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Original Article

Thyroid Function in Children on Long-Term Antiepileptic Drug Therapy: A Case-Control Study from a Tertiary Care Centre in North-West India

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ABSTRACT

Background: Antiepileptic drugs (AEDs) are the mainstay of therapy for childhood epilepsy, but long-term use has been linked to endocrine disturbances, particularly thyroid dysfunction. Data from Indian paediatric populations, especially with newer AEDs, remain limited.
Objectives: To assess thyroid function in children aged 2–18 years receiving AED therapy for at least one year, to correlate thyroid function with the type of AED used, and to assess the frequency of seizure recurrence among adherent children.
Methods: This case–control study (March 2025–March 2026) at a teria care hospital, Kota, included 60 children on AED therapy for ≥1 year and 120 age- and sex-matched healthy controls. Serum TSH and free T4 were measured by chemiluminescent immunoassay. Data were analyzed using the t-test, chi-square test, ANOVA with Tukey's post-hoc test, and logistic regression, with $p<0.05$ considered significant.
Results: Mean TSH was higher and fT4 lower in cases than controls ($p\leq0.001$). Subclinical hypothyroidism was significantly more common in cases (21.7% vs 2.5%; $p<0.001$), with the highest prevalence in children on polytherapy and valproate, and none on levetiracetam. Higher AED doses were associated with increased TSH ($p=0.01$). Children with subclinical hypothyroidism had more seizure recurrence (61.5% vs 25.5%; $p=0.01$). Valproate use, longer therapy duration, and high-dose treatment were independent predictors of subclinical hypothyroidism.
Conclusion: Children on long-term AED therapy, particularly with valproate, high doses, or polytherapy, are at increased risk of subclinical hypothyroidism, which is in turn associated with higher seizure recurrence. Periodic thyroid function monitoring is recommended in this population.

Keywords: *Antiepileptic drugs; Epilepsy; Thyroid function tests; Subclinical hypothyroidism; Children; Valproate.*

INTRODUCTION

Epilepsy is among the most common chronic neurological disorders of childhood, with active prevalence estimated at 4-10 per 1000 children and a cumulative incidence of approximately 7-8 per 1000 by 15 years of age.[1,2] Children constitute nearly a quarter of the global epilepsy burden, and low and middle-income countries, including India, account for a disproportionate share of cases due to perinatal insults, central nervous system infections, and delayed diagnosis.[3,4] A regional observational study of 191 neonates likewise identified birth asphyxia, septicaemia, hypoglycaemia and hypocalcaemia as leading seizure aetiologies, illustrating the importance of preventable perinatal and metabolic insults.[5]

Antiepileptic drugs (AEDs) remain the mainstay of treatment, achieving adequate seizure control in 60-70% of children, but often require continuation for several years.[6,7] Prolonged AED exposure has been increasingly linked to endocrine adverse effects, particularly disturbances of the hypothalamic-pituitary-thyroid axis.[8] Enzyme-inducing AEDs such as carbamazepine and phenobarbital accelerate hepatic clearance of thyroid hormones, while valproate has been associated

with elevated thyroid-stimulating hormone (TSH) through effects on hormone synthesis and peripheral conversion.[9,10] The resulting biochemical picture is most often subclinical hypothyroidism—elevated TSH with normal circulating thyroid hormones—a definition also used in contemporary clinical cohorts.[11] Although usually asymptomatic, undetected thyroid dysfunction may affect growth, cognition and metabolic health during critical developmental years.[12,13]

Existing literature on AED-associated thyroid dysfunction is heterogeneous, with most data derived from older AEDs and limited paediatric data from India, particularly regarding newer agents such as levetiracetam.[14,15] Given the essential role of thyroid hormones in neurodevelopment and the widespread use of AEDs in childhood epilepsy, we undertook this study to evaluate thyroid function in children aged 2-18 years receiving AED therapy for at least one year, to correlate thyroid function with the specific AED used, and to assess the frequency of seizure recurrence among children adherent to therapy.

MATERIALS AND METHODS

This case-control study was conducted in the Department of Paediatrics, Government Medical College, Kota, at the J.K. Lone Mother and Child Hospital, over a period of one year (March 2025 to March 2026), after approval from the Institutional Ethics Committee. Written informed consent was obtained from parents/guardians of all participants.

