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Assessment of Thyroid Function among Children with Epilepsy Receiving Anticonvulsant Monotherapy In a Rural Based Tertiary Care Centre

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Abstract:
Background*: Data on influence of antiepileptic drugs on thyroid profile in children is limited and is still controversial.*
Objective*: 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 were significant difference in TSH increment in valproate treated patients compared to other anticonvulsants. All anti-epileptics except levetiracetam was found to decrease T4 & T3 after one year of therapy but there were no significant difference among the groups,unlike TSH. Sodium valproate was most frequently used antiepileptic drug.None of the children had any symptoms of hypothyroidism, only 3% had signs of hypothyroidism which included goitre on examination.Out of the various seizure disorders generalised tonic clonic type was the most common(47.5%) followed by atypical febrile seizure (23%).*
Conclusion*: all antiepileptic drugs studied except levetiracetam had varying degrees of effects on thyroid function.*
Keywords-AED,Epilepsy,TSH,T4,T3.

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I. 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.The Subclinical hypothyroidism (SCH) is the biochemical condition having high serum Thyroid Stimulating Hormone (TSH) and normal serum T3 & T4 levels without clinical features of hypothyroidism.[1] 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.[2] Goiter was the most common manifestation. The abnormalities found most 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.

II. Methodology

Study area: The study was conducted at outpatient & inpatient department, Department of Paediatrics, BSMCH.

Study population: Patients aged 3 to 12 years, newly diagnosed with epilepsy as per International League Aganist Epilepsy(ILAE) definition receiving anticonvulsants monotherapy attending at out-patient & in-patient department of pediatrics 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: January 2019 – december 2019 (Twelve months)

Inclusion criteria:(1)Patients newly diagnosed with epilepsy.(2)Patients receiving single anticonvulsant therapy.(3)Patients receiving their drugs regularly for at least 12months.(4)Patients aged between 3 years to 12 years.**exclusion criteria**:(1)Pre existing thyroid disorders or other endocrinopathies(2)Children suffering from protein energy malnutrition(3)Chronic liver, heart or renal diseases(4)Progressive neurological or psychological illness(5)Drugs which may alter the body weight and BMI of the patient like insulin, steroid etc.(6)Recent onset acute illness causing weight loss and (6)Drug defaulters.

Study procedure: Patients attending out-patient and in-patient Department of Pediatric Medicine,3 to 12 years of age and receiving anticonvulsant monotherapy were included in this study based on the inclusion & exclusion criteria. After taking informed consent from parents/guardians each participant were investigated for serum level of T3, T4 and TSH on starting and 12^{th} 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 immunoenzymetric 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.

III. 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 1year 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.

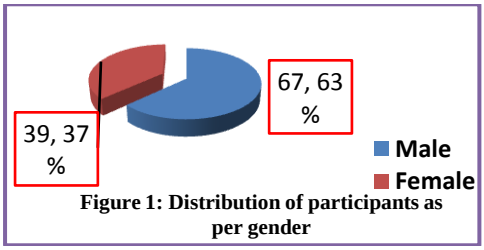

Figure 1: Distribution of participants as per gender

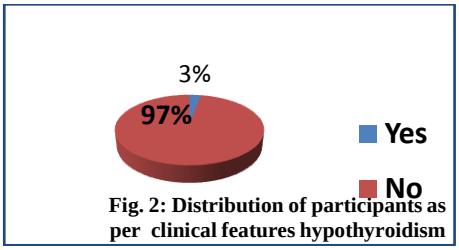

Fig. 2: Distribution of participants as per clinical features hypothyroidism

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

Antiepileptics	Frequency	Percentage
valproate	52	49
levetiracetam	28	26.4
oxcarbazepine	14	13.2
phenobarbitone	12	11.4
total	106	100

Seizure	Frequency	Percentage
GTCS	50	47.5
Atypical febrile	24	23
Complex	14	13
Epileptic	10	9
Absence	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 one year of therapy(N=106).

