Thyroid Hormone Status in Children Taking Antiepileptic Drugs (AEDs): An Experience in a Tertiary Care Hospital of Bangladesh

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Abstract:

Introduction: *Antiepileptic drugs (AEDs) may alter thyroid hormone homeostasis at the level of biosynthesis, release, transport, metabolism and excretion of thyroid hormones. The purpose of the study was to see the thyroid hormone status in children with epilepsy treating with common antiepileptic drugs.*

Materials & Method*: The cross-sectional study was carried out in department of pediatric neurology, National Institute of Neurosciences and Hospital (NINS), Dhaka. One hundred and sixty epileptic children aged 1 year to 14 years who were on monotherapy or polytherapy with the most commonly used Antiepileptic drugs (AEDs) for at least 6 months or more were enrolled. Serum TSH and FT4 were measured in all selected patients with early morning serum sample.*

Result: *Nearly one third of study subjects had thyroid dysfunction, most of which were Subclinical hypothyroidism (SCH). The frequency of SCH was 29.2% in carbamazepine(CBZ), 50% in oxcabazepine (OXC), 28.6% in phenobarbitone(PHB) and 13% in valproic acid (VPA) treated epileptic children. No child was found to have subclinical hypothyroidism with topiramate and ethosuximide monotherapy. Antiepileptic drugs (AEDs) monotherapy or polytherapy had no significant difference in alteration on thyroid hormone level. Use of CBZ for long duration significantly altered thyroid function. Doses of Antiepileptic drugs (AEDs) didn't show any significant thyroid dysfunction.*

Conclusion*: Commonly used Antiepileptic drugs (AEDs) in children with epilepsy were associated with alteration of thyroid hormones, most commonly subclinical hypothyroidism.*

Key words: *Antiepileptic drugs (AEDs), Epilepsy, Thyroid Function, Subclinical Hypothyroidism.*

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Introduction:

Epilepsy is a common chronic medical problem with an estimated prevalence of approximately 8.2-10/1000 has been reported.[1] Epilepsy is more frequent in children and adolescents.[2] The prevalence of epilepsy in Bangladesh is 8.6/1000 and in children it is 11.5/1000.[3]

Antiepileptic drugs (AEDs) are associated with effects on endocrine function, in particular, alteration of thyroid function. In 1961, Oppenheimer et al. reported that the mean serum protein-bound iodine level was reduced in patients treated with diphenylhydantoin.[4] Since then, interactions between antiepileptic drugs and thyroid hormone have been extensively investigated. Antiepileptic drugs, such as diphenylhydantoin, carbamazepine, and oxcarbazepine, has enzyme-inducing activity[5] and marked protein-binding activity typically cause reduced levels of thyroxin and free thyroxin, but have variable effects on levels of triiodothyronine, free triiodothyronine, thyroxin- binding globulin, and thyroid-stimulating hormone.[5,6] In

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contrast, most studies of valproate, which exhibits protein binding but not enzyme-inducing activity,[7] indicate that it has no appreciable effect on thyroid function, except when administered in association with enzyme-inducing antiepileptic drugs, but recent studies suggest that valproate may induce subclinical hypothyroidism (SCH).[8]

Children with epilepsy constitute about 50% of the total patients attending in the department of pediatric neurology of National Institute of Neurosciences and Hospital. For treatment of these epileptic patients most commonly used antiepileptic drugs are carbamazepine, oxcarbazepine, sodium valproate, phenobarbitone, topiramate, levetiracetam, ethosuximide and benzodiazepines (e.g. clobazam, clonazepam).

There are few studies8those were mostly retrospective showed the long and short-term effects of antiepileptic drugs on thyroid functions in children. To the best of our knowledge there is no such type of studies regarding the effect of antiepileptic drugs on thyroid function in our country. So current study will help us to observe the thyroid function status of the epileptic children of our country.

Materials & Method:

This was a cross-sectional study done from July to December, 2018 in the OPD of Paediatric Neurology Department of National Institute of Neurosciences and Hospital (NINS), Dhaka. After taking approval from ethical review committee of NINS&H, one hundred and sixty children aged 1 to 14 years diagnosed as epilepsy who were on regular antiepileptic (Monotherapy or polytherapy) drugs for > 6 months were included in the study. Seizure types were classified according to the criteria of the International League against Epilepsy (ILAE).

