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CLINICAL & BASIC RESEARCH

A Prospective Cohort Study on the Effect of Antiseizure Medications on Thyroid Function in Children Aged 6 Months to 12 Years with Epilepsy

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abstract: ***Objectives:*** This study aimed to explore the effect of antiseizure medications (ASM) on thyroid function in children with epilepsy. ***Methods:*** A prospective study involving children between 6 months and 12 years of age with new-onset seizures who took ASM within 2 months was conducted in the Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India, between August 2019 to March 2022. Thyroid function tests—free T3, free T4 and thyroid stimulating hormone (TSH)—were done at baseline and after completing 3 months by competitive immunoassay using direct chemiluminescent technology. The primary outcome was the proportion of patients diagnosed with thyroid dysfunction (subclinical or overt hypothyroidism). ***Results:*** In total, 126 patients were enrolled. Median (interquartile range [IQR]) age and follow-up months were 10 years (7–12) and 6 months (4–8), respectively. Most patients (n = 103, 81.7%) had generalised seizures, while the remaining (n = 23, 18.3%) had focal seizures. There was a significant difference noted in median (IQR) TSH (micro-IU/mL) at baseline (2.08 [1.41–3.31]) and follow-up (2.56 [1.65–4.14]; $P \leq 0.001$). Thyroid dysfunction (subclinical hypothyroidism) was noted in 7 patients. Among the 7 children with subclinical hypothyroidism, 6 (4.8%) were on sodium valproate either as monotherapy (n = 3, 2.4%) or polytherapy (n = 3, 2.4%), while the remaining child was on phenytoin. No difference was noted between the monotherapy and polytherapy groups (4% versus 11.5%; $P = 0.15$). ***Conclusion:*** The incidence of thyroid dysfunction (subclinical hypothyroidism) was 5.6% in children taking ASM with a median follow-up period of 6 months. A longer follow-up period and larger sample size study is warranted in the future.

Keywords: Child; Antiseizure Drugs; Thyroid Function; Epilepsy.

Advances in Knowledge

- *This study found that 5.6% of patients with epilepsy who were on antiseizure medication had thyroid dysfunction.*

Applications to Patient Care

- *Based on the results of this study, evaluation of thyroid hormone profile is recommended for epileptic children on long-term antiseizure medication to prevent complications due to thyroid dysfunction.*

Seizures in children is a common neurological disorder that requires a long duration of antiseizure medications (ASMs) intake. ASM is often associated with metabolic complications, including its impact on endocrine (thyroid) homeostasis, as the growth and development of children can be affected by abnormal thyroid functions. Thyroid hormones (THs) are essential for normal central nervous system development and physiological function, including Gamma-aminobutyric acid (GABAergic) and glutamatergic transmission.[1] Previous studies have demonstrated the negative impact of ASMs on the endocrine system of children and adults, including their thyroid function.[2] The ASM, namely, valproate, carbamazepine, phenobarbital phenytoin and oxcarbazepine, are known to decrease THs and increase thyroid stimulating hormone (TSH) to varying degrees.[3] Thyroid dysfunction (overt or subclinical hypothyroidism) may have varying levels of impact on development, ranging from irreversible neurological and motor deficits in younger children to subtle cognitive impairment in older children and bone health.[1,4,5] However, there is a dearth of studies reporting the incidence of ASM-induced thyroid dysfunction (overt or subclinical hypothyroidism) in lower-middle-income countries where routine thyroid function tests (TFTs) are not performed in children taking ASM for a seizure disorder, necessitating further evaluation.[6] Hence, the present study aimed to examine the effects of ASM on thyroid function in children with epilepsy and its risk factors.

Methods

This prospective cohort study was carried out in the Jawaharlal Institute of Postgraduate Medical

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Education and Research (JIPMER), Puducherry, India, between August 2019 to March 2022. Children aged 6 months to 12 years diagnosed with new-onset epilepsy who started ASM within 2 months of therapy were enrolled in the study. The following patients were excluded: (1) those with other chronic diseases (e.g. diabetes mellitus or chronic kidney diseases); (2) those with known thyroid dysfunction; (3) those who had received any drugs in the 6 months before treatment that could affect TFT (e.g. amiodarone or lithium); and (4) those with severe malnutrition. Moreover, the baseline demographic data, anthropometry, seizure types and their related investigations, details about the ASM and related complication(s) were collected in a standard case-reported proforma. Thyroid peroxidase (TPO) antibody test, antithyroglobulin antibody (anti-Tg antibody) test and thyroid ultrasound (USG) were carried out for patients with thyroid dysfunction. Epilepsy was defined and classified using the International League Against Epilepsy guidelines and World Health Organization standards were used for nutritional assessment.[7,8]

