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Original Research Article

Comparative study of sodium valproate monotherapy versus antiepileptic polytherapy on thyroid profile and serum magnesium levels in children with epilepsy

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ABSTRACT

Background: Prolonged antiepileptic drug (AED) therapy may alter thyroid homeostasis and serum magnesium levels, both of which are critical for neurodevelopment and growth in children.
Methods: This cross-sectional study enrolled 168 children aged 3–15 years with epilepsy on AED therapy for ≥6 months. Participants were categorised as group A (sodium valproate monotherapy, n=119), group A1 (other monotherapy, n=25), group B1 (polytherapy including valproate, n=17), and group B2 (polytherapy excluding valproate, n=7). Serum free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and magnesium were measured using standard methods. The chi-square test and student's t-test were applied; $p<0.05$ was considered significant.
Results: Subclinical hypothyroidism (SCH) was identified in 10 children (5.9%), with the highest prevalence in group B1 (11.8%); the inter-group difference was not statistically significant (p=0.767). Mean FT4 was 1.30±0.25 ng/dL and mean FT3 was 3.20±0.54 pg/ml. Hypomagnesemia was present in 14 children (8.3%), with a statistically significant duration-dependent increase from 3.7% at <1 year to 20.9% at >2 years (p=0.005). No significant inter-group difference in hypomagnesemia was observed (p=0.924).
Conclusions: Polytherapy was associated with a numerically higher, but statistically non-significant, rate of SCH. Hypomagnesemia showed a significant cumulative, duration-dependent increase regardless of drug regimen. Routine monitoring of thyroid function and serum magnesium is recommended for all children on long-term AED therapy, particularly those on polytherapy or treated for more than two years.

Keywords: Antiepileptic drugs, Epilepsy in children, Hypomagnesemia, Sodium valproate, Subclinical hypothyroidism, Thyroid function

INTRODUCTION

Epilepsy is one of the most prevalent chronic neurological disorders of childhood, affecting an estimated 50 million individuals worldwide, with a community-based prevalence in India of 5-10 per 1,000 population.[1,2] Children constitute a substantial proportion of those affected, and suboptimal management may impair cognition, behaviour, and psychosocial development.[3,4]

Sodium valproate is the most widely prescribed broad-spectrum AED in paediatrics, achieving seizure control in 60-70% of newly diagnosed children.[5,6] For refractory cases, polytherapy-the concurrent use of two or more AEDs-is employed, with attendant pharmacokinetic interactions and cumulative systemic toxicity.[7]

Thyroid hormones are essential for neuronal differentiation, myelination, and skeletal growth. Even subtle disruption of the hypothalamic-pituitary-thyroid (HPT) axis may impair cognition and linear growth.[8] Long-term AED therapy has been implicated in thyroid dysfunction through enhanced hepatic catabolism of thyroxine, interference with thyroxine-binding globulin, and GABA-mediated modulation of TSH secretion.[9,10]

Magnesium, the second most abundant intracellular cation, functions as a physiological NMDA-receptor antagonist that modulates seizure threshold. Chronic AED exposure may deplete magnesium through reduced intestinal absorption and increased renal excretion; the resultant hypomagnesemia may lower seizure threshold, creating an adverse cycle.[11,12-24]

Comparative data on thyroid function and magnesium homeostasis in children receiving sodium valproate monotherapy versus polytherapy remain limited, particularly from South Asian populations.[13] This study aimed to (i) evaluate serum FT3, FT4, TSH, and magnesium levels in these groups; (ii) compare biochemical profiles between treatment groups; and (iii) determine the prevalence of thyroid dysfunction and hypomagnesemia and their association with duration of AED therapy.

METHODS

Study design

This was a hospital-based, cross-sectional, observational study conducted in the outpatient and inpatient Department of Paediatrics, Maharani Laxmi Bai (MLB) Medical College and Hospital, Jhansi, Uttar Pradesh, India, from May 2025 to April 2026.

Participants

Children aged 3-15 years fulfilling the 2017 ILAE classification of the Epilepsies criteria (n=168).[1,25] Exclusion criteria were pre-existing or family history of thyroid disease, drug non-compliance, progressive neurological disorders, congenital malformations, global developmental delay, protein-energy malnutrition, chronic liver or renal disease, or concurrent use of medications known to influence thyroid function.

