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RESEARCH

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Effect of anti-epileptic drugs usage on thyroid profile in Egyptian epileptic children

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Abstract

Background The long-term use of anti-seizure medications (ASMs) adversely affects thyroid, lipid profile and other metabolic functions. Subclinical hypothyroidism and alterations in thyroid hormone serum levels are reported with older ASMs in adults with limited and conflicting data of the influence of ASMs especially newer one on thyroid function in children. This study aimed to investigate the effects of conventional and newer ASMs whether mono or polytherapy on thyroid profile in children with epilepsy and its impact on lipid profile and metabolic functions.

Results This study included 155 children with epilepsy (76 on monotherapy and 79 on polytherapy) with mean age of 9.677 ± 3.981 years (54.84% euthyroid, 31.61% hypothyroid, 9.68% subclinical hyperthyroid and 3.87% subclinical hypothyroid) and 78 healthy controls. Children with epilepsy whether on monotherapy or on polytherapy had a statistically significant thyroid profile abnormalities (hypothyroidism, sub-clinical hypothyroidism or sub-clinical hyperthyroidism), dyslipidemia, delayed growth and increase in DBP compared to control group. There was a statistically significant positive correlation between hypothyroidism and dyslipidemia as well as between hypothyroidism and delayed growth and increase in DBP. There was no statistically significant difference between polytherapy and monotherapy regarding thyroid and lipid parameters but children with epilepsy on polytherapy were associated with more statistically significant delay in growth and increase in DBP compared to monotherapy group. Carbamazepine had a statistically significant association with hypothyroidism, increase in DBP and higher total and LDL-cholesterol. Valproic acid had a statistically significant association with sub-clinical hypothyroidism with a positive dose correlation. Levetiracetam (LEV) was associated with a statistically significant lower HDL-cholesterol. All echocardiography data showed no abnormality.

Conclusion ASMs whether older or newer generations can affect thyroid and lipid profile differently through different mechanisms that are dose and duration dependent regardless of the seizure type and age of the patient. ASMs mainly conventional ones are associated with hypothyroidism, sub-clinical hypothyroidism, sub-clinical hyperthyroidism, dyslipidemia and consequently delayed growth and diastolic blood pressure abnormalities.

Keywords Children with epilepsy, Thyroid profile, Dyslipidemia, Oxcarbazepine, Carbamazepine, Levetiracetam, Valproate

Background

Epilepsy is a chronic neurological illness affecting mainly children and adolescents requiring long-term treatment with ASMs [1]. Long-term use of ASMs is associated with endocrinal disturbance mainly subclinical and clinical hypothyroidism that could lead to diastolic hypertension, dyslipidemia, coagulopathy, and atherosclerosis, which subsequently increase the risk of cardiovascular events and mortality [2, 3]. Thyroid hormones also play

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an essential role in protein synthesis in tissues; thus, disturbances of thyroid profile may cause delayed growth and development in children with epilepsy compliant on different ASMs [4].

The effect of ASMs on thyroid profile is well-studied in adults, however, disturbance of thyroid function in children on different ASMs is a matter of controversy and there is limited information in this context [5]. Previous studies have reported the effects of conventional ASMs such as valproate, carbamazepine and phenobarbital on thyroid hormones in children but there is limited information concerning the effects of newer ASMs [6]. Antiseizure medications affect thyroid hormone levels through different mechanisms, many of them increase hepatic microsomal enzyme systems, thus accelerating thyroid hormones clearance; others interfere with the hypothalamic–pituitary axis [7].

This study aimed to investigate and to compare the effects of conventional and newer ASMs whether mono or polytherapy on thyroid profile in children with epilepsy and its impact on lipid profile, coagulation profile (PT, PTT and INR), weight, body mass index (BMI), rate of growth (increase of height in one year), diastolic blood pressure (DBP) and trans-thoracic echocardiogram (TTE).

Methods

The study was an open label case control study. Between March 2021 and June 2022. We consecutively recruited 155 participants diagnosed with epilepsy and 78 healthy participants as control group from pediatric neurology out-patient clinical university hospital. Children with epilepsy were subclassified to monotherapy group (76 participants) and polytherapy group (79 participants). All subjects from 6 months to 18 years with any type of epilepsy on monotherapy or polytherapy and controlled for at least 6 months were included in the study provided normal developmental milestones and normal MRI. Those with progressive neurological disease, thyroid, endocrinal or metabolic disease were excluded. Those who had received any drug that could affect thyroid functions in the past 6 months or with persistent non-adherence to medication were also excluded.

All cases (monotherapy and polytherapy groups) were subjected to clinical evaluation, EEG and MRI epilepsy protocol. Serum thyroid hormone levels including free thyroxine (fT4) (0.65–1.97ng/dl), thyroid stimulating hormone (TSH) (0.39–6.16mlU/L) and lipid profile including triglyceride (< 150 mg/dl), total cholesterol (< 200 mg/dl), HDL-cholesterol (> 40 mg/dl) and LDL- cholesterol (< 100 mg/dl) were analyzed and the hormonal status was compared with healthy controls. Coagulation profile including PT, PTT, INR and trans-thoracic echocardiography were done for those with thyroid profile abnormalities, height, weight and body mass index were measured twice one year apart and blood pressure measured every visit. The normal height growth in the one-year duration varies according to age. At 1 year old, children typically grow 23-27cm, from 2 to 3 years 8cm, from 3 to 5 years 7cm from 5 years to puberty 5-6cm and after puberty 8–12 cm for girls and 10-14cm for boys. The diastolic hypertension was measured against the maximum for the age. The maximum blood pressure for 1–12 months is 110/75 mmHg, 1–5 years 110/79 mmHg, 6–13 years 115/80 mmHg and 14–19 years 120/80 mmHg. Control group participants were subjected to serum thyroid hormone levels including free thyroxine (fT4), thyroid stimulating hormone (TSH) and lipid profile including triglyceride, total cholesterol, HDL-cholesterol and LDL-cholesterol, height, weight, body mass index measurement one year apart, blood pressure measurement twice.

MRI was done using Philips Achieved Stream, 3 Tesla (Philips Healthcare, 2020), using epilepsy protocol including oblique axial and coronal T2-weighted, FLAIR and double-inversion recovery perpendicular on hippocampal axis.

EEG was done with Nicolet vEEG v5.71.6.2577 using the standard 10–20 system with no extra electrodes for 30 min. Chloral hydrate was used for sedation when needed.

Trans-thoracic echocardiogram was done by an expert sonographer using General Electric echocardiogram in university hospitals.

For adequate assessment and evaluation of outcome, data were collected, coded and entered to the Statistical Package for Social Science (SPSS) version 23 for analysis.

T test was used to assess the statistical significance of the difference between two study group means. ANOVA test was used for comparing data between more than two groups. Tukey's test was used then after to compare each two groups in ANOVA table separately. Correlation analysis was applied to assess the strength of association between two quantitative variables. P value < 0.05 was considered significant, P value < 0.01 was considered highly significant.

Results

The study included 155 patients 97 (62.58%) boys and 58 (37.42%) girls and 78 controls including 41 (52.56%) boys and 37 (47.44%) girls. The mean age of patients was 9.677 ± 3.981 years and that of controls was 9.279 ± 4.348. Cases (monotherapy and polytherapy groups) and controls were matched regarding age and sex distribution with no significant statistical difference between them.

Among the children with epilepsy there were 76 (49.03%) on monotherapy and 79 (50.97%) on polytherapy. Those on monotherapy were: 22 (14.9%) on levetiracetam, 27 (17.42%) on valproic acid, 14 (9.03%) on carbamazepine and 13 (8.39%) on Oxcarbazepine. Those on polytherapy were either on two ASMs (60.76%), three ASMs (34.18%) and only (5.06%) were on 4 or 5 ASMs (Table 1).

