IMPACT OF TRADITIONAL VERSUS NEWER VERSUS COMPINED ANTIEPILEPTIC DRUGS ON THYROID FUNCTION IN CHILDREN WITH EPILEPSY

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Abstract:

Background: Patients with epilepsy are often required to take antiepileptic drugs (AEDs) for a long period of time. Many studies showed that AEDs have a negative impact on the endocrine system in both pediatric and adult populations, including thyroid function, fertility, sexuality, and bone health.

Aim: To investigate the effects of traditional antiepileptic drugs (AEDs) versus newer AEDs versus both on the thyroid hormone profile of children with epilepsy.

Methods: This was a cross sectional study that was conducted at Pediatrics Neurology Unit. Group I represents patients receiving traditional antiepileptic drugs (AEDs), Group II comprises patients receiving new AEDs, and Group III comprises patients receiving mixed traditional and newer AEDs group. Thyroid profile was assessed in all patients. All patients and healthy group were subjected to laboratory Investigations including FT3, FT4, TSH, by electrochemilumenance serum level of valproic acid and carbamazipene bya homogeneous enzyme immunoassay technique**.**

Results: Sstatistically significant difference between the studied groups regarding free T3. On doing pairwise comparison, difference is significant between traditional AEDs group and mixed AEDs group. There is statistically significant difference between the groups regarding free T4. On doing pairwise comparison, difference is significant between new AEDs group and mixed AEDs group. There is statistically significant difference between the groups regarding TSH. On doing pairwise comparison, difference is significant between new AEDs group and each other group.

Conclusion: Mixed traditional and newer antiepileptic drugs had more thyroid dysfunction than monotherapy with traditional or newer antiepileptic drugs.

Keywords: Traditional, Newer, Antiepileptic Drugs, Thyroid.

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Introduction:
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 pediatric and adult populations, including thyroid function, fertility, sexuality, and bone health (**1, 2).** Certain AEDs such as carbamazepine (CBZ), phenobarbital (PHB), phenytoin (PHT), valproate (VPA), and oxcarbazepine (OXC) are known to affect normal thyroid function **(3).**

Thyroid hormones are important for maintaining lipid and carbohydrate metabolism, cell growth and development. Hypothyroidism, even in subclinical form, has been associated with an increased risk of coronary heart disease (**4, 5).**

Thyroid hormone levels may vary depending on life cycle like menopause and age, and environmental factors. The prevalence of AED-induced thyroid dysfunction and its long-term consequences remain uncertain, primarily because thyroid function tests are not routinely performed in clinical practice. AEDs can affect hormone levels by altering their metabolism and function; as such, AEDs can also affect thyroid function. Subsequently, many other studies highlighting the importance of routine thyroid function testing in patients with epilepsy have reported that long-term AED therapy could alter thyroid hormone balance and lead to hypothyroidism (**6**).

Patients and Methods
This cross sectional study was conducted at Pediatrics Neurology Unit, Pediatric Outpatient Clinic and Clinical Pathology Department at Zagazig 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 patients with epilepsy treated with mixed traditional and newer AEDs.
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.

All patients and healthy group were subjected to detailed history-taking, full clinical examination and laboratory investigations, which included : Complete blood count (CBC) was done for all samples using sysmex XN 330 (Sysmex Corporation, New York, USA). Serum level of valproic acid and carbamazipene using a homogeneous enzyme immunoassay technique on Cobas 6000 Analyzer c501 (Roche Diagnostics, Mannheim, Germany). TSH, FT4 and FT3 assays using electrochemilumenance on Cobas 8000 Modular Analyzer e602 (Roche Diagnostics, Mannheim, Germany). Creative protein: Semquantitative measurement of the level of C-reactive protein (CRP).

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 used for continuous data to test for significant disparity between more than two groups with normal distributions. The homogeneity of variances and the assumption of normality in each group were confirmed using the Shapiro-Wilk test and Levine's test, respectively. Kruskal-Wallis test: was used to compare more than two groups of skewed data when the assumptions of an ANOVA were broken. After a significant ANOVA test to determine which group had a significant difference, the Bonferroni post hoc test was used to account for multiple comparisons, whereas the Tukey honestly significant difference (Tukey-HSD) test was employed after a significant Kruskal- Wallis test.

Results:

Table (1) Comparison between the studied groups regarding thyroid profile

	Group I N=33	**Group II N=33**	**Group IIIb 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)	5.21(3.91 – 6.25)	6.542	0.038*
Pairwise	P_1 0.323	**P_2** 0.106	**P_3 0.012***		
FT4(pmol/L)	14.09(11.97-18.1)	15.52(13.8 –18.6)	13.7(10.37 –15.7)	7.47	0.024*
Pairwise	P_1 0.204	**P_2 0.006***	**P_3** 0.144		
TSH	5.96(1.35 – 8.17)	2.58(1.87 – 4.03)	5.96(3.54 – 7.23)	15.486	<0.001**
Pairwise	**P_1 0.001****	**P_2 0.001****	**P_3** 0.84		

KW Kruskal Wallis test IQR interquartile range

**p≤0.001 is statistically highly significant *p<0.05 is statistically significant

There is statistically significant difference between the studied groups regarding free T3. On doing pairwise comparison, difference is significant between traditional AEDs group and mixed AEDs group. There is statistically significant difference between the studied groups regarding free T4. On doing pairwise comparison, difference is significant between new AEDs group and mixed AEDs group. There is statistically significant difference between the studied groups regarding TSH. On doing pairwise comparison, difference is significant between new AEDs group and each other group (Table 1).

