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Research Article

EFFECT OF ANTIEPILEPTIC DRUG THERAPY ON THYROID FUNCTION AND THYROID VOLUME IN CHILDREN WITH SEIZURE DISORDERS: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Objectives: The objective of the study is to evaluate the effect of antiepileptic drug (AED) therapy on thyroid function parameters and thyroid volume in children aged 2–12 years with seizure disorders.

Methods: This prospective observational study included 45 children aged 2–12 years with seizure disorders receiving antiepileptic therapy and followed for 6 months. Serum thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), and thyroid volume by ultrasonography were assessed at baseline, 3 months, and 6 months. Participants received monotherapy or polytherapy, predominantly sodium valproate, phenytoin, and levetiracetam. Data were analyzed using repeated measures analysis of variance and the Mann–Whitney U test ($p<0.05$ considered significant).

Results: The mean age of participants was 7.29±2.69 years. On pooled analysis, mean TSH levels showed a mild, non-significant increase over time ($p=0.40$), while FT3 and FT4 levels remained stable. However, children receiving sodium valproate demonstrated a statistically significant rise in mean TSH from 3.07±1.45 to 3.24±1.56 mIU/L at 6 months ($p=0.032$), with normal FT3 and FT4 levels. Subgroup analysis confirmed that this significant change was observed only with sodium valproate ($p=0.032$). Thyroid volume showed a marginal, non-significant increase during follow-up ($p=0.15$), with no significant difference between monotherapy and polytherapy groups.

Conclusion: Sodium valproate therapy in children is associated with a significant rise in TSH levels suggestive of subclinical hypothyroidism. Periodic thyroid function monitoring every 6–12 months is advisable in children receiving long-term sodium valproate therapy.

Keywords: Antiepileptic drugs, Thyroid function, Thyroid volume, Pediatric epilepsy, Adverse drug reactions, Epilepsy.

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INTRODUCTION

Epilepsy is one of the most common chronic neurological disorders in children and often requires long-term treatment with antiepileptic drugs (AEDs) for adequate seizure control [1,2]. While AEDs are effective in reducing seizure frequency and improving quality of life, prolonged exposure has been associated with several systemic adverse effects, including metabolic, hepatic, skeletal, and endocrine disturbances [3,4]. Among these, alterations in thyroid function have received increasing attention, particularly in the pediatric population where thyroid hormones play a critical role in growth, neurodevelopment, and cognitive maturation [5].

Thyroid hormones are essential for neuronal differentiation, synaptogenesis, myelination, and regulation of basal metabolic processes during childhood [6]. Even subtle disturbances in thyroid hormone homeostasis, such as subclinical hypothyroidism, may adversely affect neurocognitive development, behavior, and academic performance in children [7]. Several AEDs, especially enzyme-inducing agents such as phenytoin and carbamazepine, and non-enzyme-inducing drugs such as sodium valproate, have been reported to interfere with thyroid hormone synthesis, metabolism, and regulation through multiple mechanisms, including hepatic enzyme induction, altered peripheral deiodination, displacement from plasma binding proteins, and effects on the hypothalamic–pituitary–thyroid axis [8-10].

Previous studies have demonstrated variable effects of AEDs on serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) levels, with sodium valproate frequently associated with elevated TSH levels suggestive of subclinical hypothyroidism [11,12]. In contrast, newer AEDs such as levetiracetam have shown minimal or no significant impact on thyroid function in most reports [13]. However, the available literature predominantly focuses on biochemical thyroid function parameters, and results remain inconsistent due to differences in study design, duration of therapy, sample size, and patient demographics.

In addition to functional changes, long-term AED therapy has been hypothesized to influence thyroid gland morphology. Compensatory thyroid enlargement secondary to altered hormone metabolism has been reported with certain AEDs, particularly enzyme-inducing drugs [14]. Thyroid ultrasonography (USG) provides a non-invasive and reliable method for assessing thyroid volume and structural changes in children, yet data evaluating the combined effect of AEDs on both thyroid function and thyroid volume remain limited [15,16]. Importantly, most existing studies originate from Western countries, with sparse data from the Indian subcontinent and very few from Eastern India, where genetic, nutritional, and environmental factors may influence drug response and endocrine outcomes.

