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Effect of antiepileptic drug on thyroid hormone function in Paediatric population

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Abstract

Background: Epilepsy can have major impacts on several important aspects of life.

Patients with epilepsy are often required to take antiepileptic drugs (AEDs) for a long period of time. Many studies have shown that AEDs have a negative impact on thyroid hormone function.

Objective: To study the effect of antiepileptic drugs on thyroid hormone function in epileptic children and to know the safest antiepileptic to least affect the thyroid hormone.

Method: This is a prospective observational study included 125 newly diagnosed paediatric epileptic children. Levels of TSH, T3, T4 were measured before starting & at the end of 3 months of antiepileptic treatment.

Data were recorded on a pre-designed proforma & Data were compared & analysed.

Results: Incidence of subclinical hypothyroidism was found in epileptic patient receiving Phenytoin, Valproate and Oxcarbazepine. In Phenytoin receiving group the level of TSH, T3, & T4 before starting the treatment was 2.1 (1.3-3.7), 1.2 (1.0-1.7) & 8.6 (6.9-10.5) respectively and after the end of 3 month of treatment level of TSH3.0 (1.7-4.2) p= 0.017, T3 1.1 (0.8 - 1.3) p = 0.007, T4 8.0 (6.2-9.3) p= 0.042.

Similarly in Valproate group reduction in T3 level (p=0.006) & T4 (p=0.001) was found at end the 3 months of therapy but it did not significantly affect level of TSH (p=0.405). In ox car azepine group statistically significant raise seen in TSH level (p= 0.0.36) but level of T3 (p=1.0) & T4 (0.401) was not significantly affected. Patients treated with pheno barbitone & Levetiracetam group didn't show any statistically significant change in level of TSH, T3 & T4 after 3 months of treatment.

Conclusion: Phenytoin, Valproate & Oxcarbazepine group significantly effect thyroid hormone profile as compared to phenobarbitone & Levetiracetam.

Keyword: Antiepileptic drugs, Thyroid hormone level.

Introduction

Epilepsy can have major impacts on several important aspects of life. The severity of the disease varies from

good seizure control or seizure freedom (50–60%) with minor side effects from medication, to a debilitating disease with several daily seizures, the need for polytherapy, the occurrence of major side effects, and problems with drug interactions.

Distinguishing the side effects of antiepileptic drugs (AEDs) from the many other factors that influence the patients can be difficult. In order to avoid the possible complexity from multiple interactions, monotherapy studies are important.

Despite these investigative difficulties, AEDs have been clearly demonstrated to have several hormonal side effects that can influence important areas in life, such as fertility, sexual function, and bone health.

Patients with epilepsy are often required to take antiepileptic drugs (AEDs) for a long period of time. Many studies have shown that AEDs have a negative impact on the endocrine system in both paediatric and adult populations. Certain AEDs such as carbamazepine (CBZ), phenobarbital (PHB), phenytoin (PHT), valproate (VPA), and oxcarbazepine (OXC) are known to affect normal thyroid function. 2 Thyroid hormones are important for maintaining lipid and carbohydrate metabolism, cell growth and development. The prevalence of AED-induced thyroid dysfunction and the long-term consequences remain uncertain, mainly because routine thyroid function tests are usually not performed in the clinic. Therefore, the aim of this study was to characterize the relationship between thyroid dysfunction and AEDs in paediatric patients with epilepsy, and to identify risk factors for its development .4

Methods

Study design Prospective Observational study.

Duration – November 2019 to September 2021

Sample Size $n = (Z\alpha + Z\ 1\text{-}\beta)^2$

$(\mathfrak{X}/\epsilon)^2$

$n = (1.96 \pm 0.84)^2 = 118.2$

$(0.0169/0.25)^2$

n= 125.

Zα= standard normal deviation =1.96

Z 1-β = standard normal deviation =0.84

ϵ = estimated standard deviation of paired response difference.