Table (2) Comparison between the studied groups regarding thyroid profile abnormalities:

	Group I N=33	**Group II N=33**	**Group IIIb n=33**	**χ^2**	**p**
TSH					
Low	0 (0%)	1 (3%)	0 (0%)		
Normal	18 (54.5%)	30 (90.9%)	20 (60.6%)	MC	<0.001**
High	15 (45.5%)	2 (6.1%)	13 (39.4%)		
P (χ^2)	P_1 <0.001**	P_2 <0.001**	P_3 0.618		
Free T4					
Low	10 (30.3%)	3 (9.1%)	15 (45.5%)		
Normal	23 (69.7%)	28 (84.8%)	18 (54.5%)	MC	<0.001**
High	0 (0%)	2 (6.1%)	0 (0%)		
P (χ^2)	P_1 0.052	P_2 0.01*	P_3 0.205		
Free T3					
Low	0 (0%)	3 (9.1%)	6 (18.2%)		
Normal	33 (100%)	30 (90.9%)	27 (81.8%)	MC	0.042*
P (χ^2)	P_1 0.238	P_2 0.282	P_3 0.024*		
Thyroid:					
Normal	19 (57.6%)	26 (78.8%)	13 (34.9%)		
Subclinical hypothyroidism	5 (15.2%)	2 (6.1%)	2 (6.1%)		
Primary hypothyroidism	9 (27.3%)	2 (6.1%)	18 (54.5%)	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 0.01*	P_2 <0.001**	P_3 0.121		

χ^2Chi square test MC Monte Carlo test **p≤0.001 is statistically highly significant

There is statistically significant difference between the studied groups regarding TSH level and thyroid gland abnormalities. on comparing each two groups, the difference is significant between newer and each other group. There is statistically significant difference between the studied groups regarding free T4 abnormalities. on comparing each two groups, the difference is significant between newer and mixed AEDs group. There is statistically significant difference between the studied groups regarding free T3 abnormalities. on comparing each two groups, the difference is significant between traditional and mixed AEDs group (Table 2).

Table (3) Correlation between thyroid profile and demographic, onset and duration of epilepsy among mixed AEDs group:

	TSH		Free T4		Free T3	
	r	p	r	p	r	p
Age (year)	-0.236	0.193	-0.097	0.591	-0.199	0.266
Weight (kg)	-0.271	0.127	-0.067	0.711	-0.207	0.247
Onset of epilepsy	-0.574	<0.001**	0.619	<0.001**	-0.244	0.171
Valproic acid	0.853	<0.001**	-0.206	0.266	0.455	0.01*
Duration of AEDs	0.072	0.691	-0.442	0.01*	-0.251	0.159

r Spearman rank correlation coefficient

There is statistically significant positive correlation between TSH and valproic acid. There is statistically significant negative correlation between TSH and onset of epilepsy. There is non-significant correlation between TSH and other parameters among patients receiving mixed AEDs. There is statistically significant positive correlation between free T4 and onset of epilepsy. There is statistically significant negative correlation between free T4 and duration of therapy. There is non-significant correlation between free T4 and other parameters among patients receiving mixed AEDs. There is statistically significant positive correlation between free T3 and valproic acid. There is non-significant correlation between free T3 and either age, weight, or onset of epilepsy among patients receiving mixed AEDs (Table 3).

Table (4) Relation between thyroid profile abnormalities and both demographic and disease-specific data:

