Research Article

Impact of Mono-therapy Antiepileptic Drugs on lipid profile of epileptic children

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Abstract
Background: Epilepsy is one of the most common neurological disorders, which required long term therapy or lifelong treatment in some cases. Chronic use of antiepileptic drugs (AEDs) therapy might modify some vascular risk factors, Since atherosclerotic vascular alterations may start early in life, this study focuses on dyslipidemia which is a major atherogenic risk factor among epileptic children. **The aim of this study**: to evaluate different effects of mono-therapy antiepileptic drugs (AEDs) on lipid profile of children with idiopathic epilepsy. **Methods**: this study was carried out on 80 children , their age rage (7-16) divided into group I included 20 healthy children their age and sex matched served as a control ,group II included 20 newly diagnosed epileptic children (according to **ILAE2014** diagnostic criteria of epilepsy) they didn't receive medication till the time of study and and lastly group III included epileptic children receiving monotherapy AEDs n=40 ,where the duration of treatment were not less than 2 months ; groupIII divided into four subgroup according to the type of AEDs . Measurement received for all participant include detailed history, clinical examination ,neurological examination and serum fasting lipid profile, while the analysis of seizure (onset ,type, frequency and classification of epilepsy according to (ILAE2017)) , inter-ictal EEG ,history of AEDs administration; daily dose and compliance to medication were for epileptic patient only. **Result:** serum TC, LDL were significantly higher in epileptic children receiving AEDs than control groups or group of newly diagnosed epileptic children , TG and VLDL were higher in epileptic children treated with old AEDs than other groups ,while newly diagnosed epileptic children have higher LDL than control group, on the other hand there is a significant higher HDL in epileptic children treated with new antiepileptic drugs than newly diagnosed epileptic children and epileptic children treated with old antiepileptic drugs. **Conclusion:** epilepsy and antiepileptic drugs especially old generation antiepileptic drugs are considered risk factors of dyslipidemias& atherosclerosis. We recommend routine monitoring of the serum lipid profile in epileptic children especially they treated with old generation AEDs (VAP and CBZ namely).
Keyword: epilepsy antiepileptic drugs AEDs serum lipid profile old AEDs new AEDs

Introduction
Epilepsy is one of the most prevalent chronic neurologic disorders (World Health Organization, 2015). Many people with epilepsy receive lifelong prescription treatment.

Older antiepileptic drugs (AEDs), mainly enzyme inducers (EIAEDs), may be associated with more adverse effects than newer AEDs. For example, they alter lipid profile, increasing serum cholesterol levels (Mintzer et al., 2009). However, there is a lack of information about the prevalence of dyslipidemia related to the use of AEDs, which would facilitate appropriate management to reduce the risk of vascular diseases. Another AED that has been related to vascular risk factors is valproic acid (VPA), which has been associated with metabolic syndrome (Kim and Lee, 2007). For these reasons, some authors have suggested starting new AEDs in newly diagnosed patients or changing EIAEDs if patients

experience metabolism-related effects (Brodie et al., 2013)

However, limited data are available especially in children to determine the effects of AEDs on lipid profile as a vascular risk factor for atherosclerosis.

Objectives

To compare the effect of different AEDs (carbamazepine, valproic acid, levetiracetam & oxacarbamazepine) on lipid profile

Materials and Methods

- This study was a hospital based cross-sectional study was conducted in Minia university hospital, This study carried out on 80 children above the age of 7 years with age range (7-16), selected subjects divided into 3 groups: the group I included control (n=20), Group II included newly diagnosed epileptic children before starting treatment with AEDs (n=20), group III (n=40) included epileptic children receive mono-therapy antiepileptic drugs for period not less than 2 months; the last group is further subdivided into 4 groups according to the type of AEDs were received (14 patients on valproic acid (VPA), 6 patients on carbamazepine (CBZ),12 patients on levetiracetam (LEV), 8 patients on ooxacarbamazepine (OXC)) .

- All participant were evaluated for all measurement including demographic & clinical data, serum lipid profile, complete clinical examination, anthropometric measures: (weight, height and BMI) and complete neurological examination except the analysis of seizure, and EEG for diseased patients only.

Measurement for epileptic patients includes

Analysis of seizures; duration of epilepsy careful history taking from patients or near relative to determine type of epilepsy according to (ILAE2017)[(2)] and history of Antiepileptic drugs administration: as regards type, dose and compliance.

Digital electro-encephalogram for all epileptic patients in the study:

All patients were submitted to Nihon Koden digital EEG, the EEG was carried out on 16 channels. (the patient hair was washed with water and soaps), crocodile electrodes were applied according to 10-20 mm international system of electrodes placement recording was made using 35 & 50 mv calibration, with eye of the patient closed, provocation with hyperventilation and photic stimulation was performed in every record. EEG was reported by double blind separation technique by 2 professional neurophysiologists and discussed with colleagues in the department of clinical neurophysiology to estimate EEG finding in diseased patient.

Specimen Collection

Sample was collected from study all participant. 5ml of venous blood was collected by trained lab technician under sterile conditions using a disposable syringe between 9.00 to 10.00 a.m. after fasting at least (8-10h) and the sample was tested for TC, HDL-C, LDL-C and TG. The blood was allowed to clot at room temperature, and centrifuged at 3000rpm for 10min to separate serum. It was then kept frozen at -20°C to be analyzed later on.

TC was calculated by enzymatic method and expressed in mg/dl. HDL-C was calculated using polyanion precipitation and expressed as mg/dl. LDL-C was calculated using Friedewald's equation and expressed in mg/dl. Triacylglycerol in serum was converted to glycerol and then estimated using glycerol kinase enzyme based kinetic method and expressed in mg/dl.