Study population and sample size

Sixty children aged 2-18 years who had received AED therapy for at least one year (cases) and 120 age-and sex-matched healthy children (controls) attending the outpatient and inpatient departments were enrolled. The sample size was calculated using an expected prevalence of thyroid dysfunction of 13.2% among AED-treated children, a 95% confidence level (Z=1.96) and an 8% margin of error, yielding a minimum requirement of 60 cases; a case:control ratio of 1:2 was used.[16]

Inclusion and exclusion criteria

Cases included all children aged 2-18 years on AED therapy for ≥1 year; controls were healthy children of the same age range with parental consent. Children with pre-existing thyroid disease, those on drugs known to affect thyroid function (e.g., dopamine agonists, amiodarone, cycloserine, rifampicin), those with a family history of thyroid or other endocrine dysfunction, non-adherent patients, and syndromic children (e.g., Down syndrome) were excluded.

Sample collection and biochemical analysis

A fasting morning venous blood sample was collected from each participant under aseptic precautions. Serum TSH and free T4 (fT4) were estimated using the DiaSorin LIAISON automated chemiluminescent immunoassay analyser and interpreted against age-specific paediatric reference ranges. Subclinical hypothyroidism was defined as an elevated TSH with a normal fT4 in the absence of overt clinical symptoms.[17] Clinical details including seizure type, age of seizure onset, AED regimen, dose, duration of therapy, adherence, and seizure recurrence were recorded on a structured proforma; EEG and MRI findings, where available, were also documented.

Statistical analysis

Data were entered and analysed using SPSS software. Continuous variables were expressed as mean±SD and compared using the independent-samples t-test (two groups) or one-way ANOVA with Tukey's post-hoc test (more than two groups). Categorical variables were compared using the chi-square test. Correlation between quantitative variables was assessed by correlation analysis. Univariate and multivariate logistic regression were used to identify predictors of subclinical hypothyroidism, with results expressed as odds ratios (OR) with 95% confidence intervals (CI). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 60 cases and 120 controls were enrolled. The mean age was comparable between cases (10.0±3.8 years) and controls (9.2±3.9 years; p=0.19), as was the sex distribution (60.0% male, 40.0% female in both groups), confirming adequate baseline matching (Table 1).

Table 1. Baseline age and sex distribution of study participants

Variable	Cases (n=60)	Controls (n=120)	p-value
Age (years), mean±SD	10.0 ± 3.8	9.2 ± 3.9	0.19
Male, n (%)	36 (60.0)	72 (60.0)	1.00
Female, n (%)	24 (40.0)	48 (40.0)	1.00

