Original Research Article

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Assessment of thyroid function among children with epilepsy receiving anticonvulsant monotherapy: a hospital based prospective study

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ABSTRACT

Background: Data on influence of antiepileptic drugs (AED) on thyroid profile in children is limited and is still controversial. This study aimed to investigate the effects of valproate, levetiracetam, phenobarbitone and oxcarbazepine monotherapy on thyroid function in children after one year of therapy.

Method: A total of 106 children (39 girls and 67 boys) with new onset and controlled epilepsy treated with valproate (n=52), phenobarbitone (n=12), oxcarbazepine (n=14) and levetiracetam (n=28) were enrolled in the study. Serum thyroxine (T4, T3) and thyroid-stimulating hormone (TSH) level were measured before and at one year of therapy.

Results: At baseline average T4, T3 and TSH concentrations were not different between the drug groups. Except levetiracetam all antiepileptics increased TSH after one year of therapy and there was significant difference in TSH increment in valproate treated patients compared to other anticonvulsants. All anti-epileptics except levetiracetam was found to decrease T4 and T3 after one year of therapy but there was no significant difference among the groups, unlike TSH. Sodium valproate was the most frequently used antiepileptic drug. None of children had any symptoms of hypothyroidism, only 3% had signs of hypothyroidism which included goitre on examination. Out of various seizure disorders generalised tonic clonic type was most common (47.5%) followed by atypical febrile seizure (23%). **Conclusions**: All antiepileptic drugs studied except levetiracetam had varying degrees of deleterious effects on thyroid function.

Keywords: Antiepileptic drugs, Epilepsy, TSH, T4, T3

INTRODUCTION

Epilepsy affects 0.5 to 1% of children and is the most frequent chronic neurologic condition in childhood. The effects of antiepileptic drugs on thyroid function are known for a long time; mostly occur subclinical hypothyroidism (SCH). The SCH is the biochemical condition having high serum TSH and normal serum T3 and T4 levels without clinical features of hypothyroidism. Most patients with SCH exhibit few or no signs and symptoms of hypothyroidism. It has been suggested that some patients have functional, clinical, or biochemical manifestations of hypothyroidism that are more common than age-matched controls. Goiter is the

most common manifestation, other abnormalities found commonly in the paediatric population include weight gain, increased cholesterol levels, impaired growth velocity, anaemia, sleepiness, weakness, and impaired psychomotor and cognitive development.³ There was significant individual variability of therapeutic response to antiepileptic therapy. As in children, thyroid hormones are important for normal mental and physical growth, the study of the effect of antiepileptic drugs on thyroid function is important. Antiepileptic drugs affect thyroid hormone levels through several mechanisms, many of them increase hepatic microsomal enzyme systems, thus accelerating clearance of thyroid hormone; others interfere with the hypothalamic-pituitary axis.^{4,5} This

study investigated the effects of widely used AEDs that included sodium valproate, phenobarbitone, oxcarbazepine and levetiracetam on thyroid function in children during a 12-months period of therapy.

METODS

Study area

The study was conducted at out-patient and in-patient department, department of paediatrics, Bankura Sammilani medical college and hospital, West Bengal.

Study population

Patients aged 3 to 12 years, newly diagnosed with epilepsy as per international league against epilepsy (ILAE) definition receiving anticonvulsants monotherapy attending at out-patient and in-patient department of paediatrics at Bankura Sammilani medical college and hospital, West Bengal.

Sample size

A total 106 children with epilepsy fitting inclusion and exclusion criteria attended during study period were included in the study.

Period of study

The study was conducted during January 2019 to December 2019 (Twelve months).

Inclusion criteria

The inclusion criteria for study included patients newly diagnosed with epilepsy, patients receiving single anticonvulsant therapy, patients receiving their drugs regularly for at least 12 months, and patients aged between 3 years to 12 years.

Exclusion criteria

Exclusion criteria for study excluded pre-existing thyroid disorders or other endocrinopathies, children suffering from protein energy malnutrition, chronic liver, heart or renal diseases, progressive neurological or psychological illness, drugs which may alter the body weight and body mass index (BMI) of the patient like insulin, steroid etc. and recent onset acute illness causing weight loss and drug defaulters.

Study methodology

A hospital based prospective study was use for the study.

