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ORIGINAL ARTICLE

Relation between Antiepileptic Drugs and Thyroid Function in Children with Epilepsy

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ABSTRACT

Background: Epilepsy is a common neurological disorder, characterized by a disturbance in the electrical activity of the brain due to different factors. It includes many types of seizures with variable severity, seizure semiology, etiology, consequences, and management.The aim was to investigate the effects of traditional antiepileptic drugs (AEDs) versus newer AEDs on the thyroid hormone profile of children with epilepsy. **Methods:**This cross sectional study was conducted at Pediatrics Neurology Unit, Pediatric Outpatient Clinic and Clinical Pathology Department at Zagazig University Hospitals on children with epilepsy attending Pediatric Inpatient and Outpatient Clinic. They were classified into: Group I represents patients receiving traditional antiepileptic drugs (AEDs), Group II comprises patients receiving new AEDs, and Group III serves as the healthy control group.Every patient and the healthy group underwent thorough history taking, a comprehensive clinical examination, and laboratory investigations **Results:** There is statistically significant difference between the studied groups regarding free T3, free T4 and TSH. On doing pairwise comparison, difference is significant between control group and each other group. While there is statistically significant difference between the studied groups regarding free T4, TSH and thyroid abnormalities (with significant difference between traditional AEDs and each other group), there is statistically non-significant difference between the studied groups regarding low free T3. **Conclusion:**Our findings suggest that traditional AEDs have significant effects on the thyroid hormone profile of epileptic children on long-term therapy and these effects were accompanied by higher subclinical and primary hypothyroidism compared to newer AEDs and control group.

Key words: Antiepileptic Drugs, Thyroid,Children, Epilepsy.

INTRODUCTION

Antiepileptic medications (AEDs) are frequently prescribed to epileptic patients for extended periods of time. Several studies have shown that AEDs adversely impact the endocrine system, thyroid function, fertility, sexuality, and bone health in both juvenile and adult populations **[1]**.

It is known that some AEDs can interfere with normal thyroid function, including

oxcarbazepine (OXC), valproate (VPA), phenobarbital (PHB), phenytoin (PHT), and carbamazepine (CBZ) **[2]**. Cell growth and development, as well as the maintenance of lipid and glucose metabolism, depend on thyroid hormones. A higher risk of coronary heart disease has been linked to hypothyroidism, even in subclinical form **[3]**.

Environmental influences and life cycle stages, such as menopause and age, might affect thyroid hormone levels. Cell growth and development, as well as the maintenance of lipid and glucose metabolism, are significantly influenced by thyroid hormones. Coronary heart disease risk is elevated in hypothyroidism, especially in the subclinical kind. There is confusion regarding the incidence of AED-induced thyroid dysfunction and its long-term implications because thyroid function tests are not routinely performed in clinical practice. AEDs can affect thyroid function because they alter hormone metabolism and activity **[4]**, as first reported by **Strandjord et al. [5]**. Long-term AED therapy may change the balance of thyroid hormones and cause hypothyroidism, according to numerous additional studies emphasizing the significance of routine thyroid function monitoring in epilepsy patients **[4]**.

This study looked at how children who epilepsy's thyroid hormone profile was affected by older versus newer antiepileptic medications (AEDs).

PATIENTS AND METHODS

This cross sectional study was conducted at Pediatrics Neurology Unit, Pediatric Outpatient Clinic and Clinical Pathology Department atZagazig University Hospitals. Children were classified into group 1 including 33 patients with epilepsy treated with traditional AEDs, group 2 including 33 patients with epilepsy treated with new AEDs and group 3 including 33 healthy children who are age and sex matched with the patient group.

Informed written consent was obtained from patient's parents. The study protocol was submitted for approval by Zagazig University Institutional Review Board (IRB number 9020). The study was conducted according to Helsinki Declaration.

Children with epilepsy treated with antiepileptic drugs for at least 6 months from the time of diagnosis, age ranged from 1 year to 16years at time of diagnosis and all patients were recruited from the Pediatric Department of Zagazig University hospitals and outpatient clinic were included in the study.

Poor compliance, the use of anti-thyroid medications and thyroid replacement therapy, signs that indicate a thyroid gland issue, chronic medical conditions or metabolic or endocrine abnormalities, patients receiving any other drugs especially for chronic diseases and critically ill patients to exclude Euthyroid Sick Syndrome were excluded from the study.