TFTs (i.e. free T3, free T4 and TSH) were performed at enrolment and after a minimum follow-up period of 3 months. The THs assay was done by competitive immunoassay using direct chemiluminescent technology ADVIA Centaur CP Immunoassay System (Siemens Healthineers, Erlangen, Germany). The intra-assay coefficient of variation was <2.3% for TSH, 2.3% for free T4 and 7.8% for free T3. The inter-assay coefficient of variation was <2.9% for TSH, 2.5% for free T4 and 12.3% for free T3. Overt hypothyroidism was defined as low free T4 (reference range: 0.89–1.76 ng/mL) and elevated serum TSH above the upper limit of the reference range (>5.5 mIU/L). Furthermore, subclinical hypothyroidism was defined as an elevation in serum TSH above the upper limit of the reference range with a normal serum-free T4 test. Based on the degree of serum TSH elevation, subclinical hypothyroidism was defined as mild (TSH 4.5–10 mIU/L) or severe (TSH >10 mIU/L).[9] The reference range cut-off was used as per international biochemistry standards. The primary outcome was the incidence of thyroid dysfunction (overt or subclinical hypothyroidism). The secondary outcomes were risk factor(s) and effects of mono- versus polytherapy.

The reported incidence of thyroid dysfunction in children with a seizure disorder receiving ASM ranged from 0% to 28%.[10] With the assumption that the expected proportion (π) of children with a seizure disorder who were receiving ASM to have thyroid dysfunction is 30% with a two-sided 95% confidence interval (1-α) and 5% degree of precision (i.e., distance from proportion to limit, ω), the sample size needed for this study was 355, including 10% attrition (nQuery advisor and nTerim 4.0; Dotmatics, Boston, USA). Due to the COVID-19 pandemic, only 126 eligible patients were enrolled.

The normality of data was checked with the Kolmogorov–Smirnov Z test. The incidence was expressed as a proportion with a 95% confidence interval (CI). The Chi-squared or Fischer's exact test (if the cell number <5) was used to compare the categorical variables. An independent t-test was used to assess the continuous independent variables meeting normality; otherwise, the Mann-Whitney U test was used. The dependent groups deviating from normality were compared using the Wilcoxon signed-rank test. The multivariate (binary logistic regression) analysis of statistically significant variables in univariate analysis ($P \leq 0.10$) and clinically relevant (age, gender, number of ASM follow-up) was done to determine predictors of thyroid dysfunction. Furthermore, the relative risk and odds ratio (unadjusted and adjusted; with 95% CI) were calculated. All tests were two-tailed and a P value of <0.05 was considered statistically significant. Data were analysed using the Statistical Package for the Social Sciences (SPSS), Version 20.0 (IBM Corporation, Armonk, New York, USA) and Epi Info, Version 7.0.9.7 (Centers for Disease Control and Prevention, Georgia, USA).

Institutional Ethics Committee for observational studies, JIPMER (JIP/IEC/2019/0129) approved the study and written informed consent was obtained from parents/legally acceptable representatives. This study was also registered at the Clinical Trial Registry – India (CTRI/2019/07/020441).

Results

Among the 168 eligible patients, 126 completed the minimum follow-up with TFT and were included in the analysis [Figure 1]. Most patients (n = 103, 81.7%) had a generalised seizure, while the remaining (n = 13, 18.3%) had a focal seizure. Among generalised seizures, the tonic-clonic was the most common (n = 92/103), and in focal seizures, the clonic seizure was the most common (n = 20/23). The median (IQR) time to enrolment after the onset of seizure was four days (1–13). There were 6 different ASMs in monotherapy and 13 combinations (8 in 2 ASMs and 5 in 3 ASMs) in polytherapy. The most common polytherapy (2 ASM) was valproate-levetiracetam (n = 5/19), followed by phenytoin-phenobarbitone (n = 4/19), phenytoin-valproate (n = 3/19), phenytoin-levetiracetam (n = 2/19) and phenytoin-topiramate (n = 2/19). The most common polytherapy (3 ASM) was phenytoin-phenobarbitone-levetiracetam (n