Study procedure

Patients attending out-patient and in-patient department of podiatric medicine, 3 to 12 years of age and receiving

anticonvulsant monotherapy were included in this study based on the inclusion and exclusion criteria. After taking informed consent from parents/guardians each participant were investigated for serum level of T3, T4 and TSH on starting and 12th months of receiving medications. Venous blood samples of the participants were collected and serum concentrations of T3, T4 and TSH were measured by Mindray microplate ELISA reader by immunoenzymatic assay (ELISA).

Statistical analysis

Data were collected, recorded, coded and compiled in Microsoft excel sheet. Continuous variables were described by estimating mean, standard deviation, median and range. Categorical variables were summarized using proportion. Continuous variables were checked for their normality of distribution with the help of Shapiro-wilk test. Statistical inference was drawn using calculated standard error (SE) for estimating population parameters. Statistical tests like unpaired t test, chi square test, Fisher exact test, ANOVA post-hoc test and relative risk (RR) with its 95% confident interval (CI) for drawing inference regarding relationship between independent and dependent variables. Statistical package SPSS version 20.0 software was used for the purpose of data analysis. P value of <0.05 was considered as significant at 5% precision level.

RESULTS

A total 106 children were enrolled in this study, of them 67 were boys and 39 were girls. Out of 106 children, 52 (49%), 28 (26.4%), 14 (13.2%) and 12 (11.4%) were taking valproate, levetiracetam, oxcarbazepine and phenobarbitone monotherapy for at least 1 year respectively. Serum T4, T3 and TSH concentrations at baseline and at twelve months of AEDs treatment were measured. There was no significant difference in the average T4, T3 and TSH concentrations between the AED groups before the initiation of therapy.

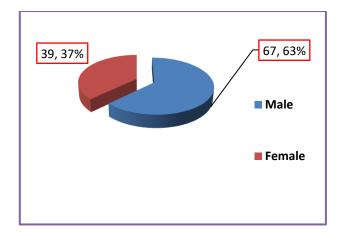


Figure 1: Distribution of study population according to gender.

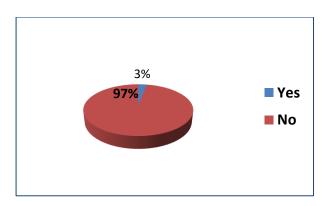


Figure 2: Distribution of study population according to clinical features of hypothyroidism.

Table 1: Distribution of participants as per seizure type and frequency of anticonvulsant monotherapy (n=106).

Variables	Frequency	Percentage (%)		
Antiepileptics				
Valproate	52	49		
Levetiracetam	28	26.4		
Oxcarbazepine	14	13.2		
Phenobarbitone	12	11.4		
Total	106	100		
Seizure disorders				
GTCS	50	47.5		
Atypical febrile	24	23		
Complex partial	14	13		
seizures				
Epileptic syndromes	10	9		
Absence seizures	8	7.5		
Total	106	100		

Analysis reflected that generalised tonic clonic seizure ranked top of the list comprising of 47.5% followed by atypical febrile seizures contributing 23%. Valproate (49%) is the most frequently used anticonvulsant followed by levetiracetam (26.6%) (Table 1).

Table 2: Distribution of participants as per serum level of thyroid profile after 1 year of therapy (n=106).

	Serum le	vel	Population		
Thyroid profile	Normal Altered no. (%) no. (%)		parameter for altered thyroid profile [proportion±2 SE (√pq/n)]		
TSH	84 (79.24)	22 (20.76)	12.73-28.63		
T4	101 (95.28)	5 (4.72)	9.12-4.12		
Т3	102 (96.22)	4 (3.78)	7.48-0.08		

The analysis revealed that 20.76, 4.72 and 3.78% of the respondents were found to have altered serum levels of

TSH, T4 and T3, respectively with population parameter ranging from 12.73 to 28.63%, 4.12 to 9.12 and 0.08 to 7.48%, respectively (Table 2).

Table 3: Distribution of respondents according to status of serum TSH level and antiepileptics (n=106).

	TSH leve	el		DD	
Antiepileptics	Normal no. (%)	High no. (%)	χ^2 , df, p	RR (95% CI)	
Sodium valproate (n ₁ =52)	32 (61.54)	20 (38.46)	14.36, 1, 0.000	1.63 (1.31- 2.01)	
Phenobarbitone (n ₂ =12)	11 (91.33)	1 (8.67)	0.300@	1.09 (0.92- 1.29)	
Oxcarbazepine (n ₃ =14)	13 (93.33)	1 (6.67)	0.333 [@]	1.08 (0.93- 1.25)	
Levetiracetam (n ₄ =28)	28 (100)		*	1.00	
Total	84 (79.24)	22 (20.76)			

Table 4: Distribution of respondents according to serum TSH level and antiepileptics (n=106).