Every patient and the healthy group underwent thorough history taking, a comprehensive clinical examination, and laboratory investigations, which included TSH, FT4 and FT3 assays using electrochemilumenance on Cobas 8000 Modular Analyzer e602 (Roche Diagnostics, Mannheim, Germany).Serum level of valproic acid and carbamazipeneusing a homogeneous enzyme immunoassay technique on Cobas

6000 Analyzer c501 (Roche Diagnostics, Mannheim, Germany).Complete blood count (CBC) was done for all samples using sysmexXN330(Sysmex Corporation, New York, USA) for red blood cell (RBC) count, hemoglobin level, hematocrit value, WBC count (total and differential), and platelet count.Creative protein: Semquantitative measurement of the level of C- reactive protein (CRP). Estimation was carried out using the test kit (Cromatest) at 0h of clinical presentation. The CRP latex particles are coated with antibodies to human CRP. When the latex suspension is mixed with serum containing elevated CRP levels on a slide, clear agglutination was seen within 2 minutes. Specimen collection and storage: Fresh sample of venous blood was allowed to clot form and retract centrifuge clotted blood sample and collect serum, store at 2-8 oC. CRP had a detection limit of 6 mg/L of CRP in the patient's serum.[6]

Statistical Analysis:

IBM SPSS Statistics for Windows, a version of the IBM Statistical Package for Social Sciences program, was used to analyze the data, Version 26.0. Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution. Continuous data was expressed as mean ± standard deviation, median & IQR while categorical data as numbers and percentage. A statistical value <0.05 was considered as significant. Chi-square test was used to study the association between two qualitative variables. Analysis of variance (ANOVA or F test): was employed to test for a significant difference between more than two groups with normal distributions in continuous data. With the use of Levine's test and the Shapiro-Wilk test, respectively, the homogeneity of variances and the assumption of normality in each group were verified. When an ANOVA's presumptions were violated, the Kruskal-Wallis test was employed to compare more than two groups with skewed data. The Bonferroni post hoc test was used to adjust for multiple comparisons following a significant ANOVA test to identify which group had a significant difference, while the Tukey honestly significant difference (Tukey-HSD) test was employed after a significant Kruskal- Wallis test.

RESULTS

There is statistically significant difference between the studied groups regarding behavior, skin changes, voicechanges, and peripheral tremor. There is statistically non-significant difference between the studied groups regarding age, weight, gender or lid retraction, radial pulse. There is statistically non-significant difference between the studied groups (with epilepsy) regarding type of seizures, or EEG changes (**Table 1)**.

There is statistically significant difference between the studied groups regarding cholesterol. The difference is significant between traditional and new AEDs groups. There is statistically non-significant difference between the studied groups regarding WBCs, platelet, SGOT, SGPT, total bilirubin **(Table 2)**.

Among patients who received traditional AEDs, 93.9% had Depakine and 6.1% received Tegretol.Among patients who received new AEDs, 90.9% had Tiratam and 9.1% received Topiramate (**Table 3).**

There is statistically significant difference between the studied groups regarding free T3, free T4 and TSH. On doing pairwise

comparison, difference is significant between control group and each other group (lowest TSH, highest free T4 and T3 prevailed in control group) (**Table 4).**There is statistically significant difference between the studied groups regarding free T4, TSH and thyroid abnormalities (with significant difference between traditional AEDs and each other group). There is statistically non-significant difference between the studied groups regarding low free T3. (**Table 5).**

There is statistically significant positive correlation between TSH and Valproic acid and duration of therapy. There is non-significant correlation between TSH and other parameters among patients receiving traditional AEDs. There is statistically significant negative correlation between free T4 and both onset of epilepsy. There is non-significant correlation between free T4 and other parameters among patients receiving traditional AEDs. There is non-significant correlation between free T3 and either age, weight, onset of epilepsy among patients receiving traditional AEDs (**Table 6).**

There is statistically significant positive correlation between TSH and both age, weight and onset of epilepsy. There is non-significant correlation between TSH and other parameters among patients receiving new AEDs. There is statistically significant positive correlation between free T4 and age. There is non-significant correlation between free T4 and other parameters among patients receiving new AEDs. There is non-significant correlation between free T3 and either age, weight, duration of AEDs or onset of epilepsy among patients receiving new AEDs (**Table 7).**

Table (1) Comparison between the studied groups regarding demographic and clinical data