$\mathfrak{X}$= difference in population mean

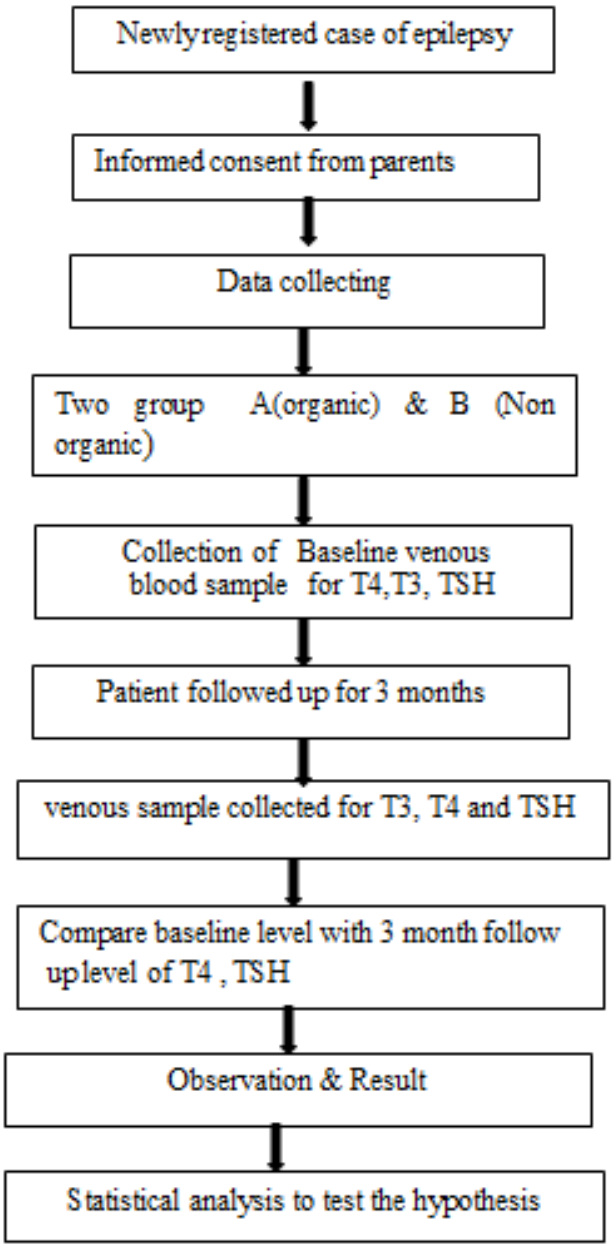
Inclusion Criteria

- Newly diagnosed children aged between 1month to 15 years

Exclusion Criteria

- Known cases of thyroid disorder,
- Have taken or stopped thyroxine in past 1 year
- Known Metabolic syndrome
- Children diagnosed with refractory seizures
- Children on more than two anti-epileptic drugs
- Consumption of any drug in past 1 year which can affect the thyroid function
- Children with poor compliance.
- Children in which a new anti-epileptic drug is added in 3 months of follow up period Family history of hypothyroidism.

Figure 1: Study Flow Chart



- All the children who were included (as mentioned above) in the study had been informed about the study in detail and consent had taken from parents, detailed information including demographic characteristics, seizure type , etiology ,epileptic syndrome, age at onset, selected anti-epileptic drug, and duration of therapy were collected and registered. Patients with epilepsy divided into two group according to organic cause or non-organic cause. The EEG was done in the same parent institute for every patient registered in the study for classifying the type of seizure. Similarly, antiepileptic drugs were selected on the basis of type of seizure which were be examined clinically. The dose and prescription of antiepileptic drugs were done according to the standard protocol of the hospital.
- During the study period each patient were assessed and followed up by the same registrar according to standard protocol.
- On follow up venous blood samples for T4, TSH were taken between 8am and 11am after an overnight fast and results were assessed accordingly. All hormonal analyses will be performed using commercial enzymatic method at the time of patient enrolment and after 3 months of follow up.
- Continuous data has been expressed as median (Interquartile range) and categorical data as frequency (percentage). The normality of the continuous data is tested by Shapiro-Wilk test. The continuous variables have been analysed by Mann-Whitney test and Wilcox an test. Kruskal-Wallis test is used for continuous variables with multiple comparison groups. p values < 0.05 are accepted as indicative of statistical significance.