Children were evaluated thoroughly with history and clinical examination. History related to age of onset and frequency of seizure, perinatal details, family history, developmental history and the ongoing treatment details (doses, duration, monotherapy and poly therapy, side effects of the drugs) were noted. Serum TSH and FT4 level were done in all selected patients with early morning serum sample between 8 AM and 10 AM after an overnight fast and measurement of FT4 and TSH levels were performed on the same day in the department of Biochemistry, NINS by the ARCHITECT system Chemiluminescent Microparticle Immunoassay (CMIA), (Abbott Laboratory, Ireland). Informed consent was obtained from all families prior to initiation of the study. Before being finally included into the study, parents were explained about the purpose of the study. Statistical analysis was performed by SPSS 22. The result was presented in tables, figures and diagrams. The qualitative data was expressed as frequency and percentage and the quantitative data was expressed as mean with standard deviation. Chi-square test was performed to compare between qualitative variables and one way ANOVA test and Pearson's correlation test was performed to compare between quantitative variables. Probability value less than 0.05 was taken as statistically significant.

For this study to measure thyroid function status biochemically standard set up was as below:

Thyroid stimulating hormone (TSH) : Normal TSH Value: 0.35micro IU/ml to 4.94micro IU/ml (used at NINS according to Abbott Laboratory, Ireland)

Free T4 (FT4): Normal Free T4:0.70 to 1.48 ng/dl (9-19.04pmol/l) (Used at NINS according to Abbott Laboratory, Ireland), Conversion formula: concentration in ngl/dl x (12.87) = concentration in pmol/L

Age specific reference value of FT4 and TSH[9]:

FT4 (31 days to 18 years) : 0.6-1.94 ng/dl (9-25.7 pmol/l)

TSH (06 months to18 years) : 0.5-4.5 μIU/ml

Subclinical hypothyroidism: TSH above the defined upper limit of the reference range (4.5 μIU/ml), with a serum free thyroxin (T4) within the reference range (0.6-1.94 ng/dl).

Euthyroid: Children with normal TSH (0.5-4.5 μIU/ml) and normal FT4(0.70 to 1.48 ng/dl) value.

Hyperthyroid: TSH below lower limit (0.5ìIU/ml) of reference value and FT4 above the upper limit (1.48ng/dl) value of reference value

Hypothyroid: FT4 below lower limit (0.70 ng/dl)of reference value and TSH above the upper limit (4.5μIU/ml) of reference value

Euthyroid hyperthyroxinemia: Increased FT4 above the upper limit (1.48 ng/dl)of reference value (0.70 to 1.48 ng/dl) but normal thyroid-stimulating hormone (TSH) concentration (0.5-4.5 μIU/ml) and no clinical signs or symptoms of thyroid dysfunction. These changes may be transient or persistent.

Results:

Table-I
Demographic profile of the study subjects (n=160)

	Frequency (%)
Age (years)	
1-5	57 (35.6)
6-10	66 (41.3)
>10	37 (23.1)
Mean age (years)	7.15 ±3.46
	(1 - 13)
Mean±SD(min-Max)	
Gender	
Male	102 (63.8)
Female	58 (36.2)
Type of Epilepsy	
Focal onset	106 (66.3)
GTCS	44 (27.5)
Myoclonic	5 (3.1)
Abscence	5 (3.1)
Age of onset of seizure (Years)	
Mean±SD(min-Max)	3.75 ±3.01
	(0.1 - 13)
EEG	
Normal	20 (12.5)
Epileptiform discharge	140 (87.5)

Most of the patients 66 (41.3%) were between 6-10 years of age. The mean age of the study populations was 7.15± 3.46 years. Amongst the study subjects majority (63.8%) were male. Focal epilepsy was the most common type of epilepsy (66.3%). The mean duration of AED therapy for most of the patients (48.1%) was 6 months to 12 months.