Figure 8. Baseline Age and Sex Distribution of Study Participants

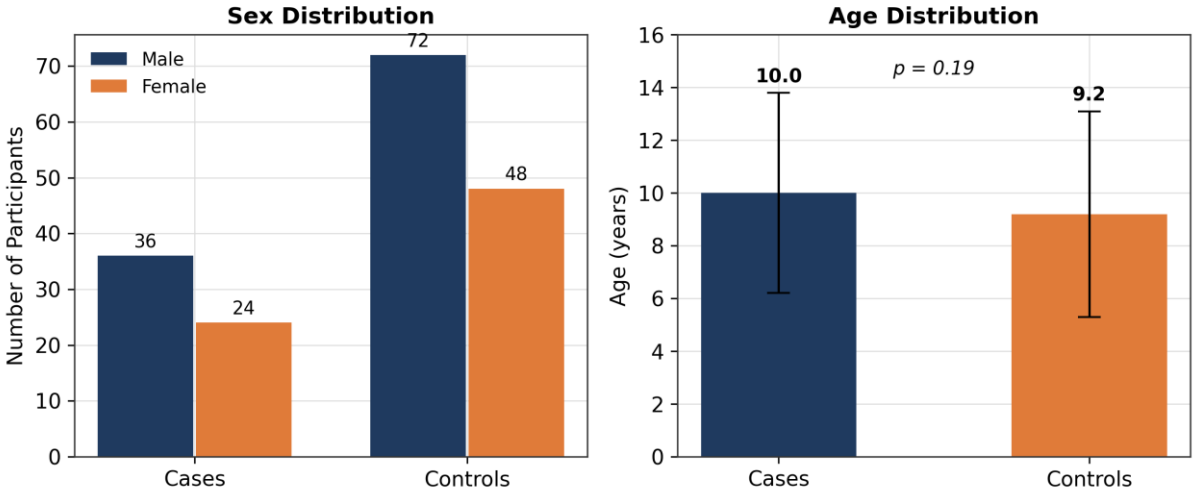

Figure 1. Baseline age and sex distribution of study participants

Mean TSH was significantly higher in cases than controls (4.50±2.80 vs 2.10±1.20 mIU/L; p<0.001), and mean fT4 was significantly lower in cases (1.10±0.33 vs 1.28±0.28 ng/dL; p=0.001) (Table 2). Subclinical hypothyroidism was present in 13/60 cases (21.7%) compared with 3/120 controls (2.5%), a highly significant difference (χ^2=18.6, p<0.001) (Table 3).

Table 2. Comparison of thyroid function test profile between cases and controls

Parameter	Cases (n=60) Mean±SD	Controls (n=120) Mean±SD	p-value
TSH (mIU/L)	4.50 ± 2.80	2.10 ± 1.20	<0.001
fT4 (ng/dL)	1.10 ± 0.33	1.28 ± 0.28	0.001

Figure 1. Comparison of Thyroid Function Test Profile Between Cases and Controls

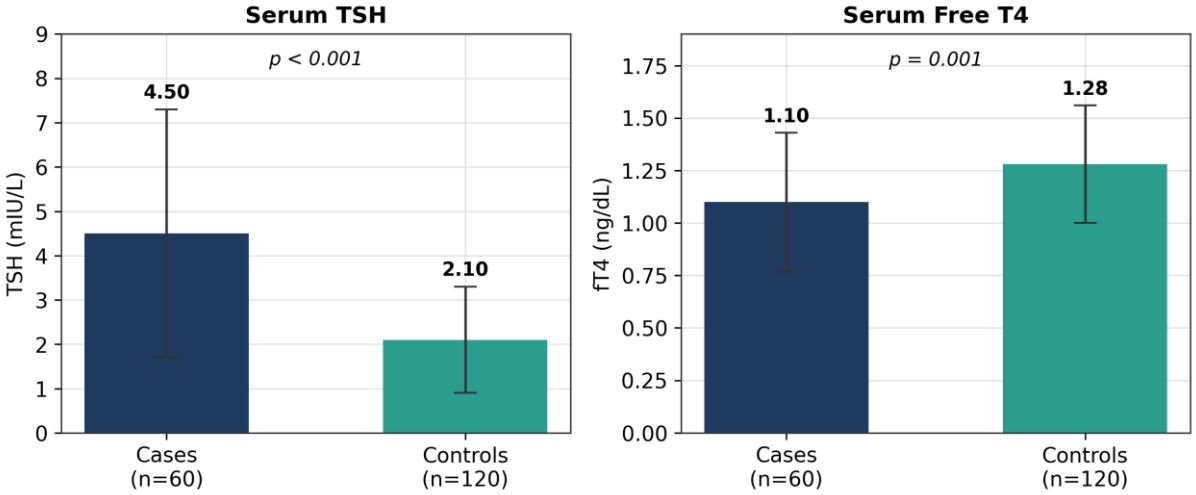

Figure 2. Comparison of thyroid function test profile between cases and controls (mean ± SD)

Table 3. Prevalence of subclinical hypothyroidism among cases and controls

Group	n with subclinical hypothyroidism	Prevalence (%)	p-value
Cases (n=60)	13	21.7	<0.001
Controls (n=120)	3	2.5	(χ^2=18.6)