	Normal	**Subclinical hypothyroidism**	**Overt hypothyroidism**	χ^2	**p**
	N=58 (%)	**N=9 (%)**	**N=29 (%)**		
Age [median(IQR)]	4(2.88 – 6.5)	5(1.13 – 5)	5(2 – 8)	1.336¥	0.513
Weight[median(IQR)]	15.5(11 – 20.25)	19(10.15 – 19)	16(10 – 28)	0.145¥	0.93
Gender					
Female	33 (56.9%)	3 (33.3%)	12 (41.4%)	MC	0.29
Male	25 (43.1%)	6 (66.7%)	17 (58.6%)		
	Median(IQR)	**Median(IQR)**	**Median(IQR)**	KW	p
Onset of epilepsy	1.5(0.5 – 3)	1.5(0.11 – 1.5)	0.5(0.08 – 2.5)	4.837	0.089
Duration of therapy	1.85(1 – 2.63)	2(0.8 – 3)	2(1.5 – 5)	5.539	0.063
Type of seizures					
Generalized tonic clonic	54 (93.1%)	7 (77.8%)	21 (72.4%)		
Absence epilepsy	0 (0%)	0 (0%)	2 (6.9%)	MC	0.021
Focal	4 (6.9%)	0 (0%)	0 (0%)		*
Focal spastic	0 (0%)	0 (0%)	2 (6.9%)		
Focal to generalized	0 (0%)	2 (22.2%)	4 (13.8%)		
P (χ^2)	**P_1 0.001****	P_2 >0.999	**P_3 <0.001****		
EEG					
Focal epileptogenic activity	9 (15.5%)	0 (0%)	0 (0%)		
Generalized activity	21 (36.2%)	4 (44.4%)	24 (82.8%)	MC	<0.00
Normal EEG	28 (48.3%)	5 (55.6%)	3 (10.3%)		1**
P (χ^2)	P_1 0.292	**P_2 0.021***	**P_3 0.01***		
Drug:					
Traditional	19 (32.8%)	5 (55.6%)	9 (31%)	MC	<0.00
Newer	26 (44.8%)	2 (22.2%)	2 (6.9%)		1**
Mixed	13 (22.4%)	2 (22.2%)	18 (62.1%)		
P (χ^2)	P_1 0.385	P_2 0.104	**P_3 0.001****		

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

There is statistically non-significant difference between the studied groups regarding age, weight, gender, onset of epilepsy or duration of AEDs. There is statistically significant difference between the studied groups regarding type of seizures. The difference is significant between euthyroid and

each other group. There is statistically significant difference between the studied groups regarding EEG changes. The difference is significant between subclinical hypothyroid and each other group. There is statistically significant difference between the studied groups regarding type of AEDs. The difference is significant between euthyroid and overt hypothyroid profile (Table 4).

Discussion:

In this study, there is statistically significant difference regarding TSH, free T4, free T3 levels between traditional, new AEDs and mixed groups. 45.5%, 6.1% and 39.4 % within traditional, new AEDs and mixed group had high TSH while 30.3%, 9.1% and 45.5% within traditional, new AEDs and mixed group had low free T4. Subclinical hypothyroidism was significantly higher in traditional monotherapy AEDs group than mixed AEDs groups while primary hypothyroidism was significantly higher in mixed AEDs group than traditional and newer monotherapy AEDs groups.

In agreement with our study, **Chakova et al. (7)** reported that AEDs altered thyroid function, especially in patients treated with polytherapy.
In addition, **Shih et al. (8)** noted that the fT4 level was significantly lower in patients treated with AED polytherapy.

Also, previous studies have also found that subclinical hypothyroidism (SCH) might develop in epileptic patients during momotherapy or polytherapy AEDs therapy (**1).**

In addition, **Mutlu (6)** reported that, although the thyroid hormone levels in the monotherapy subgroup patients receiving VPA were moderately higher and the thyroid hormone levels in the polytherapy subgroup was moderately lower, they did not find a statistically significant difference. Thyroid hormone levels did not differ in the monotherapy subgroup treated with CBZ; however, a significant negative correlation was observed between CBZ blood level and fT4 level. Additionally, in a small number of patients in the monotherapy subgroup receiving LEV and LTG, there was no change in thyroid hormone levels. Different results may be attributed to the fact that thyroid hormone levels may vary depending on many factors (**9).**

In the current study, 30.2% of patients on AEDs had overt hypothyroidism. This came in agreement with previous studies which reported rates ranging from 12.7% to 35.9% (**10-12).** In addition, **Shih et al. (8)** found that 17.4% of their patients with epilepsy who were taking AEDs had a low level of fT4.
In our study, there were no significant differences in age, weight or gender between normal, subclinical hypothyroidism, and overt hypothyroidism groups.

However, **Boelaert and Franklyn (13**) reported that older age females are known to be more likely to develop hypothyroidism. **Shih et al. (8)** observed that advanced age was risk factor for the development of low thyroid hormone levels. This difference may be due to different inclusion criteria and different comorbidities and age groups. In our study, there is statistically significant difference between control group, subclinical and overt hypothyroidism groups regarding type of seizures and EEG changes. Also there is statistically significant difference regarding type of AEDs. Subclinical hypothyroidism was significantly higher in traditional monotherapy AEDs group while primary hypothyroidism was significantly higher in mixed AEDs group.

This came in agreement with **Shih et al. (8)** who found that a higher number of AEDs was significantly associated with low fT4 and overt hypothyroidism. The rates of low fT4 were 5.2%, 14.5%, and 34.5% in the patients taking one, two, and three or more AEDs, respectively.

In the present study, there was no significant difference between control group, subclinical and overt hypothyroidism groups regarding duration of therapy, although the "Overt hypothyroidism" group tends to have a longer duration compared to the other groups.

In agreement with our study, **Shih et al. (8)** found that the patients with a longer duration of epilepsy had a higher risk of low fT4 but they found a significant difference. 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 hemostasis, 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 duration of AED treatment. This difference may be due to different inclusion criteria.

Conclusion:

Mixed traditional and newer antiepileptic drugs had more thyroid dysfunction than monotherapy with traditional or newer antiepileptic drugs.

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