Results

In this study 125 newly diagnosed epileptic paediatric children were enrolled out of which 72(57.6%) on phenytoin , 52(41.6%) were on Valproate & 20(16%) , patient taking Levetiracetam and phenobarbitone was taken by 8(6.4%) and 8(6.4%) patients on oxcarbazepine. In this study we found that Phenytoin ,Valproate & Levetiracetam have significantly affected the thyroid profile. In Phenytoin receiving group mean thyroid hormone level of patient before starting the therapy was TSH 2.1(1.3-3.7), T3 1.2(1.0-1.7) & T4 8.6(6.9-10.5) which was statistically significantly

affected at end of 3 months of therapy TSH 3.0(1.7-4.2) p=0.017*, T3 1.1(0.8-1.3) p=0.007* & T4 8.0(6.2-9.3) p=0.042*.Similarly patients receiving valproate as antiepileptic show significant reduction in level ofT3, T4 where TSH was statistically not affected . Mean level of T3 ,T4 & TSH in children receiving valproate was 2.4(1.8-3.6),1.2(1.0-1.5), 9.2(6.1-11.1) respectively and at end of 3month of therapy changes to TSH 2.7(1.6-4.0)p=0.405,T3 1.1(0.8-1.2) p=0.06* & T4 7.7 (5.7-9.1) p=0.001*. Those on oxcarbazepine shows significant raise in the level of TSH but didn't affect the level of T3,T4. In oxcarbazepine mean level of thyroid hormone before starting treatment was TSH 0.9(0.6-2.6), T3 1.4(1.2-1.6) & T47.6(3.6-12.4) and after the 3 month of treatment mean level of thyroid hormone was changed to TSH 2.7(1.9-3.3) p=0.036*, T3 1.3(1.1-1.9)p=1.00 & T4 8.4(4.9-10.2)p=0.401,.But in the Levetiracetam receiving group mean level of thyroid hormone was not changed statistically after the 3 month of treatment with mean value of thyroid hormone TSH,T3 & T4 before the beginning of treatment was 2.6,1.1 & 7.7 respectively and after 3 months of therapy changed to 3.3 (p=0.351),1.1(p=0.723) & 7.1 (p=0.970) respectively similar result was found in phenobarbitone treated epileptic children where mean level of thyroid hormone did not changed significantly .In this study we found that dose of antiepileptics drugs did not show any co-relation in change in thyroid hormone profile . In phenytoin receiving group those patients receiving phenytoin at dose of 5mg/kg/day or 5-10 mg/kg/day did not show any significant change in level of thyroid hormone TSH (p=0.641), T3(0.270) & T4(0.554). Similar result was found in Valproate & oxcarbazepine treated group where dose of AEDs did not affect change in the level thyroid hormone. In Valproate group patient were taking Valproate at different dose of 15-20mg/kg/day, 20-25mg/kg/day & 25-30mg/kg/day did not show any significant difference in level of TSH (p=0172),T3(p=0546) & T4 (p=0.308) after the 3 month of therapy. Similarly in Oxcarbazepine taking patient at different dose 15-20mg/kg/day,20-25mg/kg/day & 25-30mg/kg /day didn't so any correlation with level of TSH(p=0.07),T3(p=1.00) & T4(p=0.223) .

Table 1: General Characteristics of the study participants

Characteristics	Frequency	Percentage
Age group (in years)		
≤ 1	24	19.2
1 to 5	37	29.6
5 to 10	34	27.2
> 10	30	24
Sex		
Male	78	62.4
Female	47	37.6
Total	125	100

Table 2: Type of Epilepsy among the study participants

Type	Frequency	Percentage
Type of Epilepsy		
Generalized Tonic Clonic Seizures	113	90.4
Focal Seizures	8	6.4
Myoclonic Seizures	3	2.4
Absence Seizures	1	0.8
Etiology		
Organic	33	26.4
Non organic	92	73.6
Total	125	100

Table 3: Type of seizure across the age of the participant

Type	Age group (in years)			Total	p value
	Less than or equal to 1 year	1 to 5 years	5 to 14 years		
Type of Epilepsy					
Generalized Tonic Clonic Seizures	23 (1)	33 (0.9)	57 (0.9)	113 (0.9)	0.151#
Focal Seizures	1 (0)	1 (0)	6 (0.1)	8 (0.1)	
Myoclonic Seizures	0 (0)	3 (0.1)	0 (0)	3 (0)	
Absence Seizures	0 (0)	0 (0)	1 (0)	1 (0)	
Etiology					
Organic	16 (0.7)	11 (0.3)	6 (0.1)	33 (0.3)	<0.00005*
Non organic	8 (0.3)	26 (0.7)	58 (0.9)	92 (0.7)	
Total	24 (1)	37 (1)	64 (1)	125 (1)	