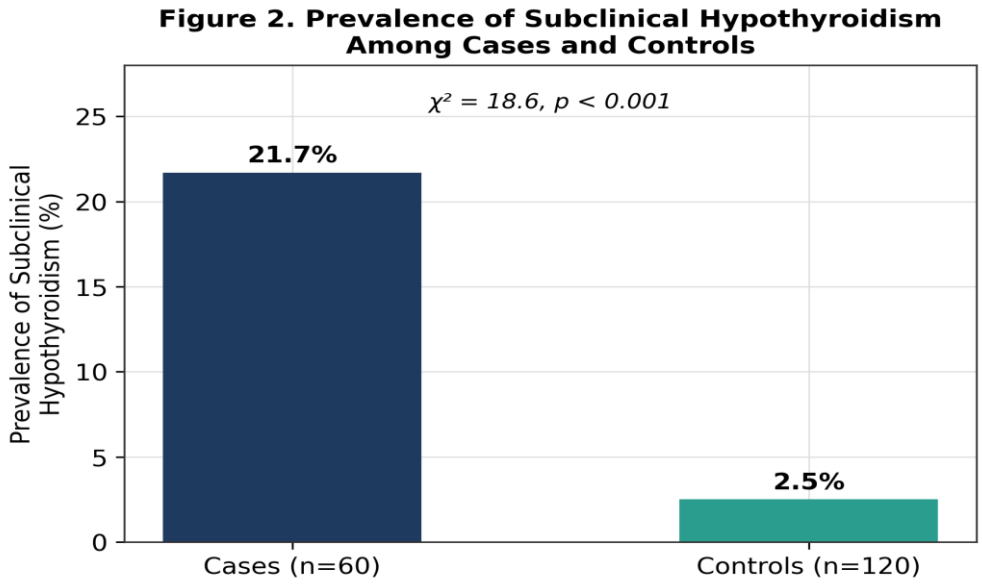

Figure 3. Prevalence of subclinical hypothyroidism among cases and controls

Among cases, seizure onset was most frequent between 6–10 years (40.0%), and generalized tonic–clonic seizures (GTCS) were the commonest type (46.7%), followed by focal seizures (33.3%). Nearly half the children (46.7%) had received AED therapy for 24–59 months, and 90.0% were adherent to treatment; seizure recurrence occurred in 33.3% despite this. Valproate was the most frequently prescribed AED (36.7%), followed by carbamazepine (23.3%) and levetiracetam (20.0%); polytherapy was used in 10.0% and had the longest mean duration of exposure (68±40 months). EEG abnormalities (63.3%) were considerably more frequent than MRI abnormalities (20.0%).

Thyroid function varied significantly across AED regimens (one-way ANOVA, p=0.003 for TSH). Mean TSH was highest with polytherapy (6.00±3.40 mIU/L) and valproate (5.10±2.90 mIU/L), and lowest with levetiracetam (2.30±1.10 mIU/L); mean fT4 showed the inverse pattern. Subclinical hypothyroidism was most prevalent with polytherapy (50.0%) and valproate (27.3%), and was not observed with levetiracetam (0.0%) (Table 4).

Table 4. AED-wise thyroid function and prevalence of subclinical hypothyroidism among cases

AED regimen	n	Mean TSH ± SD (mIU/L)	Mean fT4 ± SD (ng/dL)	Subclinical hypothyroidism n (%)
Valproate (VPA)	22	5.10 ± 2.90	1.05 ± 0.32	6 (27.3)
Carbamazepine (CBZ)	14	4.60 ± 2.30	1.08 ± 0.30	3 (21.4)
Levetiracetam (LEV)	12	2.30 ± 1.10	1.30 ± 0.25	0 (0.0)
Other AED regimen	6	4.20 ± 1.80	1.12 ± 0.28	1 (16.7)
Polytherapy (≥2 drugs)	6	6.00 ± 3.40	0.98 ± 0.35	3 (50.0)

One-way ANOVA across AED regimens, overall p=0.003.