Given the widespread use of AEDs in pediatric practice, the potential for subclinical thyroid dysfunction, and the paucity of regional prospective data integrating both biochemical and ultrasonographic assessment, there is a clear need for systematic evaluation of the thyroid effects of antiepileptic therapy in children. Early identification of drug-induced thyroid alterations may allow timely intervention and prevent long-term neurodevelopmental consequences.

Therefore, the objective of this prospective observational study was to evaluate the effect of AED therapy on thyroid function parameters (TSH, FT3, and FT4) and thyroid volume in children aged 2–12 years with seizure disorders.

METHODS

Study design

This study was designed as a hospital-based prospective observational study to evaluate the effect of AED therapy on thyroid function parameters and thyroid volume in children with seizure disorders.

Study setting

The study was conducted in the Department of Pediatrics, Burdwan Medical College and Hospital, Burdwan, West Bengal, India, a tertiary care teaching hospital catering to pediatric patients from both urban and rural regions of Eastern India.

Study duration

The study was carried out over a period of 18 months, from June 2023 to December 2024, including patient recruitment, follow-up, data collection, and analysis.

Inclusion criteria

1. Children aged 2–12 years
2. Diagnosed with seizure disorder based on clinical evaluation and electroencephalography
3. Receiving AED therapy (monotherapy or polytherapy)
4. Written informed consent obtained from parents or legal guardians.

Exclusion criteria

1. Children with known thyroid disorders
2. Presence of hepatic, renal, or other endocrine diseases
3. Children with chromosomal abnormalities or congenital syndromes
4. Children with gross developmental delay or major neurological abnormalities
5. Children receiving drugs known to interfere with thyroid function or thyroid volume.

Study sampling

All consecutive eligible children admitted to the pediatric ward or pediatric intensive care unit during the study period and fulfilling the inclusion criteria were enrolled until the required sample size was achieved.

Study sample size

A total of 45 children with seizure disorders receiving antiepileptic therapy were included in the final analysis. The sample size was determined based on feasibility, patient availability during the study period, and duration of follow-up, consistent with a prospective observational design.

Study procedure

After obtaining written informed consent, each participant underwent a detailed clinical evaluation, including demographic data, seizure type, duration of illness, and AED details such as type, dose, and duration of therapy. Clinical findings were recorded using a predesigned, pretested, and prevalidated case record pro forma. Venous blood samples (2 mL) were collected under strict aseptic precautions at baseline (0 month), 3 months, and 6 months of AED therapy. Serum was separated by centrifugation and analyzed for thyroid function parameters, including serum TSH, FT3, and FT4. Hormonal assays were performed using the electrochemiluminescence immunoassay technique in the institutional laboratory. Thyroid USG was performed to calculate the thyroid volume. Patients were followed up clinically and biochemically at scheduled intervals.

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC) of Burdwan Medical College and Hospital. IEC approval number and date: (IEC No.: BMC/I.E.C./208/Date: July 17, 2023). Written informed consent was obtained from the parents or legal guardians before enrollment. Patient confidentiality was maintained throughout the study, and participation was entirely voluntary.

Ultrasonographic assessment of thyroid volume

Thyroid USG was performed at baseline, 3 months, and 6 months using a high-frequency linear transducer. Participants were examined in the supine position with the neck hyperextended. The length, width, and anteroposterior diameter of each thyroid lobe were measured.

Thyroid volume was calculated using the standard ellipsoid formula:

Thyroid volume=length×width×depth×0.479, excluding the isthmus [15].

Total thyroid volume was obtained by summing the volumes of both lobes.

Study groups

Participants were categorized based on AED therapy as follows:

1. Monotherapy group: Children receiving a single AED (sodium valproate, phenytoin, levetiracetam, or carbamazepine)
2. Polytherapy group: Children receiving a combination of AEDs.

Outcome measures

The primary outcome measures were:

1. Changes in serum TSH, FT3, and FT4 levels at 0, 3, and 6 months
2. Changes in thyroid volume on USG over the same period.