Group classification

Group A: sodium valproate monotherapy (n=119, 70.8%); Group A1: other AED monotherapy (n=25, 14.9%); Group B1: polytherapy including valproate (n=17, 10.1%); Group B2: polytherapy excluding valproate (n=7, 4.2%). Groups A and A1 were combined to form the monotherapy arm, and Groups B1 and B2 were combined to form the polytherapy arm for comparative analysis.

Sample size

The sample size was calculated using a two-proportion z-test (p1=0.24, p2=0.44; 95% confidence interval; 80% power), yielding a minimum requirement of 84 participants per comparison group.

Laboratory investigations

A 5-mL fasting venous blood sample was collected between 08:00 and 10:00 h. Serum FT3 (reference range 2.0-4.4 pg/ml), FT4 (reference range 0.93-1.70 ng/dl), and TSH (reference range 0.27-4.2 µIU/ml) were estimated by chemiluminescence immunoassay. Serum magnesium (reference range 1.6-2.7 mg/dl) was measured by the Calmagite-EGTA colorimetric method. SCH was defined as elevated TSH with normal FT4; hypomagnesemia was defined as serum magnesium <1.6 mg/dL.

Statistical analysis

Continuous variables are expressed as mean±SD. The chi-square test was used to compare categorical variables, and Student's independent t-test was used to compare continuous variables, using SPSS software. P<0.05 was considered statistically significant.

Ethics

Ethical approval was obtained from the Institutional Ethics Committee, MLB Medical College, Jhansi (No: MLBMC/IEC/2025/XXX). Written informed consent was obtained from all parents/legal guardians prior to enrolment.

RESULTS

Demographic profile

Of the 168 enrolled children, 106 (63.1%) were male and 62 (36.9%) were female (M:F ratio 1.71:1). The majority were aged 3-<7 years (72, 42.9%), followed by 7-<11 years (51, 30.4%) and 11-15 years (45, 26.8%). Most were outpatients (163, 97.0%). Generalised tonic-clonic seizures (GTCS) predominated (153, 91.1%), followed by focal seizures (13, 7.7%) (Table 1).

Treatment groups and thyroid status

Sodium valproate monotherapy (Group A) accounted for the majority of participants (119, 70.8%). SCH was identified in 10 children (5.9%); prevalence was highest in group B1 (11.8%), though the inter-group difference was not statistically significant (p=0.767). No overt hypothyroidism or hyperthyroidism was detected, and the remaining 158 children (94.1%) were euthyroid. Hypomagnesemia was present in 14 children (8.3%); the inter-group difference was not statistically significant (p=0.924) (Table 2).

Serum FT3 and FT4

Mean FT4 was 1.30±0.25 ng/dl (median 1.22; range 0.40-2.62) and mean FT3 was 3.20±0.54 pg/ml (median 3.35; range 1.23-4.60).

Median values for both parameters were within the reference range; the minimum values observed indicated a small subset of children with reduced levels (Table 3).

Hypomagnesemia and duration of therapy

A statistically significant, duration-dependent increase in hypomagnesemia was observed: prevalence rose from 3.7% in children on AED therapy for <1 year to 5.4% at 1-2 years and 20.9% at >2 years (p=0.005) (Table 4). Thyroid abnormalities also showed a trend toward greater prevalence with longer duration of therapy, although this did not reach statistical significance.

Table 1: Demographic and clinical profile of study participants.

Variables	N	Percentages (%)
Total	168	100
Gender		
Male	106	63.1
Female	62	36.9
Age (in years)		
3-<7	72	42.9
7-<11	51	30.4
11-15	45	26.8
GTCS	153	91.1
Focal seizures	13	7.7

Table 2: Treatment group distribution with prevalence of SCH and hypomagnesemia.

Groups	Regimen	N (%)	SCH, N (%)	Hypo-Mg, N (%)	P value
A	VPA monotherapy	119 (70.8)	7 (5.9)	10 (8.4)	-
A1	Other monotherapy	25 (14.9)	1 (4.0)	2 (8.0)	-
B1	Polytherapy+VPA	17 (10.1)	2 (11.8)	2 (11.8)	-
B2	Polytherapy-VPA	7 (4.2)	0 (0)	0 (0)	-
Total	-	168 (100)	10 (5.9)	14 (8.3)	SCH=0.767; Mg=0.924

Table 3: Distribution of serum FT3 and FT4 levels.