Significant at 0.05 levels, Chi-square test used. #Fisher's exact test used

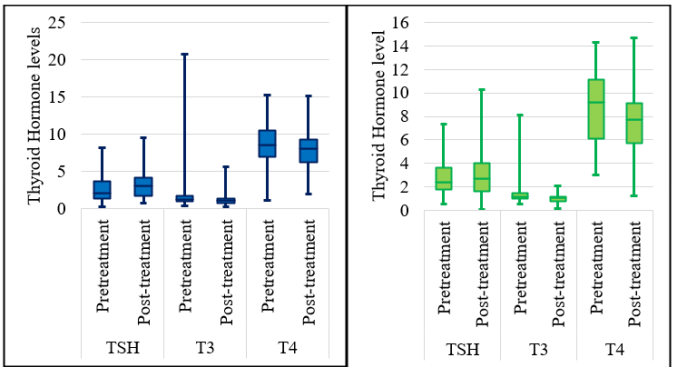
Table 4: Correlation between antiepileptic drugs and thyroid hormone level

Anti-epileptic drug given	Thyroid hormone levels [Median (Interquartile range)]		p value
	Pre-treatment	Post-treatment	
Phenobarbitone			
TSH	2.3 (1.2 – 3.4)	2.1 (0.9 – 4.4)	0.674
T3	1.2 (1.0 – 1.3)	1.1 (0.9 – 1.7)	0.779
T4	9.3 (7.0 – 12.6)	8.7 (6.5 – 10.6)	0.401
Phenytoin			
TSH	2.1 (1.3 – 3.7)	3.0 (1.7 – 4.2)	0.017*
T3	1.2 (1.0 – 1.7)	1.1 (0.8 – 1.3)	0.007*
T4	8.6 (6.9 – 10.5)	8.0 (6.2 – 9.3)	0.042*
Valproate			
TSH	2.4 (1.8 – 3.6)	2.7 (1.6 – 4.0)	0.405
T3	1.2 (1.0 – 1.5)	1.1 (0.8 – 1.2)	0.006*
T4	9.2 (6.1 – 11.1)	7.7 (5.7 – 9.1)	0.001*
Levetiracetam			
TSH	2.6 (1.7 – 4.2)	3.3 (1.8 – 4.4)	0.351
T3	1.1 (0.7 – 1.4)	1.0 (0.7 – 1.2)	0.723
T4	7.5 (6.0 – 9.3)	7.1 (6.1 – 9.3)	0.970
Oxcarbazepine			

TSH	0.9 (0.6 – 2.6)	2.7 (1.9 – 3.3)	0.036*
T3	1.4 (1.2 – 1.6)	1.3 (1.1 – 1.9)	1.000
T4	7.6 (3.6 – 12.4)	8.4 (4.9 – 10.2)	0.401

P value < 0.001 highly significant; < 0.05 significant; > 0.05 not significant

Figure 2: Effect on Thyroid hormone levels in participants treated with the anti-epileptic drugs



A. Phenytoin **B. Valproate**

Table 5: Difference in the effect of AEDs on the thyroid hormone levels based on the dosage.

A. Phenytoin

Thyroid hormone	Median difference [Pretreatment levels – posttreatment levels] (IQR)		p value
	Dose = 5 mg/kg	Dose = 5 – 10 mg/kg	
TSH	-0.7 (-2.2 – 1.0)	-1.2 (-2.6 – 0.1)	0.641
T3	0.2 (-0.1 – 0.7)	0.1 (-0.9 – 0.3)	0.270
T4	0.9 (-1.3 – 2.9)	-0.3 (-2.1 – 2.7)	0.554