	Group I N=33	**Group II N=33**	**Group III n=33**	**χ^2**	**p**
Gender:					
Female	17 (51.5%)	14 (42.4%)	22 (66.7%)	3.979	0.137
Male	16 (48.5%)	19 (57.6%)	11 (33.3%)		
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**p**
	93.52 ± 10.21	96.61 ± 15.15	99.7 ± 9.91	2.387	0.097
Weight	19.02 ± 7.68	15.08 ± 6.06	17.24 ± 8.14	2.396	0.096
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**KW**	**p**
Age (year)	5(3 – 9)	3.5(1.5 – 6.5)	3(2 – 6)	4.351	0.114
Behavior					
CP	5 (15.2%)	3 (9.1%)	0 (0%)	MC	<0.001**
Hyperactive	20 (60.6%)	17 (51.5%)	0 (0%)		
Normal	8 (24.2%)	13 (39.4%)	33 (100%)		
Skin:					
No	21 (63.6%)	26 (78.8%)	33 (100%)	MC	<0.001**
Flushing	4 (12.1%)	5 (15.2%)	0 (0%)		

	Group I N=33	Group II N=33	Group III n=33	χ^2	p
Sweating	8 (24.2%)	2 (6.1%)	0 (0%)		
Voice:					
No	26 (78.8%)	31(93.9%)	33 (100%)	MC	0.01*
Hoarseness	2 (6.1%)	0 (0%)	0 (0%)		
No voice	5 (15.2%)	2 (6.1%)	0 (0%)		
Lid retraction:					
Absent	31 (93.9%)	31 (93.9%)	33 (100%)	MC	0.586
Present	2 (6.1%)	2 (6.1%)	0 (0%)		
Peripheral tremor					
Absent	24 (72.7%)	24 (72.7%)	33 (100%)	MC	0.01*
Sometimes	0 (0%)	2 (6.1%)	0 (0%)		
Always	9 (27.3%)	7 (21.2%)	0 (0%)		
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**p**
Radial pulse	93.52 ± 10.21	96.61 ± 15.15	99.7 ± 9.91	2.387	0.097
Type					
Generalized tonic	27 (81.8%)	27 (81.8%)			
clonic	2 (6.1%)	0 (0%)			
Absence epilepsy	2 (6.1%)	2 (6.1%)		MC	0.076
Focal	2 (6.1%)	0 (0%)			
Focal spastic	0 (0%)	2 (6.1%)			
Focal generalized	0 (0%)	2 (6.1%)			
Refractory epilepsy					
EEG					
Focal epileptogenic	4 (12.1%)	8 (24.2%)			
activity	16 (48.5%)	13 (39.4%)		MC	0.426
Generalized	13 (39.4%)	12 (36.4%)			
activity.					
Normal EEG					
Onset [median(IQR)]	1.5(0.33 – 4)	0.75(0.5 – 3)		-0.368¥	0.713
Duration [median(IQR)]	2(1 – 4.5)	1(0.67 – 3)		-2.232¥	0.026*

χ^2Chi square test MC Monte Carlo test F One way ANOVA KW Kruskal Wallis test IQR interquartile range ¥Mann Whitney test
**p≤0.001 is statistically highly significant *p<0.05 is statistically significant

Table (2) Comparison between the studied groups regarding laboratory data

	Group I N=33	Group II N=33	Group III n=33	F	p
	Mean ± SD	Mean ± SD	Mean ± SD		
Cholesterol	156.78 ± 22.24	171.92 ± 28.9	167.29 ± 7.97	4.276	0.017*
LSD	P_1 0.005*	P_2 0.386	P_3 0.05		
	Median (IQR)	**Median (IQR)**	**Median (IQR)**	**KW**	**p**
Platelet(10^3/mm^3)	290(232.5 – 357)	315(287 – 375)	285(267.5– 347.5)	2.891	0.236
SGOT	23.8(18.5 – 26)	25.7(20.5 – 35.4)	28.1(20.3 – 38)	3.543	0.178
SGPT	12.1(9.85 – 17.2)	12.8(9 – 25)	15.66(12.5 – 19.5)	4.797	0.091
Total bilirubin	0.17(0.12 – 0.21)	0.21(0.15 – 0.28)	0.2(0.13 – 0.3)	4.98	0.083

F One way ANOVA KWKruskal Wallis test IQR interquartile range LSD Fisher
*p≤0.001 is statistically highly significant *p<0.05 is statistically significant

