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EFFECT OF ANTIEPILEPTIC DRUGS ON THYROID HORMONE LEVELS IN CHILDREN WITH EPILEPSY

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Abstract

Background: In this study, we wanted to evaluate the effect of antiepileptic drugs on thyroid hormone function in children with epilepsy, study and compare the thyroid status i.e. T3, T4, TSH of patients on various antiepileptics (phenytoin, carbamazepine, valproate etc.), assess the clinical findings in relation to their thyroid profile, and compare the effect of various AEDs on growth (i.e. weight and height) of subjects.

Methods: This was a hospital-based cross-sectional observational study conducted among 60 children between the age group of 2 months and 12 years with epilepsy, on antiepileptic drugs from 2019-2021, after obtaining clearance from institutional ethics committee and written informed consent from the study participants.

Results: Among the total 20 subjects on phenytoin, 45% of subjects showed low serum T3 levels, 10% of the subjects showed low T4 levels, 5% showed low TSH and 5% showed high TSH levels. Statistically significant result was seen (p=0.021) for phenytoin altering serum T4 levels. Among those on phenytoin, 10% showed low T4 levels and those without phenytoin had higher T4 levels. This finding was statistically significant that phenytoin lowers T4 levels. The drug carbamazepine had no effect on serum T3 levels, 50% subjects (n=1) showed high serum T4 levels. 50% cases showed low TSH levels, this result was statistically significant. Statistically significant results were obtained with occurrence of constipation with levetiracetam and carbamezepine, for levetiracetam (19%) and carbamazepine (50%), respectively. Lethargy as symptom of hypothyroidism was seen more commonly with phenobarbitone (20%), then followed by phenytoin (10%) and levetiracetam (9.5%). Among the 24 children with weight less than 3rd percentile, 58.3% (n=14) had deranged thyroid hormone levels. Among children with height less than 3rd percentile, 44.8% (n=13) had altered thyroid hormones levels. Analysis showed that these findings were statistically significant.

Conclusion: Routine investigation of thyroid hormone levels in children on AEDs can help us detect subclinical hypothyroidism. Ethnicity and genetic based follow-up studies on a larger population sample are essential.

Keywords: Antiepileptic Drugs, Thyroid Hormone, Children, Epilepsy.

INTRODUCTION

Long-term administration of antiepileptic drugs (AEDs) is associated with various side effects. Alteration of endocrine function, in particular, alteration in thyroid hormone levels, is well known.[1] Thyroid hormone homeostasis at the level of biosynthesis, release, transport, metabolism, and excretion of thyroid hormones may be altered. The differential effect of antiepileptic drugs on thyroid hormones may reflect different subcellular actions at the hypothalamic-pituitary thyroid axis, thyroglobulin binding, and hepatic deiodination processes.[2]

Thyroid hormones play an important role in the regulation of metabolism in many tissues. Therefore, disturbance of thyroid hormones has major implications for the growth and development of children.[3] The impact of AEDs on thyroid function is well-known in adults. However, disturbance of thyroid function in children receiving AEDs is a matter of controversy, and there is limited information in this context.[4] Among drug therapies for epileptic children, most epileptologists preferred traditional AEDs, such as valproate, carbamazepine, and phenobarbital in the past. However, recently, major attention has been paid to newer drugs, such as levetiracetam, which are used as monotherapy or as add-on therapy for children with epilepsy. Previous studies have reported the effects of traditional AEDs on thyroid hormones in children. However, there is limited evidence regarding the effects of newer AEDs such as levetiracetam.[5]

Although, various studies have been performed to investigate the interactions between various antiepileptic drugs and thyroid hormone levels in adults, only few studies have been performed in children. While some studies have reported no change in the level of thyroid hormones among children with epilepsy receiving AEDs,[6,7] others indicated significant alterations in the level of thyroid hormones.[8,9]

AIMS AND OBJECTIVES

Aim

- To estimate the effect of antiepileptic drugs on thyroid hormone function in children with epilepsy

Objectives

Primary Objective

- To study and compare the thyroid status i.e T3, T4, TSH of patients on various antiepileptics (phenytoin, carbamazepine, valproate and levetiracetam).
- To assess the clinical findings in relation to their thyroid profile.

Secondary Objective

- To compare the effect of various AEDs on growth (i.e weight and height) of subjects.

METHODS

This was a hospital-based cross-sectional observational study conducted among 60 children between the age group of 2 months and 12 years with epilepsy, on antiepileptic drugs from 2019-2021, after obtaining clearance from institutional ethics committee and written informed consent from the study participants.