Table-II
Distribution of the study subjects according to duration of the antiepileptic drugs (n=160)

Duration of AED use (months)	Frequency (%)
06-12 months	77(48.1)
13-24 months	45(28.1)
>24 months	38(23.8)

Table-III
Antiepileptic Drug used by the study subjects (n=160)

AED used	Frequency (%)
Sodium valproate (SVA)	64 (40)
Carbamazepine (CBZ)	65 (40.6)
Oxcarbamazepine (OXC)	13 (8.1)
Phenobarbitone (PHB)	7 (4.4)
Levetiracetum (LEV)	3 (1.9)
Topiramet (TPM)	6 (3.8)
Ethosuximide(ETS)	2 (1.3)
Total	160

Carbamazepine and Sodium valproate are the most commonly used antiepileptic drugs (40.6% and 40% respectively) . They were used as first line monotherapy drugs for focal onset and generalized onset epilepsy respectively. Majority of the children 116/160 (72.5%) were treated with monotherapy and 44/160 (27.5%) got polytherapy. Among the total 160 epileptic children 112(70%) were euthyroid and 43(26.9%) had sub clinical hypothyroidism (Figure-1).

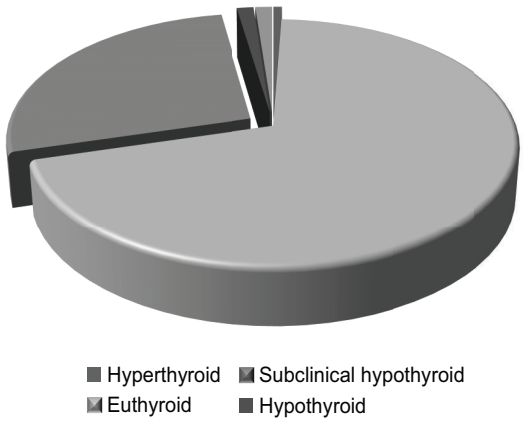


Figure-1: *Thyroid Function status of the study population*

Table-IV

Thyroid function status of the subjects treated with single AED

AED	Euthyroid n (%)	Subclinical hypothyroid n(%)	Hypothyroid n (%)	Euthyroid hyperthyroxinemia n (%)	Total N (%)
SVA	38 (82.6)	6 (13)	1 (2.2)	1 (2.2)	46 (100)
CBZ	33 (68.8)	14 (29.2)	1 (2.1)	0 (0.0)	48 (100)
OXC	5 (50)	5 (50)	0 (0.0)	0 (0.0)	10 (100)
PHB	5 (71.4)	2 (28.6)	0 (0.0)	0 (0.0)	7 (100)
TPM	4 (80.0)	0 (0.0)	0 (0.0)	1 (20.0)	5 (100)

*[SVA- Sodium valproate, CBZ- Carbamazepine, OXC-Oxcarbazepine, PHB-Phenobarbitone, TPM- Topiramate]

Table-VI

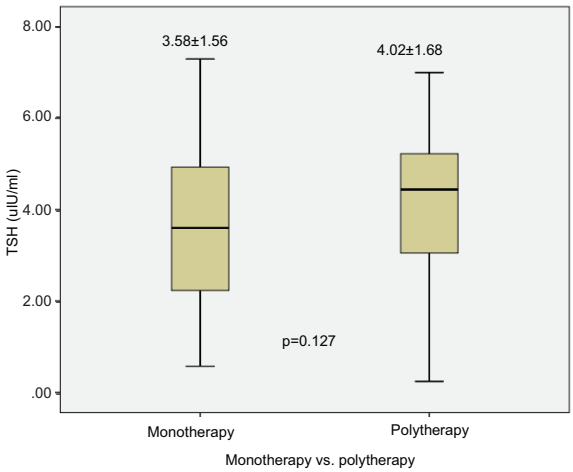
Mean TSH and FT4 level of the patients treated with single AED (Monotherapy)

AED	Frequency (n)	TSH(µIU/ml) (Mean ± SD)	FT4(ng/dl) (Mean ± SD)
Na. valproate	46	3.53± 1.51	1.00 ± 0.21
Carbamazepine	48	3.72 ± 1.64	0.93 ± 0.21
Oxcarbamazepine	10	4.10 ± 1.64	0.98 ± 0.17
Phenobarbitone	07	3.78 ± 2.04	0.96 ± 0.14
Topiramet	05	2.66 ± 1.22	1.15 ± 0.27
p-value		0.540	0.128