Table (3) Comparison between the studied groups regarding type of AEDs

	Group =33
Traditional **Depakine** **Tegretol**	31 (93.9%) 2 (6.1%)
New **Tiratam** **Topiramate**	30 (90.9%) 3 (9.1%)

Table (4) Comparison between the studied groups regarding thyroid profile

	Group I N=33	Group II N=33	Group III n=33	KW	p
	Median (IQR)	Median (IQR)	Median (IQR)		
FT3(pmol/L)	5.54(4.49 – 7.89)	5.36(4.85 – 6.52)	5.05(4.59 – 5.15)	6.773	0.034*
Pairwise	P_1 0.827	**P_2 0.033***	**P_3 0.019***		
FT4(pmol/L)	14.09(11.97-18.1)	15.52(13.8 – 18.6)	20.73(19.8 – 21.4)	33.184	<0.001**
Pairwise	P_1 0.415	**P_2<0.001****	**P_3<0.001****		
TSH	5.96(1.35 – 8.17)	2.58(1.87 – 4.03)	2.01(1.52 – 2.08)	17.412	<0.001**
Pairwise	P_1 0.054	**P_2 0.025***	**P_3<0.001****		

KW Kruskal Wallis test IQR interquartile range
**p≤0.001 is statistically highly significant *p<0.05 is statistically significant

Table (5) Comparison between the studied groups regarding thyroid profile abnormalities

	Group I N=33	Group II N=33	Group IIIa n=33	χ^2	p
TSH					
Low	0 (0%)	1 (3%)	0 (0%)		
Normal	18 (54.5%)	30 (90.9%)	33 (100%)	MC	<0.001**
High	15 (45.5%)	2 (6.1%)	0 (0%)		
P (χ^2)	P_1 <0.001**	P_2 0.566	P_3<0.001**		
Free T4					
Low	10 (30.3%)	3 (9.1%)	0 (0%)		
Normal	23 (69.7%)	28 (84.8%)	30 (90.9%)	MC	<0.001**
High	0 (0%)	2 (6.1%)	3 (9.1%)		
P (χ^2)	P_1 0.014*	P_2 0.159	P_3 0.001**		
Free T3					
Low	0 (0%)	3 (9.1%)	0 (0%)		
Normal	33 (100%)	30 (90.9%)	33 (100%)	MC	0.121
Thyroid:					
Normal	19 (57.6%)	26 (78.8%)	33 (100%)		
Subclinical hypothyroidism	5 (15.2%)	2 (6.1%)	0 (0%)		
Primary hypothyroidism	9 (27.3%)	2 (6.1%)	0 (0%)	MC	<0.001**
Abnormal pituitary	0 (0%)	1 (3%)	0 (0%)		
Thyroid resistance syndrome	0 (0%)	2 (2.6%)	0 (0%)		
P (χ^2)	P_1 0.043*	P_2 0.241	P_3<0.001**		

χ^2Chi square test MC Monte Carlo test

Table (6) Correlation between thyroid profile and demographic data, onset and duration among group receiving traditional AEDs

	TSH		Free T4		Free T3	
	r	p	r	p	r	p
Age (year)	0.312	0.077	0.026	0.888	0.027	0.882
Weight (kg)	0.294	0.097	-0.004	0.981	-0.017	0.924
Onset of epilepsy	0.005	0.979	**-0.493**	**0.004***	-0.177	0.326
Valproic acid	**0.763**	**<0.001****	-0.268	0.146	-0.172	0.356
Duration of AEDs	**0.467**	**0.007***	0.255	0.125	0.087	0.631

r Spearman rank correlation coefficient
*p<0.05 is statistically significant **p≤0.001 is statistically highly significant

Table (7) Correlation between thyroid profile and demographic data, onset an duration among group receiving new AEDs

	TSH		Free T4		Free T3	
	r	p	r	p	r	p
Age (year)	**0.368**	**0.035***	**0.438**	**0.011***	-0.174	0.332
Weight (kg)	**0.411**	**0.017***	0.262	0.141	-0.227	0.203
Onset of epilepsy	**0.693**	**0.006***	0.283	0.407	-0.154	0.6
Duration of AEDs	-0.134	0.457	0.311	0.078	-0.219	0.221

r Spearman rank correlation coefficient *p<0.05 is statistically significant

DISCUSSION

In the current study, Regarding age and gender, there was a statistically insignificant difference between the groups under study. The age of patients with epilepsy was ranged from 1.5 to 9 years. In this study, the median onset time for epilepsy was during infancy or early childhood. In group I, it is 1.5 years with an interquartile range (IQR) of 0.33 to 4 years, while in group II has a median onset of 0.75 years (IQR: 0.5 to 3 years).