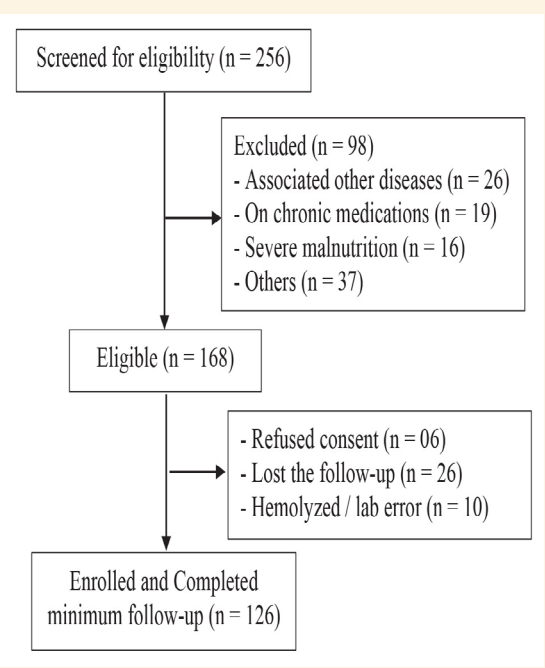

Figure 1: Flow diagram showing the screening and enrolment process in the study.

= 3/7). Overall, 80% (n = 102/126) of the patients received traditional/first-generation ASM, 8.7% (n = 11/126) received newer ASM and 10.3% (n = 13/126) received combined first-generation and newer ASM [Table 1].

The incidence of thyroid dysfunction was noted in 7 patients (n = 7/126, 5.6%, 95% CI: 2.26–11.11%). All the thyroid dysfunction patients (n = 7 /126) were classified as subclinical hypothyroidism and mild type of subclinical hypothyroidism. The median (IQR) follow-up was 6 months (4–8). Half of the patient's follow-up period was within the range of 3–6 months. A significant difference was noted in the median TSH (P <0.001) and free T4 (P = 0.022) level during the follow-up as compared to the enrolment level, with no significant difference noted in the free T3 (P = 0.071) level. Moreover, there was a significant difference in the median TSH level in thyroid dysfunction patients compared to normal thyroid function patients (P <0.001), although no difference was noted in free T4 and free T3 levels [Table 2]. Furthermore, no difference was noted between the monotherapy and polytherapy groups (4% versus 11.5%, relative risk = 0.35, 95% CI: 0.08–1.45; P = 0.15). During the follow-up TFT, polytherapy was associated with significantly lower median (IQR) free T4 (ng/dL) as compared to monotherapy (0.90, 0.81–1.03 versus 1.01, 0.92–1.21; P = 0.013) and no difference in TSH (micro-IU/mL) (2.39, 1.35–4.34 versus 2.56, 1.71–3.97; P = 0.606) and free T3 (pg/mL) (3.54, 3.29–3.93 versus 3.64, 3.21–3.99; P = 0.505). Among the 7 children with subclinical hypothyroidism, 6 (4.8%) were on sodium valproate either as monotherapy (3/2.4%) or polytherapy (3/2.4%), while the remaining child was on phenytoin [Table 3]. All 3 cases of polytherapy received lamotrigine and levetiracetam along with sodium valproate.

Anti-TPO antibodies, anti-Tg antibodies and thyroid USG were found to be normal in patients with subclinical hypothyroidism (n = 7/126). Additionally,

Table 1: Baseline characteristics of enrolled patients (N = 126)

Characteristic	n (%)
Median age in years (IQR)	5 (2–9)
Age category in years	
≥6 months–1 year	15 (12)
>1–6	49 (39)
>6–12	62 (49)
Gender	
Male	73 (58)
Female	53 (42)
Body mass index, z score	-0.47 (-1.78–0.29)
Malnutrition	30 (23.8)
Type of seizure	
Generalised	103 (81.7)
Focal	23 (18.3)
Aetiology	
Infections	22 (17.5)
Structural	14 (11.1)
Epileptic syndrome	14 (11.1)
Immune	2 (1.6)
Metabolic	1 (0.8)
Unknown	73 (57.9)
Abnormal MRI	28/71 (39.4)
Abnormal EEG	19/60 (31.7)
ASM group	
Monotherapy	100 (79.4)
Valproate	47
Phenytoin	34
Levetiracetam	9
Phenobarbitone	6
Carbamazepine	3
Lamotrigine	1
Polytherapy	26 (20.6)
2 ASM	19
3 ASM	7

IQR = interquartile range; MRI = magnetic resonance imaging; EEG = electroencephalogram; ASM = antiseizure medication

Table 2: Follow-up, thyroid function test and outcome of the study (N = 126)