Thyroid profile	Serum Level		Population Parameter for altered thyroid profile [proportion±2SE(√pq/n)]
	Normal No. (%)	Altered No. (%)	
TSH	84 (79.24)	22 (20.76)	12.73-28.63
T4	101 (95.28)	5 (4.72)	9.12-4.12
T3	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 to28.63%,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)

Antiepileptics	TSH Level		χ^2,df,P	RR (95% CI)
	Normal No. (%)	High No. (%)		
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)	---	---

*Reference group@= Fisher exact test (two tail).It was revealed that significantly higher proportion of patients(38.46%)receiving Sodium valproate [$\chi2$= 14.36, P= 0.000 at df 1 & RR= 1.63(1.31-2.01)] was found to have altered (high) serum TSH level compared Phenobarbitone .[$\chi2$= 4.01, P= 0.045 at df 1 & RR= 1.49 (1.13-1.96)] and Oxcarbazepine [$\chi2$= 4.99, P= 0.026 at df 1 & 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 & Oxcarbazepine.[table-3]

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

Antiepileptics	TSH Level	F(ANOVA), P
	Mean ± SD	
Sodium valproate (n_1=52)	4.96 ± 2.79	6.761, 0.000
Phenobarbitone (n_2=12)	3.69 ± 1.61	
Oxcarbazepine (n_3=14)	3.35 ± 1.48	
Levetiracetam (n_4=28)	2.78 ± 1.08	
Total	---	---

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]

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

Antiepileptics	Thyroid hormones	
	T4	T3
	Mean ± SD	Mean ± SD
Sodium valproate (n_1=52)	9.42 ± 1.88	1.510385 ± 0.356348
Phenobarbitone (n_2=12)	8.935833 ± 1.74804	1.4525 ± 0.379213
Oxcarbazepine (n_3=14)	1.135612± 1.802038	0.292857± 0.384245
Levetiracetam (n_4=28)	9.905± 1.376521	1.565714± 0.248632
Unpaired t, df, P	1.002, 3, 0.395	0.360, 3, 0.782

No difference in serum thyroid hormone levels could be observed among the antiepileptic groups before starting of treatment. In terms of serum T3 & T4, all antileptics except levetiracetam have decremental effect on it.there were 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 oxcarbazapine showed decreased T3 respectively.All patient treated with levetiracetam showed normal T3 and T4 even after 1 year of therapy.

IV. Discussion

This study investigated the effects of widely used AEDs that included Sodium valproate, Phenobarbitone, 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. Kari M et al.[6] had found that mean age of presentation of seizure disorders among children were 7.4 years of age with the highest incidence rate was observed during the infancy. As per the study done by Camfield P et al. [7] there was highest incidence of epilepsy in the 1st year of life and declined to adult levels by the end of 1st decade. In our study, among the children males were found to be predominant comprising of 63%. The study done by Amani HA[8] had suggested male predominance of seizure disorders among children. Khalid OA.[9] also found male predominance of seizure disorders among the children.Accoding 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 HA[8]. Generalized tonic-clonic seizures were determined in 24 patients (64.9%) and absence type in 9 (24.3%) as was observed by Murat T et al[10]. 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 N.[11] 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 SA[12]. As per a systematic review done by Egunsola O et al.[13] monotherapy regimen was varied between 58-94% and Sodium valproate was the most frequently prescribed AED. 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.[14] However, patients using AEDs did not show clinical manifestations or signs of functional hypothyroidism.[15] Violeta Ili ´c et al[16] did not observed clinical features of thyroid dysfunction in patients receiving Sodium valproate for 2-4 years. Yılmaz et al.[17] had found that frequency of subclinical hypothyroidism at month 12 was 28% in valproate, 21.4% in oxcarbazepine, 18.2% in phenobarbital, 13.9% in carbamazepine, and 0% in levetiracetam group.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 &T3.Further data analysis revealed that there was no significant difference in alteration of serum T4 & T3 levels among the antiepileptic groups unlike TSH-Yılmaz et al.[17] 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 1s 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 Alberto et al.[18] had suggest that Valproate acid monotherapy VI Carbamazepine (CBZ) treated children.Alberto et al.[19] did not found significant alteration of serum TSH level in patients receiving Sodium valproate. He also noticed reduced serum T4 level among the patients receiving Carbamazepine. Several previous studies have shown that the reduced fT4 and increased TSH concentrations returned to normal values after the withdrawal of Valproate.[20,21] Thus, the changes induced by long term administration of valproate appear to be transient and reversible. Dinesh K et al.[22] found that Sodium valproate monotherapy did not alter serum levels of thyroid hormones. On the contrary, alterations of thyroid hormone function were seen in patients treated with carbamazepine and phenytoin.Durdane et al.[23] 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, which is similar to the results obtained in this study.De Luca et al.[24] 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 .

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V. Conclusion

All AEDs studied except levetiracetam had deleterious effects on thyroid function in children of varying degrees during the period of 12-month therapy. As most of AEDs induced hypothyroidism was subclinical and subclinical hypothyroidism has been found to affect cognition of the growing brains in children, periodic monitoring of thyroid profile may be needed in children on anticonvulsants.

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