This came in agreement with **ushufRahaman [7]** who studieda total of 106 cases and found their age ranged from 3-12 years. As per the study done by **Camfield and Camfield [8]** The first year of life saw the highest incidence of epilepsy, which by the end of the first decade had decreased to adult levels.

Also these findings were explained by **Farghaly et al. [9]** who stated that the majority of the individuals under study (80%) stated that their seizures began in infancy or early childhood (less than six years old). Since GABA causes hypopolarization and inhibition of neurons in adulthood, it is possible that the reduced seizure threshold of the immature brain during early brain development accounts for some of the high incidence of seizure onset during infancy and early childhood (80%) compared to late childhood (17%) and adolescence (2.9%).

Furthermore, genetic disorders, prenatal problems, and CNS infections—all of which have a greater prevalence of brain injuries at that age—start the process of epileptogenesis in the developing brain **[10]**.

Similarly, in a comparative prospective study carried on children of Saudi Arabia by **Al-Sulaiman and Ismail [11]**, for 48.7% of the patients, the age of onset was during the first year of life.

In our study, as regard type of seizures, the majority of patients in both groups have "Generalized tonic-clonic" epilepsy (81.8%), with "Refractory epilepsy" being less common. It is apparent that "Absence epilepsy" is exclusive to the first group, while the second group contains "Focal" epilepsy cases.

As regard EEG changes, in the first group, 12.1% of patients had "Focal epileptogenic activity," and 48.5% displayed "Generalized activity," while "Normal EEG" results in 39.4% of cases in the first group. Between the epilepsy study groups, there is a statistically non-significant difference in the types of

seizures or EEG abnormalities.

This was in line with earlier studies' findings that generalised tonic-clonic seizures were more common **[12].** Also, **Rajendran [13]** discovered that 37% of seizure disorders were of the generalised tonic-clonic type, 22% were of the atypical febrile seizure type, 17% were neonatal seizures, 10% were epileptic syndromes, and 6% were absence seizures.

In addition, **Al Rajeh et al. [14]** showed that between the ages of one and five years old, generalised epilepsies were the most common type of epilepsy in Saudi Arabia (74%).

Of the youngsters with epilepsy, 56.5% had generalised seizures while only 43.5% had focal seizures **[15].** Focal onset was the most common seizure type in other research studies. **[16].**

Endziniene et al. [17] showed that just 29.9% of their paediatric epilepsy patients had generalised epilepsies, 15.9% had partial or generalised epilepsies that could not be defined, and 4.2% had no class. Fifty percent of their paediatric epilepsy patients had localization-related epilepsies.

Our study showed that, among patients who received traditional AEDs, 93.9% had Depakine (Sodium Valproate) and 6.1% received Tegretol (Carbamazepine). Among patients who received new AEDs, 90.9% had Tiratam (Levetiracetam) and 9.1% received Topiramate.

In agreement with our study, **Yılmaz et al. [18]** stated that valproate, carbamazepine, and phenobarbital are well-known and effective traditional antiepileptic medications for the treatment of a variety of paediatric epilepsy types, while levetiracetam and oxcarbazepine are more recent AEDs that are being used more frequently in children as monotherapy and add-on therapy. Furthermore**, Elshorbagy et al. [19]** reported that, among their patients, levetiracetam, topiramate were commonly used.

According to our research, there are statistically significant differences in free T3, free T4, and TSH across the groups under study. A pairwise analysis reveals a substantial difference between the control group and all other groups. In comparison to the modern AEDs group and the control group, the traditional AEDs group had greater TSH and free T3, while the traditional AEDs group had lower free T4.

In agreement with our study, **Elshorbagy et al. [19]**found a significant decrease in the serum level of fT4 and an increase in the serum level of TSH (P<0.001) in epileptic children receiving traditional AEDs, compared to the control group. However, the serum level of fT3 was not influenced by the administration of AEDs (P=0.38). T3 is derived from the transformation of T4 in peripheral tissues.

Also, a study done by **Ranga et al. [20]** stated that there was a noteworthy distinction in the mean FT4 values between the control and epileptic groups.