*One way ANOVA test was done to measure the level of significance

Among the mono-therapy group subclinical hypothyroidism was most common in oxcarbamazepine (50%) and subclinical hypothyroidism was also found in around one-fourth cases treated with carbamazepine and phenobarbitone monotherapy. Hypothyroidism was found in only one patient of each group of SVA and carbamazepine monotherapy. Two patients, one receiving valproate and another treating with t opiramate had euthyroid hyperthyroxinemia.

There was no significant variation of mean TSH and FT4 level of the study populations when compared among the monotherapy subgroups (for TSH p=0.540; for FT4 p=0.128). No significant difference was found in mean TSH level between Polytherapy vs. Monotherapy (p=0.127).



*Unpaired t test was done to measure the level of significance.

Figure-2: *Mean TSH levels of the patients (Monotherapy vs polytherapy)*

Table- V

Mean TSH and FT4 according to duration of single AED use.

Anti Epileptic Drugs		6-12 months Mean±SD	13-24 months Mean±SD	>24 months Mean±SD	p value
Sodium valproate	TSH((µIU/ml))	3.64±1.65	3.35±1.29	3.58±1.66	0.843
	FT4(ng/dl)	1.03±0.18	0.97±0.26	0.95±0.17	0.633
Carbamazepine	TSH((µIU/ml))	2.94±1.56	4.60±1.55	4.17±1.24	0.005*
	FT4(ng/dl)	1.00±0.16	0.87±0.10	0.88±0.13	0.014*
Oxcarbamazepine	TSH((µIU/ml))	4.71±1.40	3.18±1.41	4.10±1.54	0.130
	FT4(ng/dl)	0.95±0.17	1.02±0.19	0.98±0.17	0.551
Phenobarbitone	TSH((µIU/ml))	3.90±2.84	3.62±0.60	3.78±2.04	0.877
	FT4(ng/dl)	0.99±0.18	0.91±0.04	0.96±0.13	0.500

*One way ANOVA test was done to measure the level of significance. Statistically significant alteration of thyroid functions was found in participants being treated with carbamazepine for longer duration (6-12 months, 13-24 months and >24 months.