Among the children with epilepsy in this study 85 (54.84%) showed normal thyroid functions, 49 (31.61%) showed hypothyroidism, 15 (9.68%) showed subclinical hyperthyroidism and 6 (3.87%) showed subclinical hypothyroidism (Table 2). All participants with abnormal thyroid function showed no abnormality in echocardiography. On the other hand, 68 (43.87%) children with epilepsy showed normal lipid profile and 87 (56.13%) showed abnormal lipid profile (Table 3). There was no statistically significant difference between both sex regarding thyroid state whether euthyroid, hypo or hyperthyroid with a p value = 0.189.

Comparing cases and controls, there was a statistically significant difference between the cases and controls regarding thyroid parameters including T4 and TSH (*P*-value < 0.001) and lipid profile including total cholesterol, HDL-cholesterol, LDL-cholesterol (*P*-value < 0.001) and triglyceride (*P*-value 0.032) (Table 4). On the other hand, there was no statistically significant difference between cases and control regarding age, weight and BMI while there was statistically significant difference between cases and controls regarding increase height in 1 year (*P*-value 0.019) and DBP (*P*-value 0.013) (Table 5).

There was a statistically significant positive association between hypothyroid and dyslipidemia (*P*-value 0.019) while there was no significant correlation between euthyroid, subclinical hypothyroidism, subclinical hyperthyroidism and dyslipidemia. Thyroid state significantly affected lipid profile, there was a statistically significant difference between euthyroid, hypothyroid, sub-clinical hypothyroid and sub-clinical hyperthyroid group regarding total cholesterol, triglyceride, HDL-cholesterol and LDL-cholesterol with (*P*-value 0.006), (*P*-value < 0.001), (*P*-value 0.008), (*P*-value < 0.001), respectively. This was specifically significant in the hypothyroid group compared to euthyroid. Hypothyroid group had higher total cholesterol, LDL-cholesterol and triglyceride and lower HDL-cholesterol level. This was not significant in other groups (sub-clinical hypo and hyperthyroidism groups) compared to euthyroid (Table 6).

Regarding the impact of thyroid state on other study parameters, there was a statistically significant (*P*-value < 0.001) difference between euthyroid, hypothyroid, sub-clinical hypothyroid and sub-clinical hyperthyroid regarding rate of growth (increase height in 1 year). There was also a statistically significant (*P*-value < 0.001) difference between them regarding systolic and diastolic blood pressure while there was no statistically significant (*P*-value 0.651), (*P*-value 0.211) difference regarding weight and BMI. Comparing each two groups separately, there was a statistically significant (*P*-value 0.001) lower rate of growth in one year, higher SBP and DBP with in hypothyroid group compared to euthyroid one. There was also a statistically significant (*P*-value 0.007) decreased rate of growth in sub-clinical hyperthyroid group compared to euthyroid group, with no statistically significant difference between euthyroid and sub-clinical hypothyroid one regarding rate of growth, systolic and diastolic blood pressure.

Table 1 The distribution of monotherapy and polytherapy among epileptic children:

	n	%
Monotherapy	76	49.03
Levetiracetam	22	14.19
Carbamazepine	14	9.03
Oxcarbazepine	13	8.39
Valproic acid	27	17.42
Polytherapy	79	50.97
Two	48	60.76
Three	27	34.18
Four	4	5.06

n number, % percent

Table 2 Thyroid parameters among epileptic children:

Thyroid profile		
	n	**%**
Normal	85	54.84
Hypothyroid	49	31.61
Subclinical hypothyroid	6	3.87
Subclinical hyperthyroid	15	9.68
Total	155	100.00

n number, % percent

Table 3 Lipid profile parameters among epileptic children:

Lipid profile		
	n	**%**
Normal	68	43.87
Abnormal	87	56.13
Total	155	100.00

n number, % percent

Table 4 Comparison between cases and controls regarding thyroid and lipid parameters:

	Group						*T*-test	
	Cases			Control				
	Mean	±	SD	Mean	±	SD	*T*	*P*-value
T4	0.923	±	0.499	1.752	±	0.159	− 14.293	< 0.001*
TSH	2.014	±	1.734	0.885	±	0.428	5.660	< 0.001*
Total cholesterol	190.226	±	34.320	85.641	±	18.787	25.072	< 0.001*
Triglyceride	119.787	±	34.112	110.474	±	23.744	2.161	0.032*
HDL-cholesterol	40.626	±	10.883	57.372	±	4.358	− 13.062	< 0.001*
LDL-cholesterol	127.884	±	31.300	78.269	±	13.275	13.395	< 0.001*

TSH thyroid stimulating hormone, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SD* standard deviation. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

Table 5 Comparison between cases and controls regarding age, increase in height in 1 year, weight, BMI and diastolic blood pressure:

	Group						*T*-test	
	Cases			Control				
	Mean	±	SD	Mean	±	SD	*T*	*P*-value
Age (years)	9.677	±	3.981	9.279	±	4.348	0.698	0.486
Height in the 1st year (cm)	127.581	±	20.435	126.615	±	21.984	0.332	0.740
Height in the 2nd year (cm)	133.797	±	20.816	133.263	±	22.204	0.181	0.857
Increase in height in 1 year (cm)	5.868	±	2.465	6.647	±	2.204	− 2.358	0.019*
Weight (kg)	34.884	±	15.991	35.288	±	19.853	− 0.168	0.867
BMI	18.737	±	3.977	18.449	±	5.514	0.457	0.648
DBP	71.806	±	10.127	68.590	±	7.066	2.513	0.013*

BMI body mass index, *DBP* diastolic blood pressure, *cm* centimeter, *kg* kilogram, *SD* standard deviation. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

Moreover, the hypothyroid group when compared to sub-clinical hypothyroid and sub-clinical hyperthyroid group showed a statistically significant decrease in the rate of growth in 1 year (*P*-value 0.020; 0.005, respectively). Meanwhile there was no statistically significant difference between sub-clinical hypothyroid and sub-clinical hyperthyroid group regarding rate of growth and SBP and DBP (Table 7).

There was no statistically significant difference between monotherapy and polytherapy regarding effect on thyroid profile (*P*-value 0.201). But both groups were statistically significant compared to controls regarding all thyroid parameters T4 and TSH (*P*-value 0.001) and total cholesterol, HDL-cholesterol and LDL-cholesterol (*P*-value 0.001) with exception of triglyceride (*P*-value 0.092) that was statistically insignificant (Table 8).

There was no statistically significant difference between monotherapy, polytherapy and control group regarding age (*P*-value 0.644), weight (*P*-value 0.780) and BMI (*P*-value 0.653). There was a statistically significant difference between them regarding increase in height in one year (*P*-value 0.017) and DBP (*P*-value 0.012). Comparing each two groups separately the only statistically significant difference was found when comparing polytherapy with control group regarding increase height in one year (*P*-value 0.013) and DBP (*P*-value 0.009) (Table 9).

There was a statistically significant (*P*-value < 0.001) low T4 level (hypothyroidism) with carbamazepine and statistically significant (*P*-value < 0.001) high TSH level (subclinical hypothyroidism) with valproic acid. Carbamazepine significantly lowered T4 more than levetiracetam (*P*-value 0.027). There was a significantly higher (*P*-value 0.002) TSH level with valproic acid compared to carbamazepine (Table 10).

