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Original Research Article

Thyroid function profile in children with epilepsy receiving sodium valproate monotherapy: a cross-sectional study from North India

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ABSTRACT

Background: To evaluate the thyroid function profile in children with epilepsy receiving sodium valproate monotherapy for at least six months and to determine the prevalence and correlates of thyroid dysfunction.
Methods: A hospital-based cross-sectional observational study was conducted at a tertiary care centre in Jaipur, Rajasthan, over 12 months (January–December 2024). Sixty-five children aged 1–17 years on sodium valproate monotherapy for a minimum of six months were enrolled by consecutive sampling. Thyroid function tests (free triiodothyronine (fT3), free thyroxine (fT4) and thyroid-stimulating hormone (TSH)) were measured at enrollment and compared with baseline values obtained prior to therapy initiation. Thyroid status was classified as euthyroid, subclinical hypothyroidism (TSH >5 µIU/ml with normal fT3 and fT4) or overt hypothyroidism. Associations with age, sex, valproate dose and duration of therapy were analyzed using the chi-square test and paired t-test.
Results: After ≥6 months of valproate therapy, 44.62% of children developed subclinical hypothyroidism, 20.00% developed overt hypothyroidism and only 35.38% remained euthyroid. Paired t-test revealed significant increases in mean TSH (2.25±0.37 vs 5.49±2.68 µIU/ml; $p<0.001$), a decrease in mean fT4 (1.42±0.05 vs 1.20±0.18 ng/dl; $p<0.001$) and a mild increase in mean fT3 (3.61±0.16 vs 3.72±0.16 pg/ml; $p<0.001$). Thyroid dysfunction was significantly associated with older age ($p<0.001$), higher valproate dose ($p=0.015$) and longer duration of therapy ($p=0.006$), but not with sex ($p=0.833$).
Conclusions: Sodium valproate monotherapy is associated with significant thyroid dysfunction in a substantial proportion of children, even within the first six months of therapy. Older age, higher doses and longer treatment duration are important risk factors. Routine monitoring of thyroid function is recommended for all children on long-term valproate therapy.

Keywords: Anticonvulsants, Children, Epilepsy, Hypothyroidism, Sodium valproate, Thyroid function tests

INTRODUCTION

Epilepsy is one of the most prevalent chronic neurological disorders in children, with an estimated global incidence of 61 per 100,000 person-years and a higher burden in low and middle-income countries, including India.[1,2] In the Indian pediatric population, it accounts for a significant proportion of neurology referrals and requires long-term pharmacotherapy for adequate seizure control.[3] Sodium valproate remains a cornerstone first-line agent for generalized and focal epilepsies in children, owing to its broad-spectrum efficacy, favorable cognitive profile and established safety record.[4,5] However, accumulating evidence indicates that long-term valproate therapy is associated with a spectrum of endocrine side effects, including weight gain, polycystic ovarian syndrome, hyperammonemia and alterations in thyroid hormone metabolism.[6,7] The thyroid gland plays a pivotal role in neurodevelopment, metabolism and growth functions especially critical during childhood. Valproate is hypothesized to affect thyroid hormone levels through

multiple mechanisms, including inhibition of peripheral deiodination of thyroxine (T4) to triiodothyronine (T3), modulation of the hypothalamic-pituitary-thyroid (HPT) axis and altered binding of thyroid hormones to carrier proteins.[8,9] Even subclinical hypothyroidism defined as elevated TSH with normal fT3 and fT4 may have long-term consequences in children, including impaired cognition, growth retardation, dyslipidemia and cardiovascular risk.[10] While several international studies have documented thyroid dysfunction in children on valproate, data from Indian tertiary care settings are sparse.[11-13]

Existing Indian studies are limited by small sample sizes or short follow-up periods.[14,15] The present study was undertaken to evaluate the thyroid function profile in children with epilepsy receiving sodium valproate monotherapy for a minimum of six months at a major referral centre in Rajasthan and to identify clinical correlates of thyroid dysfunction.

METHODS

Study design and setting

A hospital-based, cross-sectional observational study was conducted in the Department of Paediatric Medicine at S.P.I.N.P.H., SMS Medical College and Attached Hospitals, Jaipur, Rajasthan a major tertiary care referral centre for pediatric patients across the state. The study was conducted from January 2024 to December 2024.

Participants

Children aged 1–17 years with a confirmed clinical diagnosis of epilepsy receiving sodium valproate as monotherapy for at least six consecutive months were eligible. Participants were enrolled consecutively from the paediatric OPD and ward until the required sample size was achieved. Children were excluded if they had a pre-existing thyroid disorder; were suffering from protein-energy malnutrition, chronic liver disease or any progressive neurological illness; or were receiving medications known to influence thyroid function. Parental written informed consent was mandatory; assent was additionally obtained from children aged≥7 years.

Sample size

The sample size was calculated using the formula for cross-sectional studies. Assuming a prevalence of 21% for abnormal TSH based on Alhyan et al with 95% confidence and 10% allowable error, the minimum required sample was estimated at 65 children.