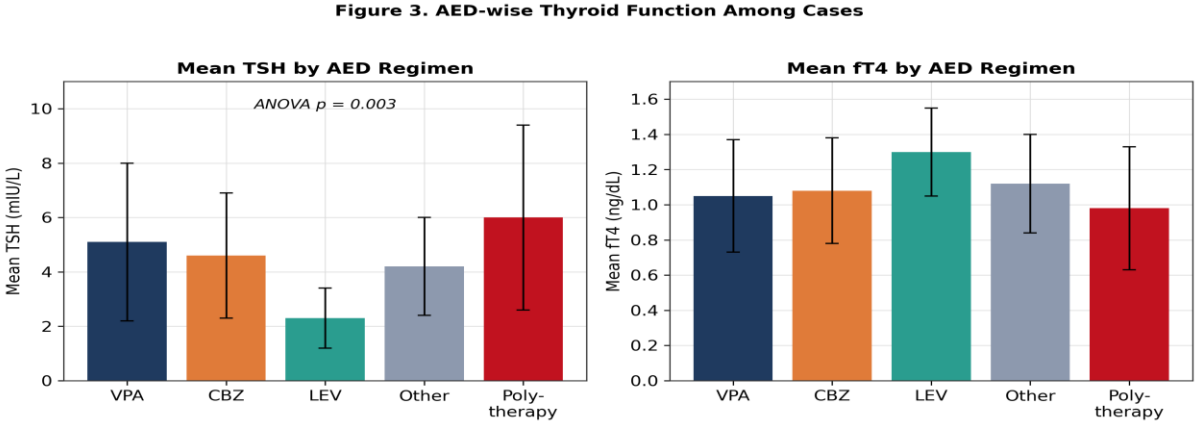

Figure 4. AED-wise thyroid function (mean TSH and mean fT4) among cases

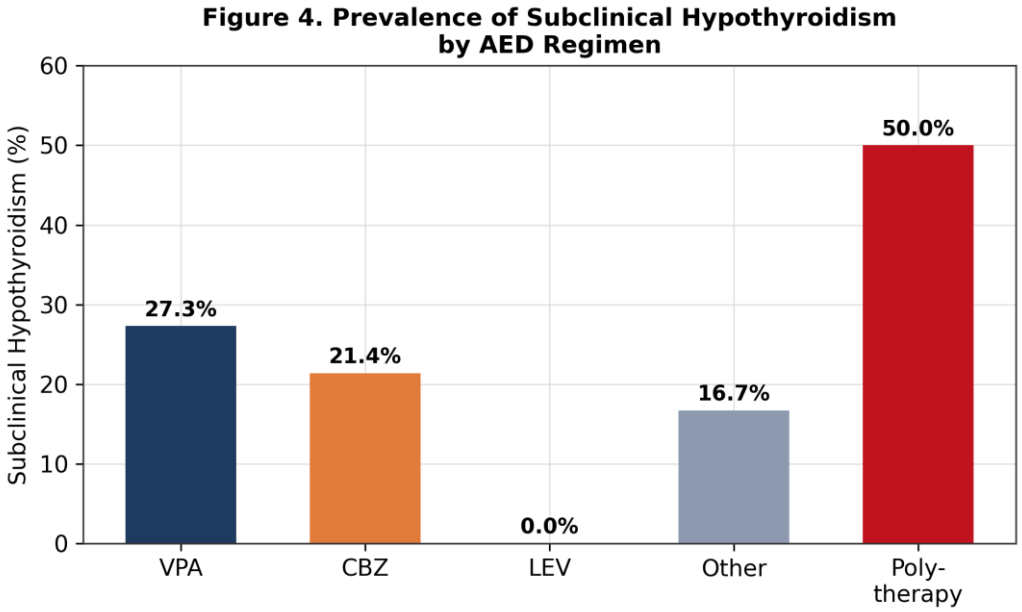

Figure 5. Prevalence of subclinical hypothyroidism by AED regimen

A clear dose–response relationship was observed between AED dose category and raised TSH: 15.0% in the low-dose group, 29.2% in the medium-dose group, and 50.0% in the high-dose group (one-way ANOVA, p=0.01). Seizure recurrence was significantly more frequent among children with subclinical hypothyroidism than euthyroid children (61.5% vs 25.5%; p=0.01), and the median number of seizure episodes was also higher in the subclinical hypothyroid group (2 [IQR 1–3] vs 1 [IQR 0–2]; Mann–Whitney U test, p=0.02).