Prior research revealed that patients receiving VPA had significantly higher serum levels of TSH and lower levels of FT4 **[18, 21].**

Eirís-Puñalet al. [22] noted a drop in FT4 following valproate treatment. Following valproate monotherapy, patients with epilepsy showed a substantial increase in TSH readings (p value < 0.0001). It has been observed that subclinical hypothyroidism occurred in 26 percent of the 51 individuals who received VPA treatment.

In accordance with our study, **Durdane et al. [23]** TSH values were higher in children receiving sodium valproate and stayed unchanged in children receiving levetiracetam, according to a study on thyroid

hormone levels in paediatric patients.

Rahman and Islam [24] stated that their data showed that changed (high) blood TSH levels were present in 20.76% of the responses to AEDs. The majority of them (90.1%) were receiving sodium valproate therapy (90.1%). The responders who were administered sodium valproate, phenobarbitone, and oxcarbazepine had altered serum TSH levels of 38.46, 8.67, and 6.67%, respectively. In their study, 4.72 and 3.78% of the patients had abnormal blood T4 and T3 levels. Of those with low T4 levels, 20% were using phenobarbitone, 60% were taking sodium valproate and the remaining individuals were taking oxcarbazepine. Levetiracetam did not lower T4 or T3, nor did it raise serum TSH. Subsequent analysis of the data showed that the antiepileptic groups did not significantly differ in how their serum T4 and T3 levels were altered.According to other research, valproate users had higher TSH levels but stable FT4 levels **[25].** Another study on teenage girls with epilepsy found that, while the values were still within the normal range, the group receiving valproate had higher serum levels of TSH and lower serum levels of FT4 **[26].Bayar et al. [27]** found that whereas patients using VPA had much higher mean levels of fT3 and T4 than those using CBZ; those using CBZ had significantly lower mean levels of fT4 and T3.

Numerous other investigations shown that CBZ medication may impact the balance of thyroid hormones in patients with epilepsy, specifically by lowering the level of fT4, while leaving fT3 and TSH unchanged **[28, 29].**Also, a study by **Bentsen et al. [30]** shown that FT4 significantly decreased while receiving carbamazepine medication.

Another study done by **Dhodi et al. [31]** revealed that while there was no discernible difference in the blood ft3 and ft4 values, patients using phenytoin (conventional AEDs) had TSH values (Mean ± SD) that were statistically higher than the usual reference value. **Shih et al. [32]** reported lowered fT4 levels in epilepsy patients receiving LEV.

However, a number of investigations discovered that valproate-treated patients' FT4 and TSH values remained unchanged **[33].** Also**, Dhodi et al. [31]** discovered that blood levels of thyroid hormones were unaffected by sodium valproate monotherapy.

Another study found no discernible variations in FT4 and TSH serum levels between phenobarbital-treated individuals and the control group **[34]. Adhimoolam and Arulmozhi [34]** found that in individuals with epilepsy, LEV had no effect on fT4, fT3, or TSH levels.

The alterations brought on by long-term valproate administration appear to be related to the provision of AED medication, as evidenced by several prior studies that demonstrated the decreased fT4 and elevated TSH concentrations reverted to normal values following valproate cessation **[28, 35].**

In the current study, the group using traditional AEDs had considerably higher TSH and lower FT4 than the group using modern AEDs. In the group receiving standard AEDs, there was a significant increase in both primary and subclinical hypothyroidism (27.3%) than newer AEDs group (6.1%).This came in agreement with **Ranga et al. [20]** who discovered that 21 of the 100 epileptic youngsters whose FT4 and TSH levels were examined had sub-clinical hypothyroidism.

Also, **Elshorbagy et al. [19]** found that 5% of children with epilepsy treated with newer medications and 20% of children with epilepsy treated with older drugs had

subclinical hypothyroidism. On the other hand, no one in the control group shown any signs of subclinical hypothyroidism. They discovered that all of their patients were clinically euthyroid and that none of them had manifested overt hypothyroidism symptoms.

Inaddition**, Eirís-Puñal et al. [22]** found that thirteen of the fifty-one children who were on valproate for 12 to 16 months had subclinical hypothyroidism documented.

Another earlier study found that when using AEDs to treat epilepsy, patients may acquire subclinical hypothyroidism. But there were no documented hypothyroidism symptoms or indicators **[36].Apak et al. [37]** detailed the detrimental effects of AEDs on thyroid function, and numerous retrospective studies revealed that thyroid function alterations did not affect the clinical euthyroid status of epileptic patients.