Antiepileptics	TSH level Mean ± SD	F (ANOVA), p
Sodium valproate (n ₁ =52)	4.96±2.79	
Phenobarbitone (n ₂ =12)	3.69±1.61	6.761 0.000
Oxcarbazepine (n ₃ =14)	3.35±1.48	6.761, 0.000
Levetiracetam (n ₄ =28)	2.78±1.08	
Total		

Table 5: Distribution of respondents according to status of serum level of thyroid profile and antiepileptics (n=106).

	Thyroid hormones					
Antiepileptics	T4	T3				
	Mean ± SD	Mean \pm SD				
Sodium valproate	9.42±1.88	$1.510385 \pm$				
$(n_1=52)$	9.42±1.88	0.356348				
Dhanabaubitana (n.—12)	$8.935833 \pm$	1.4525±				
Phenobarbitone (n ₂ =12)	1.74804	0.379213				
Overshagenine (n.=14)	$1.135612\pm$	$0.292857 \pm$				
Oxcarbazepine (n ₃ =14)	1.802038	0.384245				
Levetiracetam (n ₄ =28)	$9.905 \pm$	1.565714±				
Levetiracetain (114=28)	1.376521	0.248632				
Unneised t df n	1.002, 3,	0.360, 3,				
Unpaired t, df, p	0.395	0.782				

Table 6: Distribution of respondents according to status of serum TSH, T4 and T3 level with dosage of sodium valproate (n=52).

Dose	TSH Leve	el		RR (95%	T4 level		P (Fisher	RR	T3 level		D (Figher	DD
Valproate (mg/kg/day)	Normal	low	χ2, df, p	CI)	Normal No. (%)	Low No. (%)	exact test)	(95% CI)	Normal No (%)	Low No (%)	P (Fisher exact test)	RR (95%CI)
10-20	10 (66.6)	5 (33.33)	*	1.00	14 (93.33)	1 (6.67)	1.000	1.03 (0.89- 1.20)	14 (93,75)	1 (6.25)	1.000	1.07 (0.94-1.23)
20-30	17 (60)	12 (40)	0.27, 1, 0.603	1.14 (0.71- 1.82)	28 (96.55)	1 (3.45)	*	1.00	28 (96.55)	1 (3.45)	1.000	1.04 (0.97-1.11)
30-40	5 (62.5)	3 (37.5)	1.000@	1.07 (0.56- 2.03)	7 (93.75)	1 (6.25)	0.390	1.10 (0.84- 1.45)	8 (100)	0 (0)	*	1.00
Total	32 (61.5)	20 (38.46)			49 (94.23)	3 (5.77)			50 (96.15)	2 (3.85)		

^{*}Reference group, @=Fisher exact test (two tail) the groups were alike.

Table 7: Distribution of respondents according to status of serum TSH, T4 and T3 level with dosage of carbamazepine.

Dose	TSH level		_	RR	T4 level		_ P		T3 level			
carbamazepine (mg/kg/day)	Normal	low	P (fisher Exact test)	(95% CI)	Normal No. (%)	Low No. (%)	(Fisher exact test)	RR (95% CI)	Normal No (%)	Low No (%)	P (fisher Exact test)	RR (95%CI)
10-20	8 (100)	0 (0)	*	1.00	8 (100)	0 (0)	*	1.00	8 (100)	0 (0)	*	1.00
20-30	5 (83.33)	1 (16.67)	0.428	1.20 (0.84- 1.72)	5 (83.33)	1 (16.67)	0.428	1.20 (0.84-1.72)	5 (83.33)	1 (16.67)	0.428	1.20 (0.84- 1.72)
Total	13 (92.85)	1 (7.15)			49 (94.23)	3 (5.77)			50 (96.15)	2 (3.85)		

^{*}Reference group.

Reference group@=Fisher exact test (two tail). It was revealed that significantly higher proportion of patients (38.46%) receiving sodium valproate [χ^2 =14.36, p=0.000 at df 1 and RR=1.63 (1.31-2.01)] was found to have altered (high) serum TSH level compared phenobarbitone. [χ^2 =4.01, p=0.045 at df 1 and RR=1.49 (1.13-1.96)] and oxcarbazepine [χ^2 =4.99, p=0.026 at df 1 and RR=1.51 (1.16-1.96)]. All children on Levetiracetam had normal TSH level. So, in respect of abnormality in serum TSH level, Sodium valproate should not be relying on rather than phenobarbitone and oxcarbazepine (Table 3).