Regarding lipid parameters, there was no statistically significant difference (*P*-value 0.103) regarding triglyceride while there was a highly statistically significant (*P*-value < 0.001) difference in total cholesterol and LDL-cholesterol level with carbamazepine and low HDL-cholesterol level with levetiracetam even when compared with valproic acid (*P*-value 0.002). There was a statistically significant higher LDL-cholesterol level (*P*-value

Table 6 Effect of thyroid profile on lipid profile

	Thyroid code												ANOVA	
	Normal			Hypothyroid			Subclinical hypothyroid			Subclinical hyperthyroid				
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	*F*	*P*-value
T4	1.175	±	0.389	0.421	±	0.257	0.887	±	0.224	1.151	±	0.518	46.927	< 0.001*
TSH	2.017	±	0.988	1.644	±	1.388	7.728	±	0.651	0.914	±	2.165	45.895	< 0.001*
Total cholesterol	181.518	±	35.317	200.449	±	31.685	204.167	±	13.393	200.600	±	30.689	4.323	0.006*
Triglyceride	109.776	±	35.993	133.143	±	26.225	143.833	±	25.725	123.267	±	30.642	6.649	< 0.001*
HDL-cholesterol	43.247	±	12.151	37.143	±	8.473	40.667	±	9.852	37.133	±	6.232	4.060	0.008*
LDL-cholesterol	116.835	±	31.843	143.102	±	23.498	140.000	±	18.623	135.933	±	31.497	9.322	< 0.001*

Tukey's test

	I&II	I&III	I&IV	II&III	II&IV	III&IV
T4	< 0.001*	0.240	0.995	0.018*	< 0.001*	0.436
TSH	0.357	< 0.001*	0.012*	< 0.001*	0.210	< 0.001*
Total cholesterol	0.010*	0.375	0.175	0.994	1.000	0.996
Triglyceride	0.001*	0.066	0.447	0.871	0.730	0.555
HDL-cholesterol	0.008*	0.939	0.169	0.868	1.000	0.900
LDL-cholesterol	< 0.001*	0.237	0.092	0.995	0.837	0.991

TSH thyroid stimulating hormone, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SD* standard deviation, *ANOVA* analysis of variance. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

Table 7 Effect of thyroid profile on rate of growth, weight, BMI and blood pressure

	Thyroid code												ANOVA	
	Normal			Hypothyroid			Subclinical hypothyroid			Subclinical hyperthyroid				
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	*F*	*P*-value
Age (years)	9.666	±	3.707	9.995	±	4.399	7.792	±	2.193	9.456	±	4.684	0.563	0.640
Height in the 1st year (cm)	129.535	±	19.310	125.316	±	21.968	119.333	±	13.079	127.200	±	23.878	0.784	0.505
Height in the 2nd year (cm)	137.365	±	19.704	128.980	±	21.791	125.333	±	13.765	132.700	±	23.470	2.095	0.103
Increase in height in 1 year (cm)	7.218	±	1.812	3.622	±	1.897	6.000	±	1.095	5.500	±	2.353	38.229	< 0.001*
Weight (kg)	35.971	±	15.435	34.378	±	17.194	28.333	±	11.343	33.000	±	17.130	0.547	0.651
BMI	18.499	±	4.106	19.635	±	3.991	17.833	±	2.858	17.520	±	3.189	1.521	0.211
DBP	68.706	±	9.579	77.551	±	9.581	70.833	±	5.845	71.000	±	8.701	9.239	< 0.001*
Age of onset (years)	4.924	±	3.496	4.969	±	3.049	3.333	±	2.251	3.750	±	2.403	1.018	0.386
SBP	103.824	±	14.893	115.102	±	14.595	102.500	±	10.840	102.667	±	13.998	6.989	< 0.001*

Tukey's test

	I&II	I&III	I&IV	II&III	II&IV	III&IV
Age (years)	0.968	0.684	0.998	0.581	0.968	0.825
Height in the 1st year (cm)	0.660	0.641	0.977	0.906	0.989	0.857
Height in the 2nd year (cm)	0.110	0.512	0.850	0.977	0.928	0.881
Increase in height in 1 year (cm)	< 0.001*	0.419	0.007*	0.020*	0.005*	0.946
Weight (kg)	0.946	0.674	0.912	0.820	0.991	0.931
BMI	0.381	0.979	0.814	0.719	0.272	0.998
DBP	< 0.001*	0.950	0.820	0.353	0.089	1.000
Age of onset (years)	1.000	0.650	0.567	0.647	0.578	0.993
SBP	< 0.001*	0.996	0.992	0.194	0.023*	1.000

BMI body mass index, *DBP* diastolic blood pressure, *SBP* systolic blood pressure), *cm* centimeter, *kg* kilogram, *SD* standard deviation, *ANOVA* analysis of variance. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

Table 8 Comparison between epileptic children on monotherapy, polytherapy and control group regarding thyroid and lipid parameters

	Treatment									ANOVA		Tukey's test		
	Monotherapy			Polytherapy			Control							
	Mean	±	SD	Mean	±	SD	Mean	±	SD	*F*	*P*-value	I&II	I&III	II&III
T4	0.967	±	0.438	0.881	±	0.551	1.752	±	0.159	103.243	< 0.001*	0.408	< 0.001*	< 0.001*
TSH	2.277	±	1.753	1.761	±	1.688	0.885	±	0.428	18.839	< 0.001*	0.065	< 0.001*	< 0.001*
Total cholesterol	189.868	±	30.726	190.570	±	37.650	85.641	±	18.787	312.972	< 0.001*	0.988	< 0.001*	< 0.001*
Triglyceride	120.842	±	35.321	118.772	±	33.101	110.474	±	23.744	2.412	0.092	0.910	0.099	0.218
HDL-cholesterol	40.461	±	10.523	40.785	±	11.283	57.372	±	4.358	84.981	< 0.001*	0.974	< 0.001*	< 0.001*
LDL-cholesterol	126.276	±	29.978	129.430	±	32.638	78.269	±	13.275	89.804	< 0.001*	0.743	< 0.001*	< 0.001*

TSH thyroid stimulating hormone, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SD* standard deviation, *ANOVA* analysis of variance. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

Table 9 Comparison between epileptic children on monotherapy, polytherapy and control group regarding age, weight, BMI, increase in height in one year and DBP

	TTT									ANOVA		Tukey's test		
	Monotherapy			Polytherapy			Control							
	Mean	±	SD	Mean	±	SD	Mean	±	SD	F	P-value	I&II	I&III	II&III
Age (years)	9.465	±	3.929	9.881	±	4.046	9.279	±	4.348	0.441	0.644	0.804	0.958	0.630
Height in the 1st year (cm)	126.849	±	19.535	128.285	±	21.367	126.615	±	21.984	0.145	0.865	0.905	0.997	0.872
Height in the 2nd year (cm)	133.046	±	19.888	134.519	±	21.774	133.263	±	22.204	0.109	0.897	0.903	0.998	0.928
Increase in height in 1 year (cm)	6.184	±	2.602	5.563	±	2.302	6.647	±	2.204	4.127	0.017*	0.236	0.448	0.013*
Weight (kg)	33.908	±	15.739	35.823	±	16.274	35.288	±	19.853	0.249	0.780	0.772	0.875	0.980
BMI	18.438	±	4.216	19.025	±	3.737	18.449	±	5.514	0.427	0.653	0.702	1.000	0.707
DBP	70.592	±	9.164	72.975	±	10.905	68.590	±	7.066	4.482	0.012*	0.242	0.368	0.009*

BMI body mass index, *DBP* diastolic blood pressure, *cm* centimeter, *kg* kilogram, *SD* standard deviation, *ANOVA* analysis of variance, *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

0.047) with carbamazepine compared to valproic acid (Table 10).

Compared individually to control group, there was a statistically significant difference between each monotherapy and control group in all parameters except triglycerides in all and TSH level in carbamazepine group only (Table 10).

Regarding rate of growth and DBP, there was a statistically significant difference between different monotherapy regarding increase height in 1 year (*P*-value 0.049) and DBP (*P*-value 0.001). Individual group comparison revealed that there was statistically significant higher DBP in carbamazepine group compared to levetiracetam, oxcarbazepine, valproic acid and control group with (*P*-value 0.00), (*P*-value 0.0039), (*P*-value 0.007), (*P*-value < 0.001), respectively (Table 11).

Comparing different polytherapy subgroups together (two ASMs, three ASMs, four or five ASMs) and control group regarding thyroid and lipid parameters, there was a statistically significant (*P*-value < 0.001) difference regarding T4, TSH, total cholesterol, HDL-cholesterol and LDL-cholesterol while there was no statistically significant (*P*-value 0.181) difference regarding triglyceride level. The intergroup difference was insignificant regarding all thyroid and lipid parameters. Compared to control group each subgroup had a statistically significant difference from control except triglyceride level in all and TSH in the four polytherapy subgroup (Table 12).