The secondary outcome measures included:

1. Comparison of thyroid parameters between monotherapy and polytherapy groups
2. Identification of subclinical thyroid dysfunction associated with specific AEDs.

Statistical analysis

Data were compiled in a Microsoft Excel 2021 master chart and analyzed using the Statistical Package for the Social Sciences version 25.0. Continuous variables were expressed as mean±standard deviation (SD) and categorical variables as frequency and percentage. Normality of data distribution was assessed using the Shapiro–Wilk test. Changes in thyroid function parameters and thyroid volume over time were analyzed using repeated measures analysis of variance (ANOVA), and sphericity was evaluated using Mauchly's test. When the assumption of sphericity was violated, Greenhouse–Geisser correction was applied. *Post hoc* subgroup comparisons were performed using Bonferroni adjustment. Comparison of thyroid volume between monotherapy and polytherapy groups was performed using the Mann–Whitney U test. A $p<0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of study participants

A total of 45 children aged 2–12 years with seizure disorders were included in the study. The sample size of 45 was determined based on feasibility during the study period and is comparable to previously published prospective pediatric studies evaluating thyroid function changes during antiepileptic therapy [11-13]. The mean age of the participants was 7.29±2.69 years. Among them, 30 (67%) were male and 15 (33%) were female, with a male-to-female ratio of 2:1. Fig. 1 depicts the age group distribution of the study participants.

The most common seizure type was generalized tonic–clonic seizure, observed in 93% of cases, followed by focal seizures (6%) and focal seizures with secondary generalization (1%). The majority of children were receiving AED therapy for 6–12 months (40%), followed by <6 months (29%), 12–24 months (24%), and 24–36 months (7%).

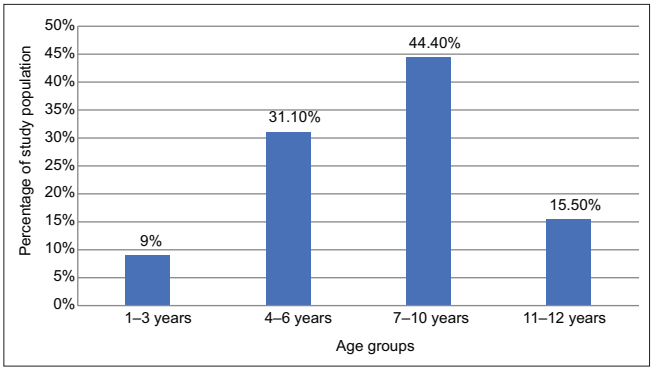

Fig. 1: Age group distribution of the study participants (n=45). Values represent percentages of the total study population (n=45). Data are presented as percentage distribution of children in each age category

Distribution of AED therapy

Among the study population, 42 children (93%) were receiving monotherapy, while 3 children (7%) were on polytherapy. Sodium valproate was the most commonly prescribed AED (58%), followed by phenytoin (20%) (Table 1).

Thyroid function parameters

At baseline, the mean serum TSH, FT3, and FT4 levels of the study cohort were within the normal reference range. On pooled analysis of all participants (n=45), irrespective of the type of AED used, there was a mild upward trend in mean TSH values from 2.89±1.23 mIU/L at baseline to 2.95±1.25 mIU/L at 3 months and 3.01±1.27 mIU/L at 6 months; however, this change was not statistically significant (p=0.40). Mean FT3 and FT4 levels also remained stable during follow-up, with no statistically significant variation over time (p=0.30 and p=0.60, respectively). p-value was calculated using repeated measures ANOVA. Table 2 summarizes the pooled longitudinal changes in thyroid function parameters in the entire study cohort. *Post hoc* subgroup analyses were performed with Bonferroni adjustment to account for multiple comparisons.

On categorical analysis, five children (11%) developed elevated TSH levels above the laboratory upper reference limit (>4.5 mIU/L) with normal FT4 concentrations during follow-up, consistent with biochemical subclinical hypothyroidism. The majority of these cases were observed in children receiving sodium valproate therapy.