Inclusion Criteria

- Children (2mo - 12 yrs.)
- Cases of epilepsy
- No history of using any other drug that may affect thyroid gland function and
- No history of endocrine, cardiovascular, neurometabolic or other chronic diseases

Exclusion Criteria

- Patients above 12 years.
- Patients with previously diagnosed thyroid disorder.
- Those with other endocrinopathies, that might predispose to hypothyroidism.

- Those taking drugs that might affect thyroid function.

Measurement of Thyroid Levels

Plasma levels of TSH, T3, T4 hormones were measured. For this 2ml of blood was collected into test tubes through venepuncture under strict aseptic precautions. Serum is separated from cells by centrifugation. The sample is then subjected to CLIA (Electro-Chemiluminescent Immuno Assay) to measure serum T3, T4 and TSH in the Seiman Advia Centaur analyser of Gandhi Hospital, Central diagnostic laboratory. The following source was used to compare the results with the age appropriate mean serum T3, T4, TSH [Annexure 4].

The weight and height of children were recorded using standard instruments. The weight and height of children was plotted on the IAP growth charts and centile of the child noted. Children above 3rd centile for the age and sex where considered as normal [Annexure 5]. Stunting is defined as height less than 3rd centile for that age and sex as per IAP growth charts.

The effect of various AEDs on serum T3, T4 and TSH levels was studied and compared. Clinical sypmtoms and signs, if any, of thyroid dysfunction were studied. The effect of AEDs on growth of children in terms of weight and height were studied and compared.

Statistical Methods

Data was entered into Microsoft Excel (Windows 7; Version 2007) and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc., Chicago). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequencies and percentages for categorical variables were determined. Association between variables was analysed using chi-square test for categorical variables. Bar charts and Pie charts were used for visual representation of the analysed data. Level of significance was set at 0.05.

RESULTS

Effect of Phenytoin on T3, T4 and TSH

	Normal	**Low**	**High**	**P-Value**
T3				
Phenytoin	11 (55.0)	9 (45.0)		0.117
No Phenytoin	25 (75.8)	8 (24.2)		
T4				
Phenytoin	18 (90.0)	2 (10.0)		0.021*
No Phenytoin	26 (78.8)		7 (21.1)	
TSH				
Phenytoin	18 (90.0)	1 (5.0)	1 (5.0)	0.871
No Phenytoin	31 (93.9)	1 (3.0)	1 (3.0)	

Table 1: Effect of Phenytoin on T3, T4 and TSH (N=53)

Among the total 20 subjects on phenytoin, 45% of subjects showed low serum T3 levels, 10% of the subjects showed low T4 levels, 5% showed low TSH and 5% showed high TSH levels. Statistically significant result was seen (p=0.021) for phenytoin altering serum T4 levels. No statistically significant result was seen for effect of phenytoin on serum T3 and TSH.

Among those on Phenytoin, 10% showed low T4 levels and those without phenytoin had higher T4 levels. This finding was statistically significant that phenytoin lowers T4 levels.

5% of the subjects showed low TSH levels and 5% showed high TSH levels. Analysis showed no statistical difference.

Effect of Carbamazepine on T3, T4 and TSH

	Normal	Low	High	P Value
T3				
CBZ	2 (100.0)			0.322
No CBZ	34 (66.7)	17 (33.3)		
T4				
CBZ	1 (50.0)		1 (50.0)	0.289
No CBZ	43 (84.3)	2 (3.9)	6 (11.8)	
TSH				
CBZ	1 (50.0)	1 (50.0)		0.002*
No CBZ	48 (94.1)	1 (2.0)	2 (3.9)	

Table 2: Effect of Carbamazepine on T3, T4 and TSH (N=53)

The drug carbamazepine had no effect on serum T3 levels, 50% of the subjects (n=1) showed high serum T4 levels. 50% cases showed low TSH levels, this result was statistically significant (p=0.002).

Effect of Levetiracetam on T3, T4 and TSH

	Normal	Low	High	P Value
T3				
Levetiracetam	17 (81.0)	4 (19.0)		0.100
No Levetiracetam	19 (59.4)	13 (40.6)		
T4				
Levetiracetam	19 (90.5)	1 (4.8)	1 (4.8)	0.333
No Levetiracetam	25 (78.1)	1 (3.1)	6 (18.8)	
TSH				
Levetiracetam	18 (85.7)	2 (9.5)	1 (4.8)	0.191
No Levetiracetam	31 (96.9)		1 (3.1)	

Table 3: Effect of Levetiracetam on T3, T4 and TSH (N=53)

Among the 21 subjects on drug levetiracetam, 19% had low levels of T3, 4.8% had low levels of serum T4, 4.8% had high serum T4 levels, 9.5% had low levels of serum TSH and 4.8% showed high serum TSH level.In Levetiracetam treated group 9.5%subjects showed low TSH.

