to the binding protein as well as an increase in thyroid hormone metabolism by induction of cytochrome P450 enzyme system in the liver. After using the drug for some time these effects get saturated leading to a reversal of the hypothyroid state. As a single patient taking carbamazepine was included in the present study, we could not evaluate this effect.

Dabla *et al* in their study found a significantly higher level of TSH in the polytherapy compared to the monotherapy group (21). There was a significant negative correlation observed between carbamazepine and FT4. However, in the present study, we did not find any significant difference between polytherapy and monotherapy, and this may be because of the small sample size as well as the use of a single combination (VPA plus levetiracetam).
In the present study, thyroid volume was within the reference range in all the cases, and even among those with high TSH levels at 0,3, and 6 months. There was no correlation of thyroid volume with AEDs, either monotherapy or polytherapy. Hirfanoglu *et al* found no correlation between AEDs and thyroid gland volume as well as with FT3, FT4, and TSH levels (19).

## CONCLUSIONS.

In this study, subclinical hypothyroidism with elevated TSH levels without any signs and symptoms of hypothyroidism was noted in children on all AEDs except levetiracetam, which had no effects on thyroid function.

## LIMITATIONS.

The sample size of the study was relatively small; it was conducted at a tertiary hospital and proper follow-up of patients on a repeated and long-term basis was beyond the scope of this study. Further studies using larger samples at multiple centers are needed for the validation of this study. A single patient in the carbamazepine group precluded evaluation of the actual effect of this drug. The study looked at the effects of AEDs on thyroid functions for a very short period. We need to see the effects of AEDs on thyroid structural and functional status after long-term therapy.

## RECOMMENDATION.

Subclinical hypothyroidism has been found to affect cognition of the growing brains in children. Thus, periodic monitoring of Thyroid function and volume may be needed in children on anticonvulsants. All patients diagnosed with seizure disorder on AEDs
should be followed up every 3 months with thyroid function and thyroid volume.

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## LIST OF ABBREVIATIONS

AED's – Antiepileptic Drugs
A-P diameter – Anterior –Posterior diameter
CBZ: Carbamazepine
Free T4 – Thyroxine
Free T3 – Triiodothyronine
IPD – In-patient door
OPD – Out-patient door
OXC: Ox carbamazepine
SCH – Subclinical hypothyroidism
SCBMCH – Sri Rama Chandra Medical College &Hospital
SVVPGIP –Sardar Vallabhbhai Patel Post Graduate Institute of Paediatrics
TSH – Thyroid-stimulating hormone
VPA: Valproic Acid

## AUTHORS CONTRIBUTION.

1. Narayan Prasad Modi - Concept designing and conducting the study & writing the manuscript.
2. Bhagabat Swain, Choudhury Jasmine Mohapatra, Kali Prasanna Swain - Conducting the study and writing the manuscript.
3. Mangal Charan Murmu - Guiding the study procedure, statistical analysis, and preparing the manuscript suitable for publication.

## CONFLICT OF INTEREST.

None

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