Analysis indicated that there was a significant difference across the antiepileptics groups in respect to serum TSH levels. For identifying the groups between which the actual difference existed, least square deviation (LSD) post-hoc test was conducted. The following results were found Table 4 sodium valproate vs phenobarbitone-not significant (p=0.071), phenobarbitone vs oxcarbazepine-not significant (p=0.691), phenobarbitone vs levetiracetam-not significant (p=0.233), oxcarbazepine vs levetiracetam-not significant (p=0.434), sodium valproate vs oxcarbazepine-significant (p=0.016), sodium valproate vs levetiracetam-significant (p=0.000) (Table 4).

No difference in serum thyroid hormone levels could be observed among the antiepileptic groups before starting of treatment. In terms of serum T3 and T4, all antileptics except levetiracetam have decremental effect on it. There was no significant difference among the different antiepileptic groups. (levetiracetam reference group, @Fisher exact test (two tail), p value>0.05). After one year of therapy 5.77, 8.67 and 6.67% of the valproate, phenobarbitone and oxcarbazepine treated patient showed decrease T4 respectively. After one year of therapy 4.35, 8.67 and 6.67% of patient treated with valproate, phenobarbitone and oxcarbazepine showed decreased T3 respectively. All patient treated with levetiracetam showed normal T3 and T4 even after 1 year of therapy.

They did not show any significant difference in TSH, T4 and T3 with various doses of valproate after one year of therapy (Table 6).

Table 8: Distribution of respondents according to status of serum TSH level and dosage of phenobarbitone (n=12).

Thyroid profile on	Serum thyr	χ^2 , df,		
phenobarbitone @ 5	Normal	Altered	$\begin{bmatrix} \chi, \mathbf{u}, \\ \mathbf{p} \end{bmatrix}$	
mg/kg/day	No. (%)	No. (%)	P	
TSH	11 (91.66)	1 (8.34)	0.00,	
T4	11 (91.66)	1 (8.34)	2,	
T3	11 (91.66)	1 (8.34)	1.000	

The proportion of study subject with altered/low serum T3, T4 and TSH level did not differ significantly across the dosages of oxcarbazepine (Table 7).

On exposure to phenobarbitone@ 5 mg/kg/day, there was no significant difference in alteration of serum thyroid profile. It was observed that 8.34% of the patients on phenobarbitone@ 5 mg/kg/day had altered (high) TSH level (Table 8).