Variable	n (%) or Median (IQR)			*P* value
	Total	Thyroid Function Status		
		Normal (n = 119)	Abnormal (n = 7)	
Follow-up period in months				0.84
≥3–6	55 (43.7)	53 (44.5)	2 (28.6)	
>6–9	45 (35.7)	42 (35.3)	3 (42.8)	
>9–12	25 (19.8)	23 (19.3)	2 (28.6)	
>12–15	1 (0.8)	1 (0.9)	0 (0)	
TFT at follow-up				
TSH in micro-IU/L	-	2.54 (1.62–3.62)	7.49 (5.73–8.11)	<0.001
Free T4 in ng/dL	-	0.99 (0.88–1.17)	0.87 (0.86–0.97)	0.141
Free T3 in pg/mL	-	3.63 (3.21–3.97)	3.73 (3.38–3.95)	0.651
Thyroid function test		**At enrolment**	**At follow-up**	
TSH in micro-IU/mL	-	2.08 (1.41–3.31)	2.56 (1.65–4.12)	<0.001
Free T4 in ng/dL	-	0.96 (0.83–1.07)	0.98 (0.87–1.17)	0.022
Free T3 in pg/mL	-	3.79 (3.17–4.30)	3.63 (3.25–3.98)	0.071

TFT = thyroid function test, TSH = thyroid stimulating hormone, IQR = interquartile range

the mean drug level was observed to be 90.17 mg/L for sodium valproate and 0.1 mg/L for phenytoin. None of the patients with subclinical hypothyroidism had clinical manifestations and required thyroxine replacement therapy. Besides, there was no difference in nutritional status during the follow-up compared to the enrolment (malnutrition 23.8% versus 18.3%). The multivariate binary logistic regression analysis identified no predictive risk factors for thyroid dysfunction [Table 4].

Discussion

The current study involved 126 children in the age range of 6 months to 12 years with newly diagnosed epilepsy who were found to have subclinical hypothyroidism of 5.6% during the median follow-up period of 6 months. All patients with subclinical hypothyroidism were considered mild cases, anti-TPO and a thyroid USG were normal. No predictive risk factors were identified. The baseline characteristics of the current study were similar to previous studies.[10,11] This study enrolled a higher proportion of patients with generalised (81.7%) and focal seizure (18.3%), similar to the study by Güngör *et al*., which reported 80% and 17%, respectively.[12] The majority of the patients had unknown aetiology (57.9%), which is consistent with the findings of Farghaly *et al*. (59.4%) but differs from those of Sokka *et al*. who reported an incidence of 35%.[13,14] This could be due to the diverse study participants in the present study. In the current study, half of the participants underwent electroencephalogram (EEG) and magnetic resonance imaging (MRI). Among them, one-third had abnormal results, in contrast to the study by Roy and Pandit which reported that 65.5% and 39.4% of the patients had abnormal EEG and MRI, respectively.[15] This lower proportion of investigations is due to the restrictions related to the COVID-19 pandemic.

In the present study, a higher proportion of patients received monotherapy (79.4%), while the remaining received polytherapy (20.6%). The recent systematic review and network meta-analysis by Han *et al*. reported that most studies focused on monotherapy on TFT, particularly on single TFT parameters.[16] They further reported that out of the 35 eligible studies, 34 focused on TSH, 32 on free T4, 32 on Free T3 and 25 on children and adolescents, with the remaining 8 on newer ASM. In contrast, the present study focused on TSH, free T4 and free T3. Notably, it found no difference between polytherapy and monotherapy in thyroid dysfunction. However, polytherapy was associated with a significantly lower free T4 and elevated levels of TSH and free T3, but the difference was not statistically significant. This variation could be due to a smaller sample size and shorter follow-up period. The most common ASM associated with thyroid dysfunction observed was sodium valproate (monotherapy as well as polytherapy), followed by phenytoin in the monotherapy, which is similar to the results of a recent systematic review by Han *et al*.[16] That study also reported that lamotrigine had no significant impact on TFT. In the present study, one patient only received lamotrigine in the monotherapy group; hence, drug effects could not be studied.