Effect of Sodium Valproate on T3, T4 and TSH

	Normal	Low	High	P Value
T3				
Valproate	17 (65.4)	9 (34.6)		0.697
No Valproate	19 (70.4)	8 (29.6)		
T4				
Valproate	20 (76.9)		6 (23.1)	0.052
.No Valproate	24 (88.9)	2 (7.4)	1 (3.7)	
TSH				
Valproate	24 (92.3)	1 (3.8)	1 (3.8)	0.999
No Valproate	25 (92.6)	1 (3.7)	1 (3.7)	

Table 4: Effect of Sodium Valproate on T3, T4 and TSH (N=53)

Among the 26 subjects on Sodium Valproate, 34.6% of them showed low levels of serum T3, 23.1% showed high levels of serum T4, 3.8% showed low serum TSH and 3.8% showed high levels of serum TSH. No statistically significant results were seen for the effect of sodium valproate on T3, T4, TSH. In this study valproate had no statistical difference on the serum levels of TSH.

Effect of Phenobarbitone on T3, T4 and TSH

	Normal	Low	High	P Value
T3				
Phenobarbitone	4 (80.0)	1 (20.0)		0.543
No Phenobarbitone	32 (66.7)	16 (33.3)		
T4				
Phenobarbitone	4 (80.0)	1 (20.0)		0.101
No Phenobarbitone	40 (83.3)	1 (2.1)	7 (14.6)	
TSH				
Phenobarbitone	5 (100.0)			0.798
No Phenobarbitone	44 (91.7)	2 (4.2)	2 (4.2)	

Table 5: Effect of Phenobarbitone on T3, T4 and TSH (N=53)

Among the total 5 subjects on drug Phenobarbitone, 20 % showed low serum T3 levels, 20% showed low serum T4 levels and no effect on serum TSH.
These values were not statistiscally significant.

Comparison of Symptoms of hypothyroidism with respect to AEDs

Drug	Symptoms			P-Value
	Lethargy	Constipation	None	
Phenytoin	2 (10.0)	3 (15.0)	17 (85.0)	0.164
No Phenytoin		1 (3.0)	32 (97.0)	
Levetiracetam	2 (9.5)	4 (19.0)	17 (81.0)	0.037*
No Levetiracetam			32 (100.0)	
Valproate	1 (3.8)	3 (11.5)	23 (88.5)	0.339
No Valproate	1 (3.7)	1 (3.7)	26 (96.3)	
Phenobarbitone	1 (20.0)	1 (20.0)	4 (80.0)	0.125
No Phenobarbitone	1 (2.1)	3 (6.2)	45 (93.8)	
Carbamazepine		1 (50.0)	1 (50.0)	0.002*
No CBZ	2 (3.9)	3 (5.9)	48 (94.1)	

Table 7: Comparison of Symptoms of hypothyroidism with respect to AEDs (N=53)

Constipation, as a symptom of hypothyroidism, was seen more commonly with carbamazepine (50%), followed by phenobarbitone (20%) and the levetiracetam (19%). Statistically significant results were obtained with occurrence of constipation with levetiracetam and carbamezepine. P=0.037 and P=0.002, for levetiracetam (19%) and carbamazepine (50%), respectively. Lethargy as a symptom of hypothyroidism was seen more commonly with phenobarbitone (20%), followed by phenytoin (10%) and levetiracetam (9.5%). None of the subjects showed signs of hypothyroidism.
In this study none of the cases had symptoms and signs of hyperthyroidism.

Effect of AED's on growth in relation to altered thyroid profile

	Total Number of subjects	Number of subjects with altered T3,T4,TSH	Percent
Weight <3rd centile	24	14	58.3
Height <3rd centile	29	13	44.8

Table 8: Distribution of subjects as per weight and height less than 3rd percentile and altered thyroid profile. (n=53)

Chi-square statistic: 4.736 p value = 0.029*

Among the 24 children with weight less than 3rd percentile, 58.3% (n=14) had deranged thyroid hormone levels and among children with height less than 3rd percentile, 44.8% (n=13) had altered

thyroid hormones levels. Analysis showed that these findings were statistically significant, p=0.029. Analysis showed that among children on Phenytoin therapy (n=20), 65% (n=13) subjects had weight less than 3rd centile (p value=0.025, significant).

	Weight		
	Normal	Less than 3rd centile	P-Value
Phenytoin	7(35.0)	13(65.0)	0.025
No Phenytoin	22(66.7)	11)33.3)	

Table 9: Effect of phenytoin on weight of subjects

DISCUSSION

This study investigated the effect of widely used antiepileptic drugs on thyroid hormone levels in children with epilepsy. In this study, a total of 53 children were enrolled between the age group of 2 months and 12 years. In our study, among the children, males were found to be predominant comprising of 62.3%. This finding is similar to the study conducted by Rahman U et al.[10] The most common type of epilepsy in this study was Generalised tonic-clonic seizures (56.6%), next common type was focal seizures (18.9%) followed by atypical febrile seizures (11.4%). This finding is also consistent with the study done by Rahman et al and Amani et al.