Comparing different polytherapy subgroups together (two ASMs, three ASMs, four or five ASMs) and control group regarding age, weight, BMI, increase in height in 1 year and DBP showed no statistically significant difference collectively and individually except the three polytherapy group with significantly higher DBP (*P*-value 0.042) compared to control group (Table 13).

Certain combination polytherapies had been compared. Concerning age, weight and BMI there was no statistically significant (*P*-value 0.150), (*P*-value 0.208),

Table 10 Effect of different monotherapy on lipid and thyroid parameters

	Monotherapy														ANOVA	
	Levetiracetam I			Carbamazepine II			Oxcarbazepine III			Valproic acid IV			Control V			
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	F	P-value
T4	1.133	±	0.289	0.806	±	0.628	0.891	±	0.328	0.951	±	0.446	1.752	±	0.159	60.452	< 0.001*
TSH	2.155	±	1.221	1.411	±	1.003	2.073	±	0.952	2.922	±	2.422	0.885	±	0.428	16.316	< 0.001*
Total cholesterol	191.955	±	37.004	202.143	±	22.215	191.462	±	23.454	181.037	±	30.818	85.641	±	18.787	168.070	< 0.001*
Triglyceride	126.545	±	31.692	127.429	±	19.262	120.077	±	37.706	113.148	±	42.815	110.474	±	23.744	1.964	0.103
HDL-cholesterol	36.045	±	7.041	38.214	±	7.797	41.846	±	11.696	44.556	±	12.176	57.372	±	4.358	50.795	< 0.001*
LDL-cholesterol	131.045	±	32.406	138.571	±	31.578	122.462	±	24.801	117.852	±	27.931	78.269	±	13.275	45.646	< 0.001*

Tukey's test

	I&II	I&III	I&IV	I&V	II&III	II&IV	II&V	III&IV	III&V	IV&V
T4	0.027*	0.199	0.281	< 0.001*	0.960	0.646	< 0.001*	0.981	< 0.001*	< 0.001*
TSH	0.388	1.000	0.190	< 0.001*	0.624	0.002*	0.572	0.243	0.012*	< 0.001*
Total cholesterol	0.758	1.000	0.554	< 0.001*	0.803	0.084	< 0.001*	0.733	< 0.001*	< 0.001*
Triglyceride	1.000	0.972	0.528	0.178	0.969	0.599	0.297	0.960	0.822	0.995
HDL-cholesterol	0.922	0.201	0.002*	< 0.001*	0.735	0.095	< 0.001*	0.834	< 0.001*	< 0.001*
LDL-cholesterol	0.867	0.814	0.257	< 0.001*	0.350	0.047*	< 0.001*	0.974	< 0.001*	< 0.001*

TSH thyroid stimulating hormone, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SD* standard deviation, *ANOVA* analysis of variance. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

(*P*-value 0.599, respectively) difference between different ASMs combination. Meanwhile there was a statistically significant (*P*-value 0.024) difference with phenytoin plus (CBZ or + phenobarbitone or + clonazepam) group regarding increase height in 1year (decreased growth). Also, there was a statistically significant (*P*-value 0.003) difference with CBZ plus (valproate or + zonisamide or + clonazepam or + lacosamide) regarding DBP (increase in DBP) (Additional file 1: Appendix S2).

The effect of different ASMs combination on thyroid and lipid parameters was evaluated. There was a statistically significant (*P*-value < 0.001) low T4 (hypothyroidism) with phenytoin plus group (+ CBZ or + phenobarbitone or + clonazepam) and a statistically significant higher TSH level (*P*-value < 0.001) and lower HDL level (*P*-value < 0.001) with CBZ plus with CBZ plus (+ valproate or + zonisamide or + clonazepam or + lacosamide) group. There was also a statistically significant higher total cholesterol level (*P*-value 0.001) and LDL-cholesterol level (*P*-value < 0.001) with oxcarbazepine and ethosuximide combination. There was no statistical significance (*P*-value 0.137) between different ASMs combination regarding triglyceride level (Additional file 1: Appendix S3).

There was no statistically significant (*P*-value 0.386) difference between the duration of use of ASMs and thyroid profile in children with epilepsy included in this study (Table 14). The correlation between dosage of ASMs and thyroid profile in children with epilepsy showed that there was only a statistically significance (*P*-value 0.002) with valproic acid (Table 15).

Discussion

This study included 155 children with epilepsy compliant on ASMs and 78 healthy controls. Among the children with epilepsy in this study, (54.84%) showed normal thyroid functions, (31.61%) showed hypothyroidism, (9.68%) showed subclinical hyperthyroidism and (3.87%) showed subclinical hypothyroidism, however none of the participants in the control group showed any abnormality in the thyroid profile. This confirmed previous data that patients with epilepsy receiving ASMs showed a significant decrease in T4 and fT4, and higher TSH levels compared to control group [8] especially CBZ with a highly statistically significant (*P*-value < 0,001) lower T4 level (hypothyroidism) and delayed growth compared to other ASMs [9]. But contradictory to this study, Hanci and colleagues reported no statistically significant effects on thyroid functions for drugs such as VPA, CBZ, OXC, LEV, PB, TPM, and LMT used as monotherapy [10].

In this study, all these ASMs affected thyroid profile except LMT. VPA was associated with significantly higher TSH. Phenytoin combination therapy was associated with lower T4 level and more delay in growth. CBZ combination therapy was associated with higher TSH level, lowest HDL-cholesterol level and increase in DBP while OXC + ESC was associated with higher total and LDL-cholesterol. This was similar to Aygün and colleagues

Table 11 Effect of monotherapy on increase in height in 1 year and diastolic blood pressure

	Monotherapy														ANOVA	
	Levetiracetam I			Carbamazepine II			Oxcarbazepine III			Valproic acid IV			Control V			
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	*F*	*P*-value
Age (years)	8.432	±	2.758	11.518	±	4.310	8.923	±	4.084	9.503	±	4.251	9.279	±	4.348	1.293	0.276
Height in the 1st year (cm)	122.682	±	15.132	134.357	±	21.048	124.692	±	19.981	127.389	±	21.503	126.615	±	21.984	0.716	0.582
Height in the 2nd year (cm)	129.568	±	16.043	139.143	±	21.828	130.231	±	20.790	134.074	±	21.450	133.263	±	22.204	0.514	0.726
Increase in height in 1 year (cm)	6.795	±	1.743	4.786	±	2.933	5.615	±	1.927	6.685	±	3.045	6.647	±	2.204	2.445	0.049*
Weight (kg)	31.136	±	13.002	39.143	±	18.418	31.308	±	15.892	34.704	±	16.326	35.288	±	19.853	0.564	0.689
BMI	17.655	±	4.046	20.493	±	4.264	18.000	±	5.050	18.222	±	3.776	18.449	±	5.514	0.791	0.533
DBP	67.727	±	7.827	78.214	±	9.924	69.615	±	8.771	69.444	±	8.243	68.590	±	7.066	4.896	0.001*

Tukey's test

	I&II	I&III	I&IV	I&V	II&III	II&IV	II&V	III&IV	III&V	IV&V
Age (years)	0.188	0.997	0.894	0.914	0.477	0.574	0.336	0.994	0.998	0.999
Height in the 1st year (cm)	0.474	0.999	0.934	0.935	0.748	0.848	0.703	0.995	0.998	1.000
Height in the 2nd year (cm)	0.677	1.000	0.946	0.951	0.810	0.950	0.874	0.983	0.989	1.000
Increase in height in 1 year (cm)	0.100	0.613	1.000	0.999	0.893	0.112	0.057	0.668	0.593	1.000
Weight (kg)	0.691	1.000	0.958	0.874	0.790	0.944	0.947	0.981	0.947	1.000
BMI	0.444	1.000	0.994	0.963	0.681	0.627	0.607	1.000	0.998	1.000
DBP	0.001*	0.958	0.940	0.991	0.039*	0.007*	< 0.001*	1.000	0.992	0.988