Jensovsky et al. [38] a subclinical hypothyroidism, which is characterized by normal thyroid hormone levels and a clinically euthyroid condition, may result from small changes in thyroid hormone activity, according to research on paediatric epilepsy patients. Additionally, they stated that these patients have mild neuromuscular abnormalities, somatic symptoms, sadness, slow thinking, poor memory, and cognitive impairment, which includes a decrease in processing speed and poor memory.

Also**, Aparicio-Claure et al. [39]** emphasized the significance of taking into account observations as early clinical markers of hypothyroidism, such as decreased motivation, weakness, lethargy, and constipation in patients using AEDs.

On the other hand, **Verrotti et al. [40]** have demonstrated that subclinical hypothyroidism is not brought on by valproate. Their study's sample size, though, was different. **Lli et al. [41]** observed no signs of thyroid impairment in patients using sodium valproate for two to four years. **Ajmariya et al. [42]** discovered that all of their patients with epilepsy were clinically euthyroid and had not shown any overt signs of hypothyroidism.

Part of the reason for the conflicting findings on standard AEDs' impact on thyroid hormones across research is that the methodologies and study designs varied. For patients with recently diagnosed epilepsy, the first AED prescription failure rate is still quite high. This can be attributed to the low efficacy and/or high frequency of adverse effects, which led to a renewed quest for more advanced medications. In general, patients tolerate newer AEDs better, they have fewer medication interactions, require less serum drug monitoring, and may even have neuroprotective effects **[43].**

In individuals receiving conventional AEDs, our study found a statistically significant positive connection between TSH and medication duration. However, among patients using conventional AEDs, there is no significant link found between the duration of AEDs and free T3 and FT4. TSH, free T4, or free T3 do not significantly correlate with the length of AED use in patients starting new AEDs.

Shih et al. [32] discovered that people with epilepsy over a longer period of time were more likely to have low fT4. This connection could be explained by a number of factors, such as increased seizure activity and/or prolonged use of AEDs. Individuals who have had epilepsy for a longer period of time are more likely to have a larger seizure burden, which may negatively affect the hemostasis of thyroid hormone, particularly through the hypothalamus and TSH. They did not, however, discover a connection between low

fT4 and recent seizure frequency.

Mutlu [4] revealed that the thyroid function parameters in the monotherapy and polytherapy categories did not significantly correlate with the length of AED use for ≤1 year, 1-5 years, or >5 years.

In the group getting traditional AEDs, there is a statistically significant positive association between TSH and Valproic acid; however, among patients receiving traditional AEDs, there is no statistically significant correlation between Free T4 and Valproic acid.

It has been suggested that VPA, rather than inducing microsomal enzymes in the liver, may influence thyroid hormone levels through its enzymatic inhibitory impact **[2].** It is highlighted that while VPA can raise TSH levels, this could be caused by its GABA ergic property. Somatostatin suppresses TSH secretion, and GABA inhibits the release of somatostatin. Moreover, VPA is firmly attached to plasma proteins, which causes T4 to separate from its position **[37].**

Yılmaz et al. [18] and**Aggarwal et al. [21]** revealed that patients receiving VPA had significantly lower serum levels of FT4 and higher levels of TSH.

Additionally, in a different research involving teenage girls with epilepsy, the group receiving valproate had serum levels of TSH and FT4 that were higher and lower, respectively, than the group not getting treatment, while the values were still within the normal range **[26].**

Zhang et al. [2] and**Adhimoolan and Arulmozhi [34]** revealed that the fT4 level was decreased by the usage of phenytoin and VPA.

EirísPuñal et al. [22] found that compared to healthy controls, epilepsy patients receiving CBZ and VPA had decreased mean T4 and fT4 levels. **Sahu et al. [25]** discovered that while FT4 levels stayed constant, TSH levels rose in valproate-using patients.However, a number of investigations discovered that valproate-treated patients' FT4 and TSH values remained unchanged **[33].**

CONCLUSION

Our findings suggest that traditional AEDs have significant effects on the thyroid hormone profile of epileptic children on long-term therapy and these effects were accompanied by higher subclinical and primary hypothyroidism compared to newer AEDs and control group. Overall, these findings underscore the importance of monitoring thyroid function in children with epilepsy, as it may be influenced by the choice of AED therapy and could have clinical relevance in optimizing treatment strategies and patient care.

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