B. Valproate

Thyroid hormone	Median difference [Pretreatment levels – posttreatment levels] (IQR)			p value
	Dose = 15-20 mg/kg	Dose = 20-25 mg/kg	Dose = 25-30 mg/kg	
TSH	-0.1 (-1.4 - 1.3)	-1.6 (-4.1 - -1.1)	0.7 (-0.7 - 1.5)	0.172
T3	0.1 (-0.1 - 0.5)	0.1 (0 - 0.2)	0.6 (0.2 - 0.6)	0.546
T4	0.8 (-0.4 - 3)	3.8 (1.9 - 4.3)	4.3 (0.9 - 4.8)	0.308

C. Oxcarbazepine

Thyroid hormone	Median difference [Pretreatment levels – posttreatment levels] (IQR)			p value
	Dose = 15-20 mg/kg	Dose = 20-25 mg/kg	Dose = 25-30 mg/kg	
TSH	-1.3 (-1.6 - -1.1)	-0.2 (-0.8 - 0)	-3.4 (-4.1 - -2.8)	0.077
T3	0.1 (0.1 - 0.1)	0.1 (-0.5 - 0.3)	-0.2 (-0.9 - 0.6)	1.000
T4	-1.8 (-2.4 - -1.3)	-1.4 (-2 - 0.2)	2.1 (-0.8 - 5)	0.223

Discussion

In present study it was found that Phenytoin, Valproate and Oxcarbazepine affect the thyroid hormone function whereas Levetiracetam and phenobarbitone did not affect the thyroid hormone function during therapy. Similarly, the studies done in different parts of India & World in past showed Antiepileptic drugs affect thyroid hormone function and cause subclinical hypothyroidism. Korkmaz et al4 found Valproate, Carbamazepine & pheno barbitone treated patients had decreased level fT4 where levetiracetam treated patients had no significant effect on fT4 &TSH. Fu Yuan Shih et al5 found Frequency of subclinical hypothyroidism in carbamazepine (30.1%) & Topiramate (28.6%). Similar result was found in Olcay et al6 15.2% of Valproic acid group & 2.9 % of phenobarbitone group have subclinical hypothyroidism at 12 months of therapy. Ushuf Rahman et al7 found that all antiepileptic drugs (valproate, Phenobarbitone & oxcarbazepine) was found to decrease T3, T4 at the end of one year of therapy (Valproate 5.77%), pheno barbitone (8.67%) & Oxcarbazepine (6.67%) shows subclinical hypothyroidism ($p=0.05^*$) except levetiracetam. Violeta Illic et al8 found that Valproic acid group had high serum TSH($p<0.001$) as compared to control group. Unsal Yilmaz et al9 also found same result of valproate (28%), pheno barbitone (13.9%) & Ox carbazepine (18.28%) had decreased fT4 & increase TSH level at month of 1,6 & 12 months where levetiracetam showed no significant difference of fT4, TSH at any times. This study found that there was no correlation related to dose of the antiepileptic drugs in change of thyroid hormone level during the treatment but duration of antiepileptic drugs can affect the level of thyroid hormone in epileptic children. Ihsan Kafadar et al10 found that serum thyroxine level did not change during valproate treatment till 6 months of therapy and after that level of TSH were significantly higher at end of 12 months. Fatih aygun et al11 also found that during the valproate monotherapy thyroid hormone level were normal at 0,3 & 6 months of treatment but significant increase in serum TSH level was observed at 9 months of treatment. Newly diagnosed epileptic children who were on antiepileptic drugs should have regular thyroid hormone levels and duration of antiepileptic drugs should be least as require. Levetiracetam found to be safest antiepileptic drug in this study who didn't significantly affect thyroid hormone level.

Conclusion

A Total of 57.8% patient in current study was treated with phenytoin, where 41.6% received valproate & 16 patient received levetiracetam. In this study 72 % patients required monotherapy to have good control of seizures as compared to 28 % patient who needed polytherapy. Patients on polytherapy had a significantly lower level of thyroid hormone as compared to the patient on monotherapy. Patients on phenytoin had significantly low level of T3 & T4 and higher level of TSH, whereas patient on valproate had low level T3 & T4 and level of TSH was unaffected similarly patients receiving oxcarbazepine had significant effect only on level of TSH where level of T3 & T4 was unaffected. Levetiracetam was found to be the safest antiepileptic to have the least side effect on thyroid hormone function.

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