BMI body mass index, *DBP* diastolic blood pressure, *cm* centimeter, *kg* kilogram, *SD* standard deviation, *ANOVA* analysis of variance. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

Table 12 Comparison between different groups of polytherapy and control group regarding thyroid and lipid parameters

	Polytherapy												ANOVA	
	Two I			Three II			Four III			Control IV				
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	*F*	*P*-value
T4	0.909	±	0.613	0.820	±	0.455	0.963	±	0.415	1.752	±	0.159	59.917	< 0.001*
TSH	1.895	±	1.822	1.648	±	1.482	0.913	±	1.285	0.885	±	0.428	7.514	< 0.001*
Total cholesterol	186.229	±	40.806	199.852	±	29.107	180.000	±	46.904	85.641	±	18.787	165.784	< 0.001*
Triglyceride	115.729	±	30.208	124.630	±	35.671	115.750	±	51.913	110.474	±	23.744	1.644	0.181
HDL-cholesterol	40.375	±	9.890	41.556	±	13.568	40.500	±	13.178	57.372	±	4.358	48.558	< 0.001*
LDL-cholesterol	126.458	±	34.928	134.963	±	28.502	127.750	±	33.500	78.269	±	13.275	55.597	< 0.001*

Tukey's test

	I&II	I&III	I&IV	II&III	II&IV	III&IV
T4	0.804	0.994	< 0.001*	0.915	< 0.001*	0.001*
TSH	0.838	0.421	< 0.001*	0.682	0.031*	1.000
Total cholesterol	0.227	0.978	< 0.001*	0.595	< 0.001*	< 0.001*
Triglyceride	0.576	1.000	0.754	0.940	0.129	0.984
HDL-cholesterol	0.941	1.000	< 0.001*	0.996	< 0.001*	0.001*
LDL-cholesterol	0.491	1.000	< 0.001*	0.949	< 0.001*	0.001*

TSH thyroid stimulating hormone, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SD* standard deviation, *ANOVA* analysis of variance. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

Table 13 Comparison between different groups of polytherapy and control group regarding age, increase in height in 1 year, weight, BMI and DBP

	Polytherapy												ANOVA	
	Two			Three			Four			Control				
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	*F*	*P*-value
Age (years)	9.955	±	4.117	9.756	±	4.070	9.835	±	4.039	9.279	±	4.348	0.278	0.841
Height in the 1st year (cm)	128.615	±	21.261	127.667	±	21.897	128.500	±	25.053	126.615	±	21.984	0.088	0.967
Height in the 2nd year (cm)	135.104	±	21.391	133.685	±	22.793	133.125	±	25.319	133.263	±	22.204	0.071	0.975
Increase in height in 1 year (cm)	5.427	±	2.299	5.907	±	2.374	4.875	±	2.016	6.647	±	2.204	3.402	0.019*
Weight (kg)	35.052	±	15.799	37.500	±	17.697	33.750	±	14.863	35.288	±	19.853	0.133	0.940
BMI	18.727	±	3.770	19.670	±	3.864	18.250	±	2.217	18.449	±	5.514	0.463	0.709
DBP	72.813	±	11.008	74.074	±	11.269	67.500	±	6.455	68.590	±	7.066	3.573	0.016*

Tukey's test

	I&II	I&III	I&IV	II&III	II&IV	III&IV
Age (years)	0.997	1.000	0.819	1.000	0.958	0.994
Height in the 1st year (cm)	0.998	1.000	0.959	1.000	0.996	0.998
Height in the 2nd year (cm)	0.993	0.998	0.969	1.000	1.000	1.000
Increase in height in 1 year (cm)	0.813	0.966	0.019*	0.829	0.460	0.422
Weight (kg)	0.944	0.999	1.000	0.981	0.948	0.998
BMI	0.840	0.997	0.988	0.943	0.654	1.000
DBP	0.941	0.685	0.064	0.543	0.042*	0.996

BMI body mass index, *DBP* diastolic blood pressure, *cm* centimeter, *kg* kilogram, *SD* standard deviation, *ANOVA* analysis of variance. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

Table 14 Effect of duration of ASMs on thyroid profile

	Thyroid code												ANOVA	
	Normal			Hypothyroid			Subclinical hypothyroid			Subclinical hyperthyroid				
	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	*F*	*P*-value
Duration of ASMs use (Years)	4.924	±	3.496	4.969	±	3.049	3.333	±	2.251	3.750	±	2.403	1.018	0.386

ASMs antiseizure medications, *SD* standard deviation, *ANOVA* analysis of variance

who reported lower T4 level with enzyme inducers such as (PHT, PB, CBZ) and subclinical hypothyroidism with VPA [4]. Ilia and colleagues confirmed this and reported thyroid hormones abnormality with increased TSH level in the VPA and the CBZ group compared with controls [11]. This was also replicated by Han and colleagues who reported that the ASMs with the least disruptive effect on thyroid profile is lamotrigine while CBZ and PHT were strongly associated with decreased in T4 and T3 level and VPA was associated with subclinical hypothyroidism [9].

There was no statistically significant difference between those on two ASMs, those on three ASMs and those on four or five ASMs regarding thyroid and lipid parameters, rate of growth and diastolic blood pressure. This could be explained by the fact that enzyme inducers stimulate the hepato-cellular binding of T4, resulting in rapid clearance of T4 from circulation and subsequent enhanced conjugation and biliary excretion [12]. Also, they exhibit a marked fall in serum protein-bound iodine increasing the peripheral disposition of thyroid hormone [7, 13] and this is a result of increased hepatic UGT activity and induction of T4 glucuronidation with the formation of glucuronide conjugate which is the rate-limiting step in the biliary excretion of T4 that is substantial enough to lower systemic thyroid hormone concentrations [14]. Increased TSH and thyroid gland activation may also be the consequence of increasing both T4 glucuronidation and T3 glucuronidation simultaneously, in conjunction with some amount of increased hepatic uptake [15].

Table 15 Correlation between ASMs dosage and thyroid profile

Correlations				
	T4		TSH	
	r	*P*-value	*r*	*P*-value
Levetiracetam (mg)	− 0.086	0.480	0.054	0.658
Carbamazepine (mg)	− 0.004	0.983	− 0.317	0.108
Oxcarbazepine (mg)	− 0.071	0.700	− 0.248	0.171
Lacosamide (mg)	− 0.162	0.729	− 0.623	0.135
Valproic acid (mg)	− 0.382	0.002*	− 0.008	0.952
Lamotrigine (mg)	0.253	0.245	0.286	0.185
Ethosuximide (mg)	− 0.033	0.906	0.268	0.335
Topiramate (mg)	− 0.113	0.644	− 0.132	0.590
Phenytoin (mg)	0.632	0.093	0.337	0.414
Zonisamide (mg)	− 0.455	0.442	− 0.221	0.721
Clonazepam (mg)	− 0.827	0.381	0.344	0.776

ASMs antiseizure medications, *mg* milligram, *TSH* thyroid stimulating hormone. *P* value < 0.05 statistically significant, *P* value < 0.01 statistically highly significant

In this study LEV was the least affecting thyroid profile compared to other ASMs but compared to control group it was associated with significant higher TSH and lower T4. Two out of 19 patients on LEV monotherapy showed sub-clinical hyperthyroidism while four out of 8 patients on LEV and enzyme inducers (PHT or CBZ or PBT) showed hypothyroidism (2 of them with dyslipidemia and delayed growth and 1 with increase in DBP). On the other hand, from 44 patients on LEV and non-enzyme inducer drugs (OXC, LMT, ZNS, ESM, VPA, CLZ) 4 showed subclinical hypothyroidism, 12 hypothyroidism, 4 subclinical hyperthyroidism, 10 dyslipidemia, 11 delayed growth and 8 increased diastolic blood pressure. This was contradictory to other studies who reported no effect of LEV monotherapy on thyroid hormone levels, after one year of therapy [6, 16–19]. This could be explained by the difference in dosage and duration of use of LEV.