Table 3: Effect of antiseizure medication on thyroid function test during follow-up as compared to baseline (N = 126)

Name of ASM	Median (IQR)		*P* value*
	Baseline TFT	Follow-up TFT	
Valproate (n = 47)			
TSH in micro-IU/L	2.08 (1.45–3.27)	2.74 (1.65–3.82)	0.033
Free T4 in ng/dL	0.96 (0.83–1.12)	0.98 (0.87–1.24)	0.165
Free T3 in pg/mL	4.01 (3.23–4.41)	3.47 (2.84–3.95)	0.002
Phenytoin (n = 34)			
TSH in micro-IU/L	2.09 (1.51–3.36)	2.69 (1.70–4.59)	0.010
Free T4 in ng/dL	0.96 (0.85–1.04)	1.07 (0.96–1.24)	0.002
Free T3 in pg/mL	3.58 (3.09–4.22)	3.70 (3.24–4.18)	0.694
Levetiracetam (n = 9)			
TSH in micro-IU/L	2.01 (1.34–3.14)	2.48 (1.58–4.06)	0.678
Free T4 in ng/dL	0.97 (0.89–1.24)	0.93 (0.87–1.00)	0.173
Free T3 in pg/mL	3.64 (3.00 – 3.96)	3.89 (3.60 – 4.14)	0.173
Phenobarbitone (n = 6)			
TSH in micro-IU/L	2.47 (1.30–2.65)	1.86 (1.44–2.75)	0.345
Free T4 in ng/dL	1.03 (0.91–1.39)	1.03 (0.97–1.20)	0.344
Free T3 in pg/mL	3.94 (3.38–4.63)	3.63 (2.52–4.16)	0.249
Carbamazepine (n = 3)			
TSH in micro-IU/L	4.19 (3.89–4.96)	2.50 (2.13–2.96)	0.109
Free T4 in ng/dL	0.90 (0.88–1.09)	0.86 (0.82–1.02)	0.655
Free T3 in pg/mL	4.20 (3.98–4.84)	4.48 (4.43–4.56)	1.000

ASM = antiseizure medications; IQR = interquartile range; TFT = thyroid function test; TSH = thyroid stimulating hormone.

**P value calculated using the Wilcoxon signed ranks test.*

In the present study, thyroid dysfunction was found to be subclinical hypothyroidism (5.6%), and none of these patients reported having any apparent clinical presentation of hypothyroidism. All 7 children with thyroid dysfunction had TSH elevation, suggesting no evidence of pituitary dysfunction.

Furthermore, all patients had normal anti-TPO antibody levels and thyroid USG. A similar finding was reported by Svalheim *et al*., where these changes did not affect growth and puberty development.[17,18] The current study did not find any difference in the growth during follow-up. Although the manifestation of clinically significant hypothyroidism rarely occurs due to ASM, once it develops, it affects the multisystem.[6] Hence, TFT should be monitored in children taking long-term ASM. The effects of age, gender and development in the thyroid hormone synthesis and reference range need to be considered while interpreting the TFT in addition to the effects of ASM, duration of therapy and number of ASM.[19] This study did not find any independent predictive risk factors for thyroid dysfunction, and the model explains only 15.8% due to the limitation in the sample size and number of outcome events.

The study's strength was focused on three parameters of TFT and involved diverse semiology

Table 4: Multivariate logistic regression analysis for predictors of thyroid dysfunction

Variables*	Unadjusted odds ratio	95% confidence interval	*P* value	Adjusted odds ratio	95% confidence interval	*P* value
Age	6.75	0.79–57.79	0.081	6.98	0.78–62.28	0.082
Gender	1.04	0.22–4.83	0.965	1.31	0.25–6.78	0.748
Mono- versus polytherapy	3.13	0.66–4.96	0.153	3.30	0.65–16.76	0.150
Follow-up duration	2.00	0.37–10.76	0.416	1.96	0.34–11.39	0.454

**Variables entered in the model are age (<6-ref / ≥6 years), gender (male/female-ref), antiseizure drug (mono-ref/polytherapy) and follow-up duration (<6-ref / ≥6 months). Hosmer and Lemeshow goodness of fit model P = 0.176. The overall percentage of the model is 94.4% and r^2 = 0.158.*

of seizures and reasonable representation of different age groups. In contrast, the study's limitations were its small sample size, short follow-up period, inability to check drug levels for all patients due to restrictions imposed by the COVID-19 pandemic and the consequent limited availability of resources. Therefore, future studies involving larger sample sizes and more extended follow-up periods need to be considered.

Conclusion

The study concludes that the incidence of subclinical hypothyroidism was 5.6% among children taking ASM during a 6-month median follow-up and 4.8% were on sodium valproate either as monotherapy or polytherapy. No significant difference was noted between monotherapy and polytherapy.

AUTHORS' CONTRIBUTION

TS and RR contributed to the concept, literature review and critical review of the manuscript. SM contributed to the data collection, literature review and drafting the manuscript. HN contributed to protocol writing, supervision of biological sample analysis and manuscript writing. TS, RR, SM and CGDK were involved in the management of patients. TS, RR, CGDK and HN performed study supervision. All authors approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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