Parameters	FT4 (ng/dl)	FT3 (pg/ml)
Mean±SD	1.30±0.25	3.20±0.54
Median	1.22	3.35
Range	0.40-2.62	1.23-4.60
Reference range	0.93-1.70	2.0-4.4

Table 4: Thyroid abnormality and hypomagnesemia by duration of AED therapy.

Durations	N	Thyroid abnormality, N (%)	Hypomagnesemia, N (%)	P value (Mg)
<1 year	85	3 (3.7)	3 (3.5)	-
1-2 years	38	3 (8.1)	2 (5.3)	-
>2 years	45	4 (9.3)	9 (20.0)	0.005
Total	168	10 (5.9)	14 (8.3)	-

DISCUSSION

The overall prevalence of SCH (5.9%) in this cohort is consistent with earlier paediatric studies. Eiris-Puñal et al found SCH in children on long-term valproate or carbamazepine, while Yılmaz et al confirmed that enzyme-inducing AEDs exert greater thyroid suppression than non-inducers.[9,14] Enzyme-inducers accelerate hepatic catabolism of thyroxine via CYP450 induction, reducing FT4 with compensatory TSH elevation.[16] Sodium valproate, a non-inducer, may cause mild TSH elevation through GABA-mediated HPT-axis stimulation or interference with thyroid hormone transport.[8,9] Additive suppression in polytherapy-reflected in the numerically higher SCH rate in group B1-is mechanistically plausible but did not reach significance here, likely owing to the small polytherapy subgroup and inter-individual variability. Ahmad et al and Dhodi et al similarly found

no significant thyroid dysfunction with valproate monotherapy.[17,18] de Vries et al observed subclinical biochemical changes in adolescent girls on valproate without overt hypothyroidism.[23]

The statistically significant, duration-dependent association between AED therapy and hypomagnesemia (p=0.005) constitutes the principal finding of this study, with prevalence rising more than fivefold between the <1 year and >2-year groups. These results align with Verrotti et al who attributed this to additive drug effects on intestinal absorption and renal tubular reabsorption, and with Attilakos et al who noted that combination therapy amplifies the mild magnesium reduction seen with valproate alone.[19,15] Abdullahi et al and Shahnawaz et al further demonstrated a correlation between hypomagnesemia and increased seizure frequency, while Chen et al documented seizure resolution following magnesium repletion.[20-22] Abdelmalik et al confirmed magnesium as an effective adjunct in drug-resistant seizures.[24] Suparman et al similarly documented an association between low magnesium and poor seizure control.[29] As a physiological NMDA-receptor antagonist, magnesium deficiency may reduce inhibitory tone and lower seizure threshold, reinforcing the clinical importance of proactive monitoring.

This study provides contemporaneous, centre-specific data from a tertiary paediatric institution in North India using standardised biochemical assays. Limitations include the cross-sectional design, which precludes causal inference; the small polytherapy subgroup, particularly group B2; and potential residual confounding from nutritional status, seizure severity, and drug-combination heterogeneity. Larger, multicentre, longitudinal studies are warranted.

Baseline and six-monthly monitoring of thyroid function (FT3, FT4 and TSH) and serum magnesium is recommended for all children on long-term AED therapy. Intensified surveillance is particularly important when polytherapy is initiated or when therapy extends beyond two years. Monotherapy should remain the preferred strategy; timely detection of subclinical abnormalities enables intervention before clinically significant consequences on neurodevelopment, growth, or seizure control arise.

CONCLUSION

In this study of 168 children with epilepsy, no statistically significant difference in the prevalence of SCH and hypomagnesemia was observed between sodium valproate monotherapy and antiepileptic polytherapy, although rates were numerically higher in the polytherapy arm. Hypomagnesemia demonstrated a statistically significant, duration-dependent increase with long-term AED exposure, rising from 3.7% at <1 year to 20.9% beyond two years. The monitoring of thyroid function and serum magnesium can be considered for all children on long-term AED therapy, with intensified surveillance for those on polytherapy or treated for more than two years.

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Ethical approval: The study was approved by the Institutional Ethics Committee MLB Medical College, Jhansi (No: MLBMC/IEC/2025/XXX)

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