In this study there were 19 patients on LEV monotherapy. Three of them required dose titration (up to 20mg/kg) four of them (up to 30 mg/kg) four of them (up to 35 mg/kg) and eight of them (up to 40mg /kg) while in the other studies 23 of the children required a minimal dose titration (up to 20 mg/kg) and 5 of them needed a significant dose titration up to 35 mg/ kg. Also, there was difference in duration of LEV treatment as they used it for less than 1 year compared to this study that ranged from 1 to 6 years. On the other hand, other studies reported subclinical hypothyroidism with LEV [9] that may be duration dependent with high TSH at 6th months of LEV therapy and low T4 level at 12 months of therapy [20]. Dawajani and colleagues also reported hypothyroidism and subclinical hypothyroidism in children with epilepsy on LEV therapy more than 6 months duration [21]. This could be explained by the fact that LEV increases tissue concentrations of GABA, neutralizes the action of negative modulators of the GABAA receptor,

and reduces the excitatory action of glutamate by modulation of AMPA receptors [22]. That effect on AMPA receptors is not unique to LEV, topiramate also at high concentrations acts on AMPA/kainate receptors [23, 24] with several reports of topiramate-induced thyroiditis with positive thyroid peroxidase antibodies [25, 26]. Shih and colleagues reported that LEV and TPM were significantly associated with the presence of low fT4 compared to other ASMs including PHT, PB, VPA, LMT and OXC [27]. This is consistent with this study where there were 40 patients using topiramate with other ASMs, 18 on LEV + TPM; 6 sub-clinical hyperthyroidism, 3 hypothyroidism, dyslipidemia and delayed growth while 2 increase in DBP. One out of 4 patients on VPA + TPM showed sub-clinical hyperthyroidism, 3 out of 6 patients on OXC + TPM showed sub-clinical hyperthyroidism and 1 showed hypothyroidism. one out of 3 patients on TPM + ESM showed hypothyroidism, dyslipidemia, delayed growth and increase in DBP, two out of 6 patients on LMT + TPM showed subclinical hypothyroidism and two hypothyroidism. Two patients on TPM + PHT and the other on TPM + CLZ both showed sub-clinical hyperthyroidism.

The relation between thyroid abnormalities and AMPA receptors antagonist could be explained by the fact that the excitatory amino acids are important in the regulation of hormones secretion from the pituitary–thyroid axis as well as the importance of the NMDA in this stimulatory effect which will be affected as AMPA receptors depolarize the membrane enough to dislodge Mg + + from the NMDA receptor channel, this allows NMDA receptors to respond to glutamate binding [28]. A glial neuronal circuit in the floor of third ventricle projecting to medial eminence is involved in the regulation of TRH secretion by a feed-back loop circuit through glutamate action on AMPA receptors [29]. So AMPA antagonist (LEV and TPM) at high dose will cause decrease in TSH secretion and subsequently decrease in T4 level due to dysregulation of hormones secretion from pituitary–thyroid axis or paradoxically may cause impairment of the ultra -short negative feed-back loop involving the suppression of TSH by its own concentration leading to marked increase in TSH level. Thus, AMPA antagonism affects thyroid profile in various ways, causing subclinical hypothyroidism, hypothyroidism or sub-clinical hyperthyroidism. This was confirmed by Angehagen and colleagues who reported correlation between increase dosage of topiramate and action on AMPA receptor [23, 24] and that explain the higher thyroid dysfunction with increase dose of levetiracetam in this study (35 and 40 mg per kg) is correlated to its action on AMPA receptors.

Thyroid abnormalities were reported to be higher in children than adult population receiving ASMs [11]. In this study about (31.61%) of children with epilepsy showed low T4 (hypothyroidism) compared to 17.4% [27], and 25% [11] in adults and 24.3% to 26.9% in children [11]. The rationale is the higher prevalence in children on valproate and carbamazepine monotherapy compared to levetiracetam monotherapy [11, 31].

We did not find sex difference regarding susceptibility to thyroid dysfunction contradicting previous results where low fT4 were more common in females with older age, which is likely representative of the background risk [27]. May be this is attributed to the difference in age group as that study was conducted on adult rather than children. We also did not find any correlation between duration of epilepsy and duration of usage of ASMs and low T4 level contrary to other studies who found positive correlations between duration of treatment and TSH [27, 32]. This could not be explained by the difference in the age of the study population as this positive correlation was replicated in children with epilepsy using CBZ [33]. This could be explained by the difference in the epoch time in which the effect of duration of treatment was tested each study. ASMs affect thyroid profile early with stead state effect of duration till a steady state level with no effect of duration. Children on VPA [21], [34] or LEV [21] showed low T4 and TSH level starting at seventh month of therapy [21] or early in course of treatment and persist stable thereafter [34]. Simko and colleagues reported a significant decrease in T4, starting from the first week of treatment and remaining stable thereafter concluding that there was no correlation between duration of use of ASMs and thyroid profile [35]. Yilmaz and colleagues reported low T4 level in children with epilepsy treated with OXC after 1 month of starting treatment [6]. This could explain why there was no correlation between duration of treatment in this study and thyroid profile as the minimum duration in this current study was one year.

There were no significant associations between individual types of seizure, etiology, and seizure frequency with the development of low fT4 among all ASMs replicating the same findings of Shih and colleagues [27].

CBZ remained significantly associated with low fT4 as Shih and colleagues [27]. In this study eight out of 14 children on CBZ monotherapy developed low T4 level, dyslipidemia and delayed growth, 7 of them had increase in DBP and 1 of them developed high TSH and diastolic hypertension level. Also, CBZ combination therapy significantly affected thyroid function. Similarly, several studies reported that monotherapy with CBZ and PHT (enzyme inducers) was significantly associated with a reduction of T4 and fT4 levels; But in contrast to this study those studies reported that these changes did not seem to affect growth or pubertal development [8, 35, 36]. In this study patients on CBZ as monotherapy or

as polytherapy showed significant increase in DBP compared to control group and other monotherapy groups (LEV, OXC and VPA) also Phenytoin and CBZ combination was associated with delayed growth in children with epilepsy [8, 9, 37].

We found that CBZ reduces serum thyroid hormone concentrations with normal TSH level in children with epilepsy that was concordant with many reports [6, 30, 35, 36, 38–46]. This could be explained by the fact that CBZ being enzyme inducer accelerated hormone metabolism of free and bound thyroid [47]. The reduction in thyroid hormone concentrations in the periphery is associated with compensatory increase in serum TSH [48], also subclinical hypothyroidism was reported with CBZ in many studies [6, 49]. Few studies reported significant increase in the peak TSH level, the absolute change from the basal TSH level and an integrated TSH response expressed as a cumulative response to TRH with CBZ, which suggest alterations in the hypothalamic–pituitary–thyroid axis with CBZ [50–53]. This is supported by the fact that the majority of ASMs block voltage dependent sodium and calcium channels, enhance GABA-ergic transmission and/or antagonize glutamate receptors. A similar neurochemical mechanism may be suggested in the interaction of these drugs with the synthesis of hypothalamic neurohormones such as gonadotropin-releasing hormone, TRH, corticotropin-releasing hormone and growth hormone releasing hormone [54].