Effect of individual AEDs on thyroid function

When thyroid function parameters were analyzed according to individual AEDs, a statistically significant change was observed only in children receiving sodium valproate. In this subgroup, mean serum TSH levels increased from 3.07±1.45 mIU/L at baseline to 3.24±1.56 mIU/L at 6 months (p=0.032). In contrast, no statistically significant changes were observed in children receiving phenytoin, levetiracetam, or polytherapy. FT3 and FT4 levels in the sodium valproate group remained within normal reference ranges throughout the follow-up period.

In contrast, children receiving phenytoin and levetiracetam did not demonstrate statistically significant changes in TSH, FT3, or FT4 levels during follow-up (*p>0.05). Similarly, no statistically significant changes in thyroid function parameters were observed in children receiving polytherapy.

Thyroid volume assessment

Thyroid volume assessed by USG remained within age-appropriate reference ranges in all participants at baseline and during follow-up. The mean thyroid volume increased marginally from 3.12±1.45 mL at baseline to 3.15±1.47 mL at 3 months and 3.18±1.49 mL at 6 months; however, this change was not statistically significant (p=0.15). p-value calculated using repeated measures ANOVA (Table 3).

Table 1: Distribution of antiepileptic drug therapy among study participants (n=45)

Antiepileptic drug therapy	Frequency (n)	Percentage
Sodium valproate	26	58
Phenytoin	9	20
Levetiracetam	6	13
Carbamazepine	1	2
Polytherapy (valproate+levetiracetam)	3	7
Total	45	100

Data are presented as n (%). Polytherapy refers to the concurrent use of more than one antiepileptic drug and, in this study, consisted of sodium valproate plus levetiracetam

Table 2: Overall changes in thyroid function parameters during antiepileptic drug therapy in the entire study cohort

Parameter	Baseline (0 month) mean±SD	3 months mean±SD	6 months mean±SD	p-value
TSH (mIU/L)	2.89±1.23	2.95±1.25	3.01±1.27	0.40
FT3	4.56±0.78	4.60±0.79	4.65±0.80	0.30
FT4	15.12±1.45	15.05±1.43	15.10±1.44	0.60

Data are presented as mean±standard deviation. p-values were calculated using repeated measures ANOVA. *Post hoc* subgroup comparisons were adjusted using Bonferroni correction. ANOVA: Analysis of variance, SD: Standard deviation, TSH: Thyroid-stimulating hormone; FT3: Free triiodothyronine; FT4: Free thyroxine. Normal reference ranges: TSH 0.5–4.5 mIU/L; FT3 3.5–6.5 pmol/L; FT4 10–23 pmol/L

Table 3: Longitudinal changes in thyroid volume during antiepileptic drug therapy

Time point	Thyroid volume (mL) mean±SD	p-value
Baseline (0 month)	3.12±1.45	–
3 months	3.15±1.47	0.15
6 months	3.18±1.49	0.15

Data are presented as mean±standard deviation. Thyroid volume (mL) was calculated using the ellipsoid formula (length×width×depth×0.479 for each lobe, excluding the isthmus). p-value was calculated using repeated measures analysis of variance

Comparison of thyroid volume between monotherapy and polytherapy

When thyroid volume was compared between the monotherapy and polytherapy groups, no statistically significant difference was observed at baseline, 3 months, or 6 months. The mean±SD thyroid volume in the monotherapy group was 3.16±1.64 mL, 3.21±1.64 mL, and 3.25±1.67 mL at 0, 3, and 6 months, respectively. Corresponding values in the polytherapy group were 2.32±1.93 mL, 3.11±1.20 mL, and 3.86±1.86 mL, with p-values of 0.495, 0.755, and 0.435, respectively. Comparison was performed using Mann–Whitney U test; *p<0.05 was considered statistically significant (Table 4).

Clinical correlation

None of the children who demonstrated biochemical abnormalities in thyroid function parameters during the study period exhibited clinical features suggestive of hypothyroidism. Notably, the observed elevation in serum TSH levels occurred predominantly in children receiving sodium valproate and was not associated with clinical symptoms or alterations in FT3 and FT4 levels. Ultrasonographic evaluation did not reveal clinically significant thyroid enlargement or nodularity in these children.