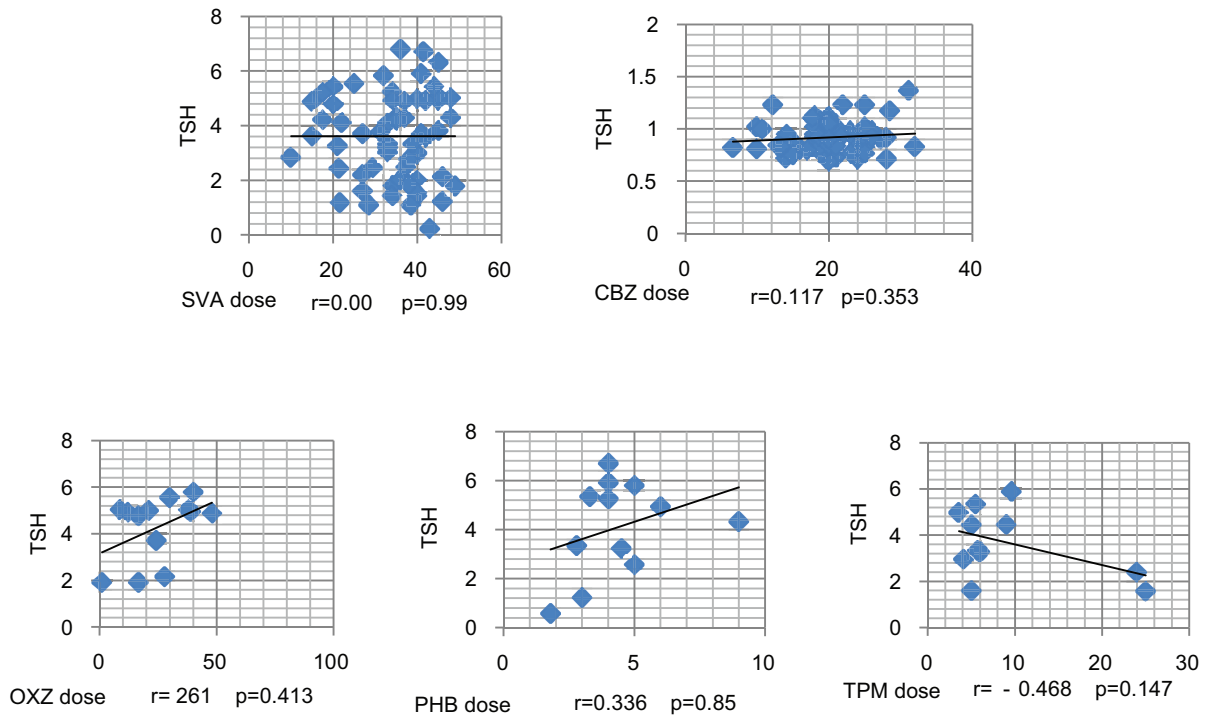


Fig.-3: *Correlation of TSH with doses of first line AED monotherapy*

** Pearson correlation test was done to measure the level of significance. There was a positive correlation of TSH with the doses of SVA, CBZ, OXC, and PHB but TSH was negatively correlated with the dose of TPM (Figure-5). None of them were statistically significant.

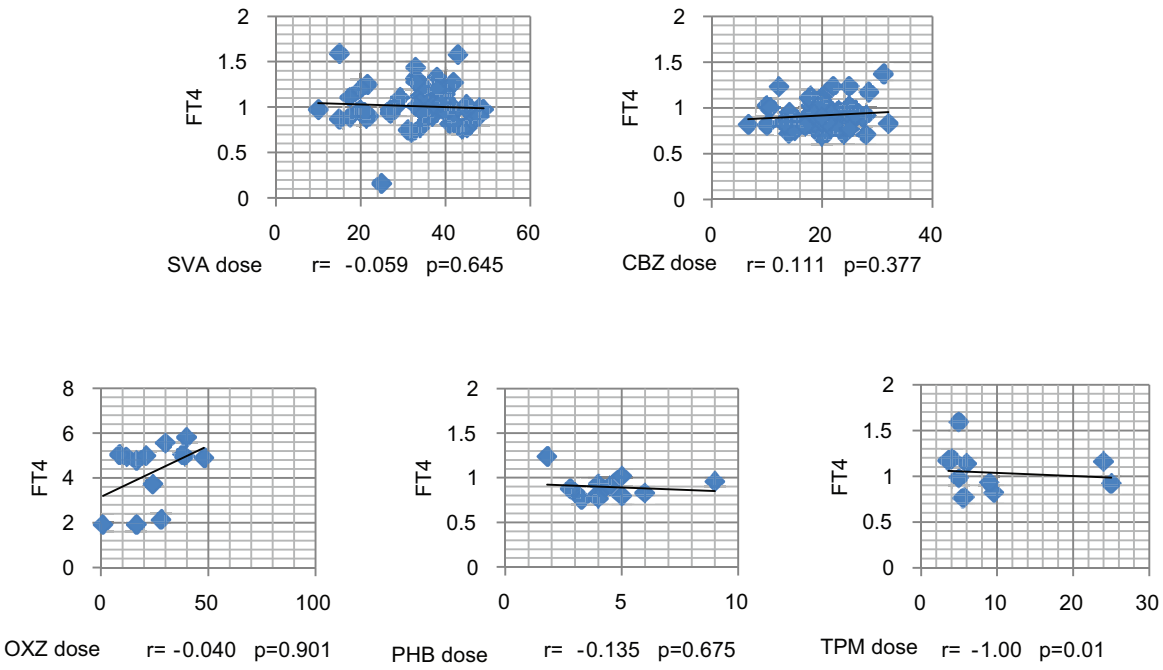


Figure 4: Correlation of FT4 with doses of first line antiepileptic monotherapy

Pearson's correlation test was done to measure the level of significance. Positive correlation was found between FT4 and the doses of CBZ and OXC but FT4 has negative correlation with doses of SVA, PHB and TPM. None other than the dose of topiramte had statistically significant correlation with FT4.