In this study, 25 patients were on VPA, five of them developed low T4 level and four of them developed high TSH level and thyroid profile abnormality was correlated specifically to VPA dosage not to other ASMs dosage. Mikati and colleagues in a case control study showed significant higher TSH level in cases compared to control group and sub-clinical hypothyroidism that was correlated with duration of treatment between 6 and 24 months, VPA polytherapy with enzyme-inducing agents or polytherapy with non-enzyme-inducing agents compared with VPA monotherapy [55]. Similarly in this study the minimum duration on VPA therapy was 6 months, VPA with enzyme-inducing agent was associated with hypothyroidism, 2 patients were on VPA + CBZ, one of them had low T4 level, dyslipidemia, delayed growth and increase in DBP, also 3 patients were on VPA + PHT two of them showed low T4 level, dyslipidemia, delayed growth and increase in DBP, also VPA in combination with non-enzyme inducer ASMs such as 4 patients on VPA + OXC 2 of them showed low T4 level and delayed growth and 1 of them developed high TSH level without clinical manifestations, also 9 patients on VPA + lamotrigine 4 of them showed low T4 level, dyslipidemia and delayed growth and 3 of them developed increase in DBP, also 5 patients were on VPA + ethosuximide 3 of them showed low T4 level and delayed growth, 2 of them developed dyslipidemia and increase in DBP, 2 patients were on VPA + clonazepam both of them showed low T4 level, delayed growth and increase in DBP and 1 of them showed dyslipidemia and 1 patient was on VPA + vigabatrin showed low T4, dyslipidemia, delayed growth and increase in DBP.

The effect of VPA on TSH level could be attributed to its gamma amino butyric acid (GABA) like effect because GABA is inhibitory of somatostatin release and somatostatin inhibit TSH secretion [58, 59]. VPA binds to plasma protein at high rate causing thyroxine to separate from where it binds [60]. While the alteration in thyroid profile associated with VPA may be attributed to the reduction in serum Cu levels. The Cu level in the 6th months of VPA therapy was positively correlated with T4 level and negatively correlated with TSH level [56]. Zinc and selenium deficiencies are other suggestions [61].

Twelve patients were on OXC monotherapy 3 of them showed hypothyroidism, dyslipidemia and delayed growth and 2 of them showed increase in DBP. Also, patient in OXC polytherapy showed similar abnormalities. Concordant to this study, Yilmaz and colleagues in a prospective study showed that oxcarbazepine-treated patients had decreased fT4 levels at first month [6]. In a prospective study on children with epilepsy comparing OXC and VPA therapy, OXC group showed decrease in serum T4, fT4, T3, fT3, and rT3 levels at the third and sixth months while VPA group showed no affection. On the other hand, the mean serum thyroid stimulating hormone levels increased significantly at the 6th month compared to the baseline values in the VPA group while it remained unchanged in the OXC group [57]. This could be explained by the fact that accelerated hormone metabolism or increase in turnover of free and bound thyroid hormones by stimulating the drug metabolizing enzyme system (hepatic cytochrome P-450 isoenzymes) has been considered the main mechanism for reduced concentrations of free and bound thyroid hormone concentrations during treatment with enzyme-inducing ASMs (such as PB, PHT, CBZ and OXC) [47]. The reduction in thyroid hormone concentrations in the periphery is associated with compensatory increase in serum TSH [48]. Some studies reported return of serum levels of T4 and fT4 to normal after replacing CBZ with OXC [62]. This could be explained by the fact that OXC has less enzyme induction activity compared to CBZ as it is mainly reduced instead of being oxidized as with CBZ [63]. However, when given in high doses, OXC could induce the hepatic P-450 enzyme system [7, 64].

A prospective study on 23 children receiving OXC showed that FT4, but not FT3, was significantly reduced after 8 and 18 months treatment, while TSH was

significantly increased. Alterations in thyroid function seem to be reversible after withdrawal of medication [65]. Similarly, in this study OXC was associated with significant decrease in T4 and significant increase in TSH compared to control. Also, Park and colleagues in a prospective study showed similar results as he found T3, T4 and fT4 levels decreased significantly during 5 years of follow-up, in particular, T3 and fT4 levels were reduced steeply in the first 2 years of oxcarbazepine treatment. But in contrast to this study there was no significant change in thyroid-stimulating hormone during oxcarbazepine treatment [66]. Reduction of thyroid hormones with no increase in TSH was replicated in several studies. Schweiger and colleagues case series including 3 cases on OXC treatment for a duration more than 2 years on high doses (from 1300 to 1800mg), the 3 cases showed central hypothyroidism [67]. Similarly, Einarsdottir and Shi and colleagues showed central hypothyroidism with OXC [17, 46, 53].

Central hypothyroidism is a deficiency in thyroid hormone production, usually due to dysfunction in thyroid-stimulating hormone production or secretion from the pituitary, thyrotropin-releasing hormone production or secretion from the hypothalamus, or both with clinical manifestations of hypothyroidism including delayed growth, weight gain and fatigue. We propose that treatment with oxcarbazepine can also be associated with central hypothyroidism, a condition requiring treatment with thyroid replacement necessary for growth, pubertal development, and metabolism [67].

If thyroid-stimulating hormone can stay stable in patients using OXC, but there is a continued decrease in free T4, so there are two possible mechanisms could be responsible: disruption of the hypothalamic–pituitary axis or a decreased hormonal level that could result in new homeostasis in the tissue still allowing for the biological function to occur. ASMs, including OXC, have been shown to possibly alter the pituitary response to hormonal feedback and cause central hypothyroidism [38]. Previous studies suggested that because of oxcarbazepine's minimal effect on the P450 system, a disruption in the hypothalamic–pituitary system could be the root problem, mainly a decreased response by thyrotropin-releasing hormone–thyrotropin axis [53].

Also, most of the studies reported normal TSH responses to TRH in patients treated with ASMs which indicates that pituitary interference by such drugs seems unlikely. However, few studies reported significant increase in the peak TSH level, the absolute change from the basal TSH level and an integrated TSH response expressed as a cumulative response to TRH with CBZ, which suggest alterations in the hypothalamic–pituitary–thyroid axis with CBZ [50–53]. This is supported by the fact that the majority of ASMs block voltage-dependent sodium and calcium channels, enhance GABA-ergic transmission and/or antagonize glutamate receptors. A similar neurochemical mechanism may be suggested in the interaction of these drugs with the synthesis of hypothalamic neurohormones such as gonadotropin-releasing hormone, TRH, corticotropin-releasing hormone and growth hormone releasing hormone [54].

Contradictory to these findings, previous studies reported that there were no significant changes in the serum levels of fT3, fT4, and TSH in children with epilepsy using levetiracetam, topiramate, and oxcarbazepine compared to the controls [6, 31, 68]. This could be explained by difference in doses as TPM and LEV in high dose act as AMPA antagonist and OXC in high dose induce hepatic cytochrome P-450 activity resulting in alteration of thyroid profile. On the other hand, similar to this study, Zhai and colleagues showed that the occurrence of hypothyroxinemia was higher in patients who received OXC compared to those who did not. OXC use was associated with greater reduction in TSH index and thyroid feedback quantile-based index (TFQI) suggesting that impaired set point of thyroid homeostasis might be involved in the mechanism of OXC induced hypothyroxinemia [69].

TFQI is a newly proposed indicator to assess sensitivity to thyroid hormones in the pituitary [70]. It was positively associated with mean arterial pressure, pulse pressure and rate pressures product (used to indirectly represent arterial stiffness, so reduced sensitivity to thyroid hormones was related to increased risk of hypertension) [71]. This could explain the occurrence of hypothyroidism and diastolic hypertension associated with OXC therapy.

In this study on different ASMs developed dyslipidemia, increase in DBP and delayed in growth. Dyslipidemia was higher among children with hypothyroidism and subclinical hypothyroidism that is concordant with few studies that reported a significant association between serum LDL-cholesterol or hypercholesterolemia and TSH levels with ASMs [38, 65], that might affect up to 27.3% patients with abnormal thyroid hormonal levels [49]. In this study, CBZ increase total cholesterol and LDL-cholesterol that was consistent with previous studies [34, 42, 72]. The effect of CBZ on lipid profile is reversible. Lossius and colleagues reported a significant decrease in serum levels of total cholesterol and LDL-cholesterol and apolipoprotein B (ApoB) after withdrawal of CBZ from epileptic patients [73].