DISCUSSION

The present prospective observational study evaluated the effect of AED therapy on thyroid function parameters and thyroid volume in

Table 4: Comparison of thyroid volume between monotherapy and polytherapy groups

Time point	Monotherapy (mL) mean±SD	Polytherapy (mL) Mean±SD	p-value
Baseline (0 month)	3.16±1.64	2.32±1.93	0.495
3 months	3.21±1.64	3.11±1.20	0.755
6 months	3.25±1.67	3.86±1.86	0.435

Data are presented as mean±standard deviation. Comparisons were performed using the Mann–Whitney U test. $p<0.05$ was considered statistically significant. The monotherapy group included 42 children and the polytherapy group included 3 children

children aged 2–12 years with seizure disorders. The findings indicate that although most children maintained normal thyroid hormone levels during treatment, a subset developed biochemical thyroid dysfunction, predominantly in the form of elevated serum TSH levels. These changes were observed mainly among children receiving sodium valproate, while FT3 and FT4 levels remained within normal limits, consistent with subclinical hypothyroidism. Thyroid volume assessed by USG throughout the study period did not show any statistically significant changes.

The observation of elevated TSH levels in children receiving sodium valproate is consistent with earlier pediatric studies that have reported an association between valproate therapy and subclinical hypothyroidism [4,11-13]. The presence of raised TSH with normal FT3 and FT4 concentrations suggests an adaptive alteration of the hypothalamic–pituitary–thyroid axis rather than overt thyroid failure. Valproate has been shown to induce endocrine and metabolic changes, which may influence thyroid hormone regulation through central and peripheral mechanisms [4]. Similar biochemical patterns have been documented in children and adolescents receiving long-term valproate therapy [11,12]. Persistent elevation of TSH, even within the subclinical range, may exert trophic effects on thyroid follicular cells. Sustained TSH stimulation over prolonged durations can potentially lead to compensatory thyroid hyperplasia and a gradual increase in thyroid volume. Although no significant thyroid enlargement was observed during the 6-month follow-up in the present study, longer exposure to sodium valproate may have different structural implications.

In the present study, children treated with phenytoin and carbamazepine did not demonstrate statistically significant changes in thyroid function parameters. Enzyme-inducing AEDs such as phenytoin and carbamazepine are known to enhance hepatic metabolism of thyroid hormones by inducing microsomal enzymes, potentially leading to reduced circulating hormone levels [3,8-10,14]. The absence of significant biochemical alterations in this cohort may be attributed to the relatively short duration of follow-up and the limited number of children receiving these medications.

Children receiving levetiracetam maintained normal thyroid function throughout the study period. Although levetiracetam is not directly addressed in early enzyme-induction studies, recent comparative studies evaluating newer versus older AEDs have demonstrated minimal impact of newer agents on thyroid function [13]. From an applied pharmacology perspective, this finding supports the endocrine safety of newer AEDs and their suitability for long-term use in pediatric populations.

Thyroid volume assessment by USG did not reveal any significant changes during the study period, either in the overall cohort or when analyzed according to treatment groups. Thyroid volume remained within age-specific reference ranges at baseline and during follow-up. These findings are consistent with studies that reported no significant association between AED therapy and thyroid gland enlargement in children [15,16]. Although compensatory thyroid hypertrophy has been postulated in response to altered hormone metabolism, such structural changes may require longer exposure durations to become evident.

Comparison of thyroid volume between monotherapy and polytherapy groups did not demonstrate statistically significant differences at any time point. While this suggests that polytherapy may not exert an additional short-term effect on thyroid morphology beyond individual drugs, this finding should be interpreted cautiously due to the small number of children receiving polytherapy. Similar observations have been reported in pediatric studies where thyroid volume did not correlate significantly with treatment duration or number of AEDs used [15].