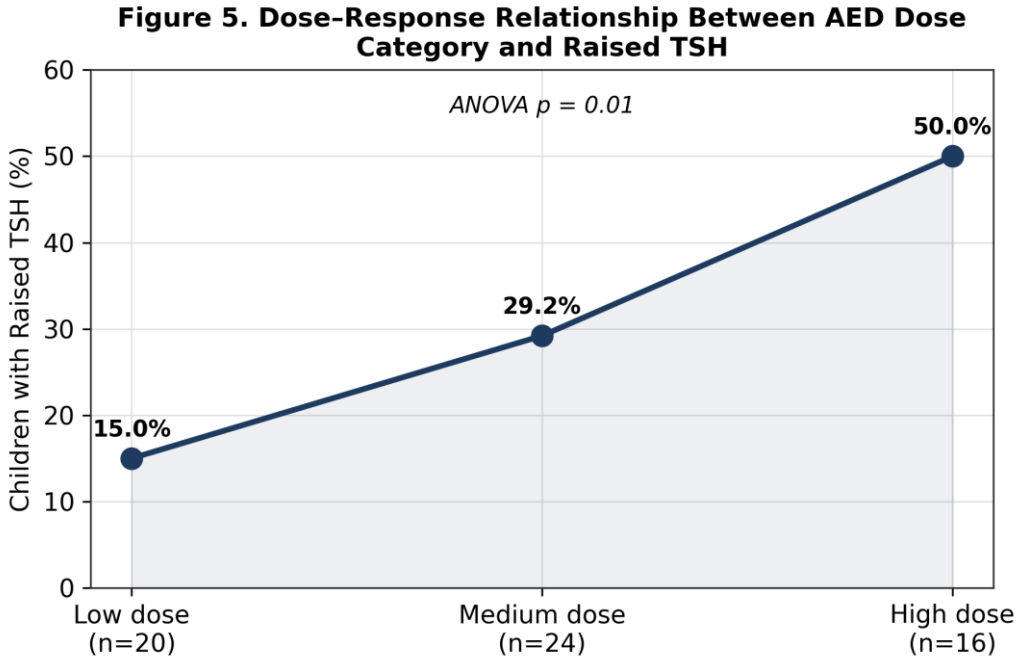

Figure 6. Dose–response relationship between AED dose category and raised TSH

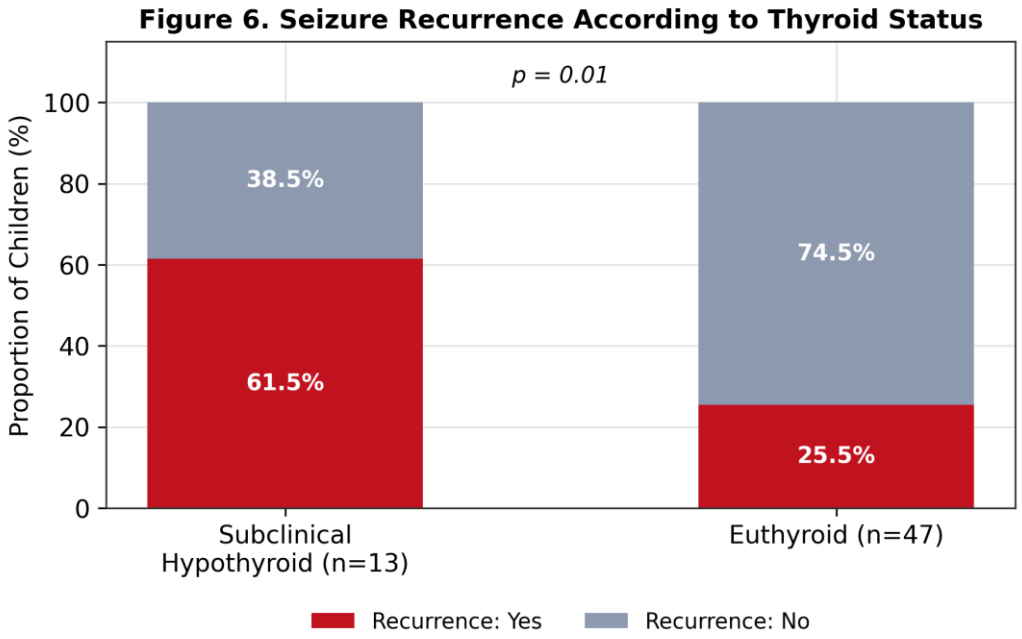

Figure 7. Seizure recurrence according to thyroid status

On univariate logistic regression, longer duration of AED therapy (OR 1.15/year, 95% CI 1.02–1.30, p=0.02), high-dose therapy (OR 2.40, 95% CI 1.10–5.20, p=0.03), valproate use (OR 3.20, 95% CI 1.45–7.20, p=0.005) and polytherapy (OR 2.80, 95% CI 1.05–7.40, p=0.03) were significantly associated with subclinical hypothyroidism; age, sex and age of seizure onset were not significant predictors (Table 5).