Similarly, Bramswig and colleagues reported significant increases in total cholesterol, ApoB-containing lipoproteins [very-low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), and low-density lipoprotein

(LDL)], and in triglycerides, but not in high-density lipoprotein (HDL), with CBZ. The increase is neither related to increased ApoB production nor to decreased catabolism but is rather due to changes in the conversion cascade of IDL particles, most likely as an indirect effect to a decrease in thyroid hormones, as a significant correlation between the decrease in free thyroxine and the increase in IDL cholesterol was observed [74]. This could be explained by the fact that hepatic cholesterol synthesis is stimulated by ASMs that induce microsomal enzymes, and this cholesterol load is transported to the plasma by LDL. Excess LDL in plasma is taken up by endothelial cells and microcytes by way of a receptor-independent method. This LDL cannot be converted to HDL, and thus foam cells are formed and hence the risk of atherosclerosis is higher with enzyme inducer ASMs [75]. Several prospective studies showed increase in total and LDL-cholesterol while HDL-cholesterol remained unchanged with enzyme inducers ASMs [76]. However, others have reported that children treated with carbamazepine had high levels of total cholesterol, triglycerides, LDL but contradictory to this study there was elevated high-density lipoprotein (HDL) cholesterol [77].

In the contrary, Nishiyama and colleagues reported low T4 level in children with epilepsy on CBZ while lipid profile was not affected [19]. This contradiction may be attributed to the short duration of this prospective study which is only 6 months and the small sample of participants which are only 6 patients. Zeitlhofer and colleagues as well as Tekgul and colleagues also reported no significant changes in lipid profile with CBZ therapy [78, 79]. This difference may be due to small sample size also there are other variables that may influence lipid levels including dietary habits and physical exercise.

In this study, OXC was associated with high total and LDL-cholesterol and lower HDL-cholesterol compared to control group and OXC + ESC combination was associated with higher total cholesterol level; this may be due to high dose of OXC used in this study and OXC in high dose act as enzyme inducer also secondary to alteration of thyroid profile. This was similar to previous studies [80–82]. Similarly, Garoufi and colleagues in a prospective study reported high total and LDL-cholesterol and decrease T4 level, moreover they found positive correlation between GGT and HDL level and TSH and total cholesterol level indicating that increase in serum LDL-C during OXC monotherapy may be associated with induction of the liver enzymes and increase in total cholesterol may be attributed to alteration of thyroid profile [65]. However, other studies showed no significant changes in lipid parameters with OXC therapy [81, 83] which could be attributed to smaller dose of OXC and short duration of follow-up in these studies.

In this study VPA affected Total Cholesterol, HDL and LDL-cholesterol compared to control group but compared to other ASMs (CBZ, OXC and LEV) it was least ASM affecting lipid profile. This confirms George and colleagues cross-sectional study; that reported that TC and LDL-C were higher among children with epilepsy on VPA compared to control group [84]. This may be attributed to increased long chain fatty acid, high insulin levels, dysregulation of adipocytokines and leptin that activate lipogenesis [85]. Thus, long-term use of VPA cause weight gain which may cause dyslipidemia [86].

Contradictory to this study, several studies reported decreased TC and LDL-C with VPA [87–89]. This may be explained by the fact that VPA is an enzymatic inhibitor and the main route for VPA biotransformation is glucuronidation; the glucuronidase enzyme may be inhibited by VPA or its metabolites, leading to decreased synthesis of TC, LDL-C, and HDL-C [90]. VPA can inhibit the glycogen synthase kinase 3/b pathway, which is associated with increased cholesterol metabolism and the pathogenesis of atherosclerosis [91]. Furthermore, 70% of cholesterol is synthesized from acetyl-coenzyme A (CoA) in hepatocytes. The main metabolic pathway of VPA is b-oxidation, which typically causes the depletion of coenzyme A [92]. Therefore, VPA-induced deficiency of acetyl-CoA partially accounts for the decreased cholesterol level that occurs after VPA treatment. In contrast, LDL-C and HDL-C are synthesized in the liver and secreted into the plasma, and VPA-induced hepatic steatosis also leads to a decrease in the plasma levels of LDL-C and HDL-C [93]. Lastly, VPA affect thyroid profile leading to secondary alteration in lipid profile [94]. These differences in results thus could be attributed to differences in the study populations with regard to age, sex, and the duration of VPA treatment and the study method.

In this study, LEV was associated with increased TC and LDL-C and decreased HDL-C compared to control group also it has no favorable effect on lipid profile this may be explained by its effect on thyroid profile. This was similar to a study by Kolekar and colleagues who reported high TC, LDL and TG with LEV [95]. On the contrary, many prospective studies showed no effect of LEV on lipid profile [18, 72, 96].

This study has its limitations, only levetiracetam was studied as monotherapy from the newer ASMs. Other drugs as lamotrigine and lacosamide were in the polytherapy arm (Additional file 1: Appendix S1), so we could not draw conclusions on them. The polytherapy arm was not homogenous so we could not subclassify into major combination therapies to compare.

Conclusion

In conclusion, ASMs whether older or newer generations can affect thyroid and lipid profile differently through different mechanisms, peripheral and central, that are dose dependent regardless of the seizure type and age of the patient. Also, children with epilepsy compliant on ASMS are associated with a statistically significant delayed growth and increase in DBP that is significantly correlated with hypothyroidism and more prominent in polytherapy and conventional ASMs. So, thyroid and lipid profile, height measurement, and blood pressure should be monitored on regular basis for all children with epilepsy receiving ASMs. It is better to shift to newer ASMs and to shift from polytherapy to monotherapy to avoid those disturbance as long as with equivalent efficacy. Echocardiography data were uneventful in those with abnormal thyroid function in this study.

Abbreviations

AMPA	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANOVA	Analysis of variance
ASMs	Anti-seizure medications
BMI	Body mass index
CBZ	Carbamazepine
CLZ	Clonazepam
CoA	Acetyl-coenzyme A
Cu	Copper
DBP	Diastolic blood pressure
EEG	Electroencephalography
ESC	Eslicarbazepine
ESM	Ethosuximide
fT4	Free thyroxine
GABA	Gamma-aminobutyric acid
HDL	High-density lipoprotein
IDL	Intermediate density lipoprotein
INR	International normalized ratio
LDL	Low-density lipoprotein
LEV	Levetiracetam
LMT	Lamotrigine
Mg	Magnesium
MRI	Magnetic resonance imaging
NMDA	N-Methyl-D-aspartate
OXC	Oxcarbazepine
PBT	Phenobarbital
PHT	Phenytoin
PT	Prothrombin time
PTT	Partial thromboplastin time
SBP	Systolic blood pressure
SPSS	Statistical Package for Social Science
TFQI	Thyroid feedback quantile-based index
TPM	Topiramate
TRH	Thyrotropin-releasing hormone
TSH	Thyroid stimulating hormone.
TTE	Trans-thoracic echocardiogram
UGT	UDP-glucuronosyltransferase
VLDL	Very-low-density lipoprotein
VPA	Valproic acid
ZNS	Zonisamide

Supplementary Information

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Additional file 1: Appendix S1. ASMs used in the whole study. **Appendix S2.** Effect of different ASMs combination on age, increase height in 1 year, weight, BMI and diastolic blood pressure. **Appendix S3.** Effect of different ASMs combination on thyroid and lipid profile.

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Author contributions

AR: data collection, research project execution, contribution to the concept and design, drafting the manuscript. NS: conception of the work, manuscript revision. NM: conception of the work, approved the version to be published. MN: revised the manuscript critically for important intellectual content. EM: analysis and interpretation of data. All authors have agreed to conditions noted on the Authorship Agreement Form and have read and approved the final version submitted. The content of the manuscript has not been published, or submitted for publication elsewhere.

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Availability of data and materials

All raw data will be available on the editor request through communication with the corresponding author.

Declarations

Ethics approval and Consent to participate

All procedures performed in the study were in accordance with the ethical standards of the faculty of medicine, Ain Shams university research and ethical committee. We obtained approval from research ethics committee no. FWA 000017585. An informed consent was obtained from the leading guardian of the study participants, and this conformed to the standards of the Ethical Review Committee, Ain Shams University.

Consent for publication

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Competing interests

All authors declare that they have no conflict interest.

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