Discussion

Among the total 160 epileptic children 112(70%) were euthyroid, and 43(26.9%) had sub clinical hypothyroidism. The frequency of subclinical hypothyroidism (SCH) varies in children with epilepsy.[10] Subclinical hypothyroidism (SCH) was much higher (55%) in the study of Kundil MR[2] compared to our study (26.9%). This difference in frequency of SCH may be due to the fact that their study subjects received combination of only two anti-epileptic drugs (CBZ and VPA) whereas in our study patients were treated with different add on drugs. Highest frequency of SCH was observed in patients treated with OXC (50%) followed by CBZ (29.2%) monotherapy. For CBZ treated subjects this result was nearly similar to studies of Hamed SA et al.[11] But in case of OXC treated subjects SCH was much higher in our study than other study of Betteridge T et al.[12] Openheimer JH et al. found SCH was approximately 21.4% with OXC monotherapy and they also found that OXC-associated changes in serum thyroid hormone are seen with low and high doses of the drug.[4] In this study oxcarbazepine was used in very small number (13) of subjects but subclinical hypothyroidism was higher in oxcarbazepine treated patients. Due to its dose independent effect on thyroid hormone and small sample size (n=10) may be SCH was found higher in OXC treated subjects. A further study with larger sample size of OXC might be valuable to see its effect on thyroid function.

In this study 13% of the VPA (monotherapy) treated subjects had SCH and this result is similar with the study done by Ylmaz U et al.[13] but differed from study of Verrotti A et al.[14] where they found no change of thyroid function, whereas Mikati MA et al. in their studies documented high thyroid-stimulating hormone levels.[15] Manuel Castro-Gago et al.[10] found in one study that 25% children with SVA monotherapy had subclinical hypothyroidism. These different results seem partly due to different study methods (mostly retrospective studies). Thyroid stimulating hormone levels also seem to vary widely among different populations. In the current study 28.6% of the subjects who received PHB monotherapy were found to have SCH, this finding correlate with another study of Verrotti A et al.[14] In this study levetiracetam was used as add on drug, so its effect on thyroid function couldn't be evaluated.

In our study we found only 1 case (0.6%) with hyperthyroidism without clinical features of thyrotoxicosis. Similar finding was found in a previous study by Erricson et al.[16] In our cases none of the patients developed overt symptoms of hypothyroidism, only two children who were treated with VPA and CBZ monotherapy for prolong duration (more than 2 years) had high TSH and low FT4 suggestive of hypothyroidism. A previous study found one patient who developed overt hypothyroidism with phenytoin.[17] Hamed SA et al. found that 10% from the OXC group, 8.3% from the CBZ group, and 19.3% from the VPA group had hypothyroid status.[11] The findings of this study didn't match with that of current study.

When compared the thyroid function status of the subjects who were on monotherapy or poly therapy of AEDs, this study showed no significant difference. These findings differed from the study of Chakova L et al.[18] which reported that AEDs altered thyroid function, especially in patients treated with polytherapy. Shih FY et al.[19] noted that the FT4 level was significantly lower in patients treated with AED polytherapy. In present study a significant change in the thyroid hormone levels (increased TSH and decreased FT4) were found among the subjects treated with CBZ monotherapy throughout the 13-24 months period of therapy. A previous study showed similar findings with Carbamazepine.[20] There are several possible explanations for this association, including more seizure activity and/or longer duration of AED exposure. Patients with a longer duration of epilepsy are more likely to have a higher seizure burden, which may have a negative impact on thyroid hormone homeostasis, especially through the hypothalamus and TSH. Another possibility is that patients with a longer duration of epilepsy are more likely to be exposed to a longer AED treatment.

Conclusion:

Commonly used AED's were found to be associated with thyroid hormones dysfunction, most commonly subclinical hypothyroidism. Thyroid function was mostly altered by OXC, CBZ and PHB. VPA has relatively less effect on alteration of thyroid function than other first line antiepileptic drugs. Duration of CBZ mono therapy has significant effect on thyroid function.

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