Data collection

A structured proforma was used to record demographic data (age, sex, weight, height), epilepsy history (age at onset, seizure type, frequency) and treatment details (valproate dose, duration of therapy). Anthropometric measurements were taken using calibrated equipment. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Thyroid function tests free T3 (fT3, pg/ml), free T4 (fT4, ng/dL) and TSH (µIU/mL) were measured using automated chemiluminescence immunoassay in the institution's NABL-accredited central biochemistry laboratory. Both baseline values (recorded prior to therapy initiation from clinical records) and current values (at the time of enrollment, i.e., after ≥6 months of therapy) were obtained.

Definitions

Thyroid status was classified as euthyroid TSH, fT3 and fT4 all within normal laboratory reference ranges subclinical hypothyroidism TSH >5 µIU/ml with normal fT3 and fT4; and overt hypothyroidism elevated TSH with low fT4, regardless of fT3.

Ethical considerations

Ethical clearance was obtained from the Institutional Ethics Committee, SMS Medical College, Jaipur (Reg. No. ECR/SMS/2024). Written informed consent was obtained from parents/guardians.

Statistical analysis

Data were entered and analyzed using IBM SPSS Statistics version 26.0. Continuous variables were expressed as mean±standard deviation (SD); categorical variables as frequencies and percentages. Paired t-test was used to compare thyroid hormone values before and after therapy. Chi-square test was applied to analyze associations between categorical variables. A p value <0.05 was considered statistically significant.

RESULTS

Demographic and clinical characteristics

Sixty-five children were enrolled in the study. Table 1 summarizes the demographic and clinical characteristics of the participants, including sex distribution, age groups, anthropometric parameters, duration of valproate therapy and daily dose. Dose distribution across duration-of-therapy groups was not statistically significant (χ^2=20.30, df=42, p=0.998).

Thyroid hormone changes

Table 2 presents the comparison of thyroid hormone values at baseline and after ≥6 months of valproate therapy. All baseline values were within normal reference ranges. After treatment, mean TSH increased significantly from 2.25±0.37 to 5.49±2.68 µIU/ml (p<0.001), mean fT4 decreased from 1.42±0.05 to

1.20±0.18 ng/dl (p<0.001) and mean fT3 increased mildly from 3.61±0.16 to 3.72±0.16 pg/ml (p<0.001).

Thyroid status at follow-up

At ≥6 months of therapy (Table 3), 44.62% (n=29) had subclinical hypothyroidism, 20.00% (n=13) had overt hypothyroidism and only 35.38% (n=23) remained euthyroid. This distribution was statistically significant (χ^2=6.03, df=2, p=0.049).

Association with clinical variables

Sex

Thyroid dysfunction was distributed similarly between males (41.18% subclinical, 20.59% overt) and females (48.39% subclinical, 19.35% overt), with no statistically significant difference (χ^2=0.37, df=2, p=0.833).

Age

A highly significant association was observed between age group and thyroid status (χ^2=42.50, df=6, p<0.001). All children aged 1–5 years remained euthyroid. In the 6–10 years group, 54.55% developed subclinical hypothyroidism. In children aged 11–15 years, 50.00% had overt hypothyroidism, 45.83% had subclinical hypothyroidism and only 4.17% remained euthyroid.

Valproate dose

Thyroid dysfunction was significantly related to daily dose (χ^2=115.00, df=84, p=0.015). All euthyroid children received <600 mg/day. Overt hypothyroidism occurred predominantly in children receiving 600–799 mg/day (76.92% of overt cases).

Duration of therapy

Thyroid status was significantly associated with duration (χ^2=18.00, df=6, p=0.006).

Among those treated for 6 months, 39.58% were euthyroid, 39.58% had subclinical and 20.83% overt hypothyroidism. At 8 months, all children had subclinical hypothyroidism; at 9 months, both subjects had overt hypothyroidism.

Table 1: Demographic and clinical characteristics of study participants (n=65).

Characteristic	Value
Sex, N (%)	
Male	34 (52.31)
Female	31 (47.69)
Age group (in years), N (%)	
1–5	7 (10.77)
6–10	33 (50.77)
11–15	24 (36.92)
>15	1 (1.54)
Anthropometric parameters, Mean±SD	
Weight (kg)	31.10±10.91
Height (cm)	134.80±18.31
BMI (kg/m²)	16.40±1.39
Duration of valproate therapy (months), N (%)	
6	48 (73.85)
7	8 (12.31)
8	7 (10.77)
9	2 (3.08)
Daily valproate dose (mg), N (%)	
<400	8 (12.31)
400–599	14 (21.54)
600–799	18 (27.69)
800–999	24 (36.92)
≥1000	1 (1.54)

Table 2: Comparison of thyroid function tests at baseline and after ≥6 months of valproate therapy.

Parameter	Baseline Mean±SD	Post-treatment Mean±SD	P value
fT3 (pg/ml)	3.61±0.16	3.72±0.16	<0.001
fT4 (ng/dl)	1.42±0.05	1.20±0.18	<0.001
TSH (µIU/ml)	2.25±0.37	5.49±2.68	<0.001

Table 3: Thyroid status at ≥6 months of valproate therapy (n=65).