DISCUSSION

This study investigated the effects of widely used AEDs sodium valproate, phenobarbitone, included oxcarbazepine and levetiracetam on thyroid function in children during a one year of period of therapy. In this study a total of 106 cases were included in the age group of 3-12 years. As per the study done by Camfield et al, there was highest incidence of epilepsy in the 1st year of life and declined to adult levels by the end of 1st decade.6 In our study, among the children males were found to be predominant comprising of 63%. The study done by Amani had suggested male predominance of seizure disorders among children.7 Khalid also found male predominance of seizure disorders among the children.8 According to our study, out of the various seizure disorders generalised tonic clonic type was the most common, accounted to 47.5%, the next most common seizure type was atypical febrile seizure (23%), 13% had complex partial seizures, 9% had epileptic syndromes and 7.5% had absence seizures. This result was consistent with the previous study done by Amani.7 Generalized tonic-clonic seizures were found in 24 patients (64.9%) and absence type in 9 (24.3%) as was observed by Murat et al.9 Out of seizure disorders generalised tonic clonic type accounted to 37%, the next most common seizure type was atypical febrile seizure around 22%, 17% had neonatal seizures, 10% had epileptic syndromes and 6% had absence seizures as per the study done by Rajendran.¹⁰ In this study, among the respondents, 49% was on sodium valproate, the next group 26.6% was on levetiracetam, 13% was on oxcarbazepine and 11.5% was on phenobarbitone. The majority of patients were on carbamazepine (CBZ) while small number of patients (16.4%) was on valproate (VAP) as per study done by Obeid.¹¹ As per a systematic review done by Egunsola et al. monotherapy regimen was varied between 58-94% and sodium valproate was the most frequently prescribed AED.¹² In this study, none of the respondents had any symptoms of hypothyroidism and only 3% had signs of hypothyroidism in the form of mild enlargement of the thyroid gland. Previous studies have also found that subclinical hypothyroidism (SCH) might develop in epileptic patients during AED therapy. 13 However, patients using AEDs did not show clinical manifestations or signs of functional hypothyroidism.¹⁴ Violeta et al did not observed clinical features of thyroid dysfunction in patients receiving sodium valproate for 2-4 years. 15 Yılmaz et al had found that frequency of subclinical hypothyroidism at 12th month was 28% in valproate, 21.4% in oxcarbazepine, 18.2% in phenobarbital, 13.9% in carbamazepine, and 0% in levetiracetam group. 16 The analysis revealed that 20.76% of the respondents were found to have altered (high) serum levels of TSH. Most of them (90.1%) were on sodium valproate (90.1%) therapy. Alteration of serum TSH level among the respondents receiving sodium valproate, phenobarbitone and oxcarbazepine were 38.46, 8.67 and 6.67% respectively. In this study serum T4 and T3 values were abnormal in 4.72 and 3.78% of the participants. Among those with low T4 levels, 60% were on sodium valproate, 20% were on phenobarbitone and remaining was on oxcarbazepine. Levetiracetam did not increase serum TSH or decrease T4 and T3. Further data analysis revealed that there was no significant difference in alteration of serum T4 and T3 levels among the antiepileptic groups unlike TSH-Yılmaz et al concluded that valproate-treated patients had decreased fT4 and increased TSH levels at 1st, 6th and 12th months of therapy. Carbamazepine-treated patients had decreased fT4 levels at 1st, 6th and 12th months of therapy and had increased TSH levels at 1st and 6th month of therapy. Phenobarbital-treated patients had decreased fT4 levels at 1st and 6th months and had increased TSH levels at 6th and 12th months of therapy. Oxcarbazepine-treated patients were noted decreased fT4 levels at 1st month of therapy. Levetiracetam-treated patients showed no significant change of fT4 and TSH at any times. On the contrary, Verrotti et al had suggest that valproate acid monotherapy does not alter thyroid profile.¹⁷ Increased serum T4 level, normal T3 and normal TSH levels were noted in carbamazepine (CBZ) treated children. Several previous studies have shown that the reduced fT4 and increased TSH concentrations returned to normal values after the withdrawal of valproate, thus, the changes induced by long term administration of valproate appear to be transient and reversible. 18,19 Dinesh et al found that sodium valproate monotherapy did not alter serum levels of thyroid hormones.²⁰ On the contrary, alterations of thyroid function were seen in patients treated with carbamazepine and phenytoin. Durdane et al conducted a study on thyroid hormone levels in children on sodium valproate and levetiracetam and found that TSH values were elevated in children on sodium valproate and remained unchanged in children on levetiracetam.²¹ Similar results obtained in our study. De Luca et al studied T4, and FT4 level in five hypothyroid children with partial epilepsy receiving L. Thyroxin, they found that serum total T4 and FT4 significantly decreased following 2 months of CBZ administration.²² It was revealed from the analysis that 27.5, 15.0, 11.5 and 7.5% of the participants were on 20-30 mg of sodium valproate, 20-30 mg of levetiracetam, 5 mg of phenobarbitone and 10-20 mg of oxcarbazepine per kg/day, respectively. In a study done by Rajendran, among the children on sodium valproate 1.3% were on a suboptimal dose of 5 mg/kg/day, 6% were on 10-15 mg/kg/day, 24.7% were on 15-20 mg/kg/day, 3.3% were on 20-25 mg/kg/day, 10.7% were on 25-30 mg/kg/day. 11 Among the phenobarbitone group all were on a constant dose of 5 mg/kg/day. Among the carbamazepine group 6% were on 10-15 mg/kg/day and 4% were on 15-20 mg/kg/day.

Limitations

One of the limitations of our study was that we were not able to form a control group because of ethical reasons. This limitation may be omitted with using baseline values as controls. Another limitation of the study was the lack of adjustment of fT4 and TSH values for BMI. The small sample size and lack of follow up beyond one year is another limitation.

CONCLUSION

All AEDs except levetiracetam studied had deleterious effects on thyroid function with varying degrees in children during the period of 12-month therapy. The effects on thyroid function induced by valproate appear to be more marked than those induced by phenobarbital and oxcarbazepine. As thyroid hormone is important for cognitive and physical development, we recommend periodic monitoring of thyroid function of those taking long-term AEDs. we did not find any study with predominant tribal population; our study has been done on rural based medical college with significant tribal population.

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