Table 5. Univariate logistic regression for predictors of subclinical hypothyroidism

Predictor	OR (95% CI)	p-value
Age (per year)	1.03 (0.96–1.11)	0.40
Male sex	1.10 (0.45–2.70)	0.85
Age of onset (per year)	0.95 (0.84–1.07)	0.39
Duration of AED therapy (per year)	1.15 (1.02–1.30)	0.02
AED high dose (vs low)	2.40 (1.10–5.20)	0.03
Valproate use	3.20 (1.45–7.20)	0.005
Carbamazepine use	2.10 (0.80–5.40)	0.12
Levetiracetam use	0.45 (0.10–1.95)	0.29
Polytherapy	2.80 (1.05–7.40)	0.03

On multivariate analysis, valproate use (adjusted OR 2.90, 95% CI 1.24–7.00, p=0.015), duration of AED therapy (adjusted OR 1.13/year, 95% CI 1.01–1.27, p=0.035) and high-dose therapy (adjusted OR 2.05, 95% CI 1.01–4.20, p=0.046) remained independent predictors of subclinical hypothyroidism; polytherapy (adjusted OR 2.40, p=0.06) and carbamazepine use (adjusted OR 1.45, p=0.45) were not independently significant (Table 6).

Table 6. Multivariate logistic regression for predictors of subclinical hypothyroidism

Predictor	Adjusted OR (95% CI)	p-value
Valproate use	2.90 (1.24–7.00)	0.015
Duration of AED therapy (per year)	1.13 (1.01–1.27)	0.035
AED high dose	2.05 (1.01–4.20)	0.046
Polytherapy	2.40 (0.95–6.20)	0.06
Carbamazepine use	1.45 (0.55–3.80)	0.45