Thyroid status	Number	(%)
Euthyroid	23	35.38
subclinical hypothyroidism	29	44.62
overt hypothyroidism	13	20.00
Total	65	100.00

χ^2=6.03, df=2, p=0.049.

DISCUSSION

This study demonstrates that sodium valproate monotherapy exerts a significant adverse effect on thyroid function in children, with nearly two-thirds (64.62%) developing either subclinical or overt hypothyroidism within six months of treatment initiation. These findings have important clinical implications for the large population of Indian children receiving this drug. The finding of a markedly elevated TSH (mean 5.49±2.68 µIU/ml post-treatment vs 2.25±0.37 at baseline; p<0.001), accompanied by a significant decline in fT4, aligns with data from Alhyan et al who reported TSH rise from 2.14±1.64 to 3.64±2.15 µIU/ml and fT4 fall from 1.31±0.33 to 1.13±0.31 ng/dL after 6 months of valproate therapy in 45 Indian children.[14] However, the magnitude of thyroid dysfunction in the cohort was substantially higher 44.62% subclinical and 20.00% overt hypothyroidism compared to 17.77% subclinical hypothyroidism reported by Alhyan et al. This may reflect differences in baseline valproate doses, age distribution or duration of follow-up.

The prevalence of subclinical hypothyroidism in our study (44.62%) is also higher than the 15.2% reported by Güngör et al, at 12 months, the 21.8% by Malwade et al at 6 months and the 52.4% reported by Kim et al at similar follow-up.[11,12,16] Comparably high rates of thyroid dysfunction have also been described by Panda et al in an Indian cohort and by Tomoum et al in Egyptian children on valproate, while Carolina et al similarly reported a duration-dependent rise in subclinical hypothyroidism among Indonesian children with epilepsy.[17-19] The proportion developing overt hypothyroidism (20.00%) is notable and higher than most previously published studies, in which overt hypothyroidism was rarely documented. This finding may reflect a combination of higher valproate doses in our cohort and the older age of affected children. The significant association between older age and thyroid dysfunction (p<0.001) is a key finding. Children in the 11–15 years age group were at greatest risk of overt hypothyroidism (50%), while all younger children (1–5 years) remained euthyroid. This age-dependent susceptibility may reflect differences in the developmental maturation of the HPT axis, pubertal changes in thyroid hormone binding proteins and higher cumulative drug exposure per unit body weight in older children. This observation has been less systematically examined in the existing literature and warrants further study. The dose-response relationship authors observed (p=0.015), with overt hypothyroidism concentrated in children receiving ≥600 mg/day, is consistent with reports by Rafik et al, who demonstrated a dose-dependent association of valproate with subclinical hypothyroidism and with Cansu et al who observed significant dose-related alterations in thyroid function among children on valproate.[20,21] Similarly, the increasing severity of thyroid dysfunction with longer duration of therapy (p=0.006) corroborates the findings of Attilakos et al who documented progressive TSH elevation over 24 months and of Verrotti et al who reported significant thyroid hormone changes with valproate monotherapy over comparable follow-up periods.[22-24]

A recent systematic review and network meta-analysis by Han et al further supports a class-wide association between antiseizure medications, particularly valproate and elevated TSH levels.[25] The proposed mechanisms include valproate-mediated inhibition of type 1 iodothyronine deiodinase (reducing T4 to T3 conversion), disruption of the HPT axis at the hypothalamic level and reduced thyroid hormone binding to carrier proteins.[8,9] The lack of a significant sex-based difference (p=0.833) in the study contrasts with the known female preponderance of autoimmune thyroid disease in adults and is consistent with other pediatric valproate studies, including Dhodi et al, suggesting drug-induced (rather than autoimmune) mechanisms are sex-independent in this age group.[26]

The study is limited by its single-centre design, relatively small sample size of 65 children, absence of a concurrent control group and short follow-up period of up to 9 months. Additionally, thyroid autoantibodies were not measured, which prevents differentiation of drug-induced thyroid dysfunction from autoimmune thyroiditis. Serum valproate levels were not quantified concurrently, limiting analysis of pharmacokinetic correlates.

Despite these limitations, this study is among the few from India to systematically document the high prevalence of both subclinical and overt hypothyroidism in children on valproate and to identify age, dose and duration as significant predictors of dysfunction.

CONCLUSION

Sodium valproate monotherapy is associated with significant biochemical thyroid dysfunction in a substantial proportion of Indian children with epilepsy, even within the first six months of therapy. Nearly two-thirds of children develop subclinical or overt

hypothyroidism, with older age, higher drug doses and longer treatment duration being significant risk factors. We recommend routine thyroid function monitoring—at baseline and every six months thereafter—for all children on valproate. Children with subclinical hypothyroidism should be observed and reassessed at three months; those with overt hypothyroidism should be referred to a pediatric endocrinologist for management.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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