From a clinical and applied pharmaceutic perspective, these findings are important because AEDs are often administered for prolonged periods during critical phases of growth and neurodevelopment. Even mild biochemical abnormalities such as subclinical hypothyroidism may adversely affect neurocognitive development and behavior if left unrecognized [5-7]. The present study underscores the importance of periodic thyroid function monitoring in children receiving long-term antiepileptic therapy, particularly sodium valproate. The absence of significant thyroid dysfunction with newer AEDs may influence therapeutic decision-making in pediatric epilepsy. Based on the present findings, a practical monitoring approach may include assessment of serum TSH and FT4 at baseline, at 6 months after initiation of sodium valproate therapy, and annually thereafter during continued treatment. Our findings are consistent with recent Indian pharmacovigilance and prescription-pattern studies highlighting the need for systematic safety monitoring in children receiving sodium valproate and other AEDs [17-19].

Recent evidence from applied pharmaceutics research further supports the importance of therapeutic monitoring and rational drug selection in epilepsy management. A systematic review published in the International Journal of Applied Pharmaceutics demonstrated that generic substitution of AEDs does not significantly increase seizure frequency, adverse events, or hospitalization rates, highlighting the clinical stability of well-monitored antiepileptic therapy. Similarly, a review in the International Journal of Pharmacy and Pharmaceutical Sciences emphasized the role of biomarkers and therapeutic monitoring in optimizing long-term epilepsy outcomes and improving drug safety evaluation. These findings collectively reinforce the need for structured monitoring protocols in children receiving chronic antiepileptic therapy, particularly with agents such as sodium valproate that may influence endocrine function [20,21].

The strengths of this study include its prospective design, serial assessment of thyroid function and thyroid volume, and the combined evaluation of biochemical and ultrasonographic parameters. In addition, the study provides valuable data from Eastern India, where literature on AED-induced endocrine effects in children is limited.

Future research should focus on larger multicentric studies with longer follow-up periods to better characterize the long-term effects of AEDs on thyroid function and morphology in children. Comparative studies involving newer antiepileptic agents may further guide safer long-term pharmacotherapy in pediatric epilepsy.

Limitations

Certain limitations must be acknowledged. The sample size was relatively small with short duration of follow-up, particularly in the polytherapy group, and the study was conducted at a single center, which may limit the generalizability of the findings. The follow-up duration was relatively short and may not have been sufficient to detect long-term structural changes in the thyroid gland. Furthermore, micronutrient levels such as selenium and zinc were not assessed, which could have provided additional insight into the mechanisms underlying valproate-associated thyroid dysfunction. In addition, urinary iodine excretion was not assessed in this study, and variations in iodine status may have independently influenced thyroid function parameters.

CONCLUSION

This prospective observational study demonstrates that AED therapy in children with seizure disorders is associated with alterations in

thyroid function, particularly in those receiving sodium valproate. A statistically significant rise in serum TSH levels with normal FT3 and FT4 concentrations was observed in the sodium valproate subgroup, consistent with subclinical hypothyroidism. In contrast, levetiracetam and other AEDs did not show significant effects on thyroid function parameters. Thyroid volume remained within age-appropriate reference ranges throughout the study period and did not demonstrate significant longitudinal changes or differences between monotherapy and polytherapy groups. These findings suggest that short-term antiepileptic therapy predominantly affects thyroid function rather than thyroid morphology. Periodic monitoring of thyroid function tests, particularly serum TSH and FT4, is recommended at baseline, at 6 months after initiation of sodium valproate therapy, and every 6–12 months thereafter during continued treatment to facilitate early detection and appropriate management of drug-induced subclinical hypothyroidism.

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AUTHORS' CONTRIBUTION

Bodhisatya Das, Wasim Akram, and Mahaprasad Pal were involved in the conception of the study and formulation of the research question. They contributed to the study design, determination of intellectual content, literature review, data collection, and data analysis. They also participated in drafting the manuscript, revising it critically, and approving the final version. Pranab Das contributed to the conceptualization of the study and played a key role in the study design, defining intellectual content, literature review, and data analysis. He was involved in manuscript preparation and revision.

CONFLICT OF INTEREST

The authors have disclosed no known conflicts of interest.

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