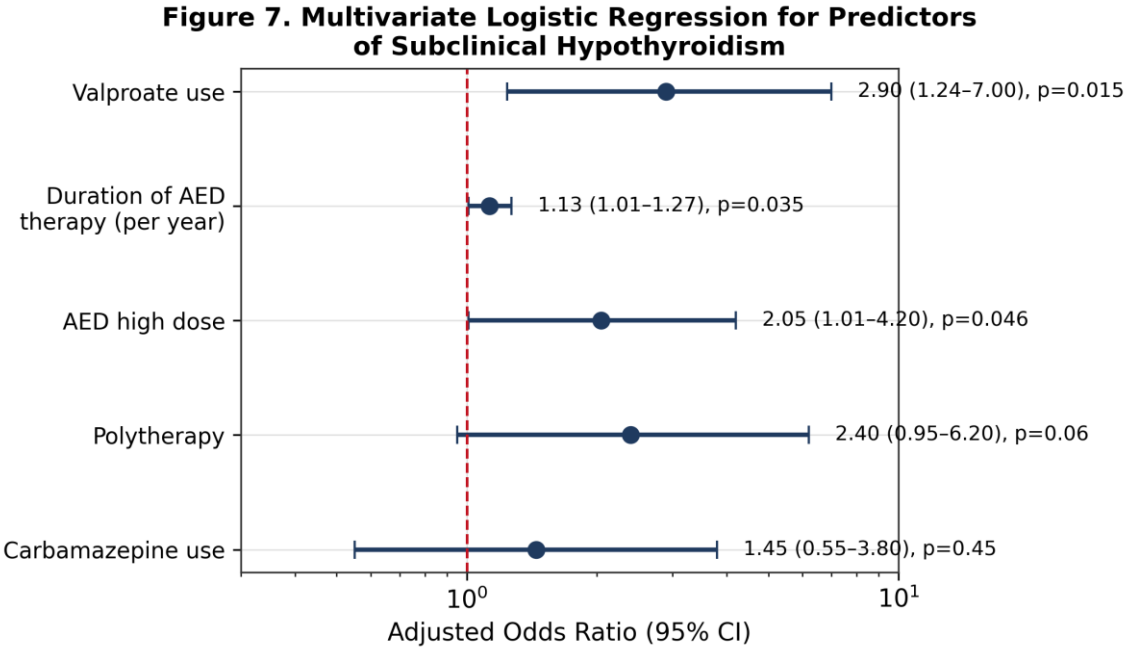

Figure 8. Forest plot: multivariate logistic regression for predictors of subclinical hypothyroidism

DISCUSSION

This case–control study demonstrates a significant alteration in thyroid function among children receiving long-term AED therapy, characterised by elevated TSH, reduced fT4, and a markedly higher prevalence of subclinical hypothyroidism compared with healthy controls (21.7% vs 2.5%). These findings are in agreement with Zhang et al., whose meta-analysis of 35 studies showed a consistent rise in TSH and fall in T4/fT4 among AED-treated patients, and with Elshorbagy et al., who reported elevated TSH and reduced fT4 specifically among children on conventional AEDs.[10,18] The prevalence of subclinical hypothyroidism in our cohort is comparable to that reported by Sarker et al. (nearly one-third of AED-treated children) and by Karatoprak et al. (16% among children on valproate).[19,20]

Drug-specific analysis showed that valproate and polytherapy carried the greatest risk of thyroid dysfunction, while levetiracetam was not associated with any case of subclinical hypothyroidism. This pattern mirrors previous reports describing valproate-induced elevation of TSH through effects on hormone synthesis and metabolism, in contrast to the favourable endocrine profile of levetiracetam.[20,21] A significant dose–response relationship between AED dose and raised TSH further supports a cumulative-exposure-related mechanism, consistent with the findings of Sepahi et al. and Rafik et al. regarding endocrine effects of valproate.[21,22]

An important and clinically relevant observation in our study was the association between subclinical hypothyroidism and seizure recurrence: children with subclinical hypothyroidism had more than twice the recurrence rate of euthyroid children (61.5% vs 25.5%) and a higher seizure-episode burden. This finding is biologically plausible given the essential roles of thyroid hormones in brain maturation and neurological function.[12,13,23,24] However, the present case–control study cannot establish the direction of causality; prospective longitudinal studies are required before thyroid dysfunction can be considered a determinant of seizure recurrence.

On multivariate analysis, valproate use, longer duration of therapy, and high-dose treatment were independent predictors of subclinical hypothyroidism, findings that closely parallel those of Karatoprak et al. and Mohankumar et al., who similarly identified valproate as an important drug-related determinant of thyroid dysfunction in children with epilepsy.[20,25] EEG abnormalities were more frequent than MRI abnormalities in our cohort (63.3% vs 20.0%).

Our study has certain limitations. The case–control design precludes assessment of pre-treatment thyroid status and therefore cannot establish a temporal or causal relationship between AED exposure and thyroid dysfunction. The study was conducted at a single tertiary care centre with a relatively modest sample size, which may limit generalisability. Thyroid autoantibodies, iodine status, and detailed nutritional profiling were not assessed and could be potential confounders. Finally, cross-sectional assessment does not capture longitudinal evolution of thyroid function with drug dose escalation or changing adherence over time.

CONCLUSION

Children on long-term antiepileptic drug therapy, particularly those receiving valproate, high drug doses, or polytherapy, show a significantly higher burden of subclinical hypothyroidism than healthy peers, and this thyroid dysfunction is

associated with a higher rate of seizure recurrence. These findings support incorporating periodic thyroid function testing (TSH and fT4) into the routine follow-up of children on AED therapy exceeding one year, with closer surveillance for those on valproate, high-dose, or combination regimens. Levetiracetam appears to have a relatively favourable thyroid safety profile and may be preferred in susceptible children where clinically appropriate. Larger, prospective, multicentric studies with longitudinal thyroid assessment are needed to confirm causality and to guide evidence-based monitoring protocols.

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