Among the various AEDs studied, Sodium Valproate was the most commonly used drug (49.1%), next common was levetiracetam (39.6%), followed by phenytoin (37.7%). As per a systematic review done by Egunsola et al. sodium valproate was the most frequently prescribed AED.[11]

In our study among the 53 cases, 67.9% of them had normal serum T3 values and 32.1% (n=17) of the subjects had low T3 levels compared to age. This finding is consistent with the study done by Yeo and Bates et al in 1978.[12] This finding is also in contrast to the study done by Rehman et al where only 3.78% subjects showed low T3 levels. Most common drugs associated with low serum T3 levels were Phenytoin (16.9%) and Valproate (16. 9%). The finding of low T3 levels with Valproate is consistent with the study done by Ali Cansu et al.[13]

Among the 53 subjects on AEDs, 83% (n=44) had normal serum T4. Serum T4 levels were altered in 17% (n=9) of the subjects. High T4 levels were seen in 13.2% (n=7) of subjects, of which 11.3%(n=6) were on Sodium Valproate monotherapy. Out of total 17%, 3.8% (n=2) of the subjects had low T4 levels, and both the children were on Phenytoin. Statistically significant result was seen (p=0.021) for phenytoin altering serum T4 levels.

In this study, serum TSH levels were altered in only 7.6% (n=4) of children of which 3.8% had low TSH and 3.8% had high TSH level. All the drugs under study had effect on TSH except phenobarbitone and. Only 1.9% (n=1) showed low TSH and was on phenytoin therapy. Effect of carbamazepine causing low TSH level was statistically significant.

Among the Sodium Valproate treated subjects, 34.6% of them showed low levels of serum T3, 23.1% showed high levels of serum T4, 3.8% showed low serum TSH and 3.8% showed high levels of serum TSH. No statistically significant results were seen for the effect of sodium valproate on T3, T4, TSH. This finding of our study is similar to a study by Dinesh et al which found that sodium valproate monotherapy did not alter serum levels of thyroid hormones.[14]

Among levetiracetam treated children (n=21), 19% had low levels of T3, 4.8% had low levels of serum T4, 4.8% had high serum T4 levels, 9.5% had low levels of serum TSH and 4.8% showed high serum TSH level. No statistical significance was seen for this finding. This finding is similar to a study done by Rahman U et al which suggests that Levetiracetam did not increase serum TSH or decrease T4 and T3.

Among the phenobarbitone treated group, 20% showed low serum T3 levels, 20% showed low serum T4 levels and no effect on serum TSH.

Carbamazepine showed statistical significant results for low TSH levels (p=0.002) and had no effect on serum T3 levels.

In this study, among the children who showed symptoms of hypothyroidism, constipation and lethargy were commonly seen. Presence of constipation showed statistical significance with the drug levetiracetam and Carbamazepine.

None of the subjects had signs of hypothyroidism. None of the subjects had signs and symptoms of hyperthyroidism. This finding is consistent with the study done by Rahman et al[10] and Amani et al.[15]

The weight and height of the children were compared to standard IAP growth charts. 45.3% of the study population were underweight (weight less than 3rd centile). Phenytoin was the most commonly used drug (53.3%) in children, whose weight was less than the 3rd percentile (45.3%, n=24) whereas levetiracetam and valproate showed 13.3% prevalence. This finding was in contrast to the finding of weight gain seen with phenytoin and valproate.

In children with height less than 3rd percentile (54.7% n=29) for the age and sex, Sodium valproate was the most commonly implicated drug (31.8% n=7). This finding was similar to a study conducted by H.M.A. Maksoud et al and Lee et al.[16] The next common drug affecting the height was phenytoin (27.7% n=6).

Among the study subjects on Antiepileptic drugs with weight and height less than 3rd percentile, thyroid hormones were deranged. This finding was statistically significant on analysis (p=0.029). The limitation of this finding was that other parameters affecting the nutritional status of the subjects were not studied.

CONCLUSION

- In the study group, serum T3 levels were in children on AEDs. None of the study subjects showed signs of hypothyroidism or hyperthyroidism.
- Phenytoin altering the serum T4 levels showed statistical significance
- Carbamazepine treated subjects showed low TSH levels.
- Among the study subjects on antiepileptic drugs, with weight and height less than 3rd percentile, thyroid hormones were deranged.
- Sodium valproate was the most commonly used drug in children with height less than 3rd percentile.

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