Ethical Permission

Ethical permission to conduct the hospital based study was obtained as written & verbal consent from all participants.

Exclusion criteria

1. Patients with secondary epilepsy,
2. Patients with other neurological or psychiatric disorder,

3. Patients with other genetic or medical disorder,
4. Patients with serious illness, malignancy or other complications,
5. Patients on more than one antiepileptic drug.

Statistical Analysis

Data obtained from patients with epilepsy and control cases were fed into computer soft were package (SPSSS, version 20) through which, descriptive statistics were calculated descriptive statistics, i.e. .mean ± Standard deviation (SD), Range, median and inter quartile range (IQR).

One-way ANOVA test for parametric quantitative data between the four groups followed by post Hoc Tukey's analysis between each two groups, Kruskal Wallis test for non-parametric quantitative data between the four groups followed by Mann Whitney test between each two groups

Chi square test (if expected values within cell > 5) and Fisher's exact test (if expected value within cell < 5) for qualitative data between the groups

Superscripts with same small letter indicate insignificant difference between each two groups, otherwise there was significant difference between each two groups

Results

The results of this study were summarized and illustrated in the following tables and figures

Table (1): demographic of all studied groups:

		Group I N=20	Group II N=20	Group III N=40	P value
Age	*Range*	(7-16) [a]	(7-16) [a]	(7-14) [a]	*0.154*
	Mean ± SD	9.9±2.8	10.9±2.1	10±2.29	
Sex	*Male*	9(45%) [a]	10(50%) [a]	26(65%) [a]	*0.274*
	Female	11(55%)	10(50%)	14(35%)	
BMI	*Range*	(10.2-21.8) [a]	(15.4-21.5) [a, d]	(14.4-24) [b, d]	***0.018****
	Mean ± SD	17.1±3	18.3±1.7	19.1±2.7	
Residence	*Rural*	10(50%) [a]	13(65%) [a]	24(60%) [a]	*0.613*
	Urban	10(50%)	7(35%)	16(40%)	
Education	*Elementary*	13(65%) [a, c]	14(70%) [b, c]	28(70%) [a]	*0.620*
	Primary	3(15%)	5(25%)	6(15%)	
	Secondary	4(20%)	1(5%)	6(15%)	

*: Significant level at P value < 0.05

demographic data of all participants shows that no significant difference among all studied groups as regard demographic data except significant higher BMI in epileptic children receiving AEDs than other groups with p value=0.018. (Table1)

Table (2): clinical data of epileptic children

		Group II	Group III	P value
		N=20	N=40	
`	*Idiopathic generalized*	17(85%) [a, c]	24(60%) [c, d]	*0.024**
	Partial epilepsy	3(15%)	14(35%)	
	Epileptic syndromes	0(0%)	2(5%)	
Seizure type	*Partial*	2(10%) [b]	12(30%) [b]	***0.031****
	Partial with secondary generalization	1(5%)	4(10%)	
	Generalized with motor element	14(70%)	24(60%)	
	Absence	3(15%)	0(0%)	
Duration of Epilepsy	**Mean ±SD**	1.3±.47	27.8±20.5	***<0.001***
	Range	(1-2)	(5-80)	
Compliance	*Fair*		30(75%)	
	Poor		10(25%)	
EEG	*Normal*	7(35%)	4(10%)	*0.008*
	Focal sharp and slow	3(15%)	12(30%)	
	Generalized sharp and slow	7(35%)	22(60%)	
	Generalized slow	0(0%)	2(0%)	
	3HZ	3(15%)	0(0%)	

Clinical data of all diseased groups represented in (Table2)

Table (3): serum lipid profile among studied groups

		Group I	Group II	Group III	P value
		N=20	N=20	N=40	
TC	*Median*	107.5 [a]	117.5 [a]	[b]155.5	***<0.001****
	IQR	(90.5-117.8)	(105.5-134.8)	(127-222.2)	
TG	*Median*	109.5 [b]	125 [b]	150.5 [a]	***0.27***
	IQR	(80.8-133.3)	(94.5-139.8)	(89.2-246)	
LDL	*Median*	51 [b]	60.7 [c]	89.9 [a]	***<0.001****
	IQR	(34.5-55)	(43-76.4)	(69.3-117.8)	
HDL	*Median*	31 [a, c]	30 [a]	35 [a]	*0.349*
	IQR	(24-45)	(26-37.5)	(26.5-42)	
VLDL	*Median*	21.9 [b]	25 [b]	30.1 [a]	***0.26***
	IQR	(16.2-26.7)	(18.9-28)	(17.8-49.2)	

There are no significant difference between groups in lipid profile except there are significant higher TC and LDL in group III than other groups with p value among groups = (<0.001) for each (Table 3).

Table (4): Differences of total lipid profile among studied subgroup.

		Na Valproate	Carbamazepine	Levitracetam	Oxacarbamazepam	P value
		N=14	N=6	N=12	N=8	
TC	*Median*	146 [a]	236 [b]	137 [a]	161 [a]	*0.053*
	IQR	(126-223)	(173-339)	(115-156)	(106.3-206.8)	
TG	*Median*	173 [a]	178 [a]	89.5 [b]	99 [b]	***0.004****
	IQR	(149-304)	(152-344)	(88-128)	(78-255.8)	
LDL	*Median*	75.2 [a, c]	169.4 [b, d]	81.5 [c, d]	102.9 [c, d]	*0.160*
	IQR	(64.4-96.2)	(81.2-285.6)	(69-100.2)	(50.5-117.8)	
HDL	*Median*	37 [c, d]	23 [a, c]	40 [b, d]	36.5 [b, d]	***0.018****
	IQR	(25-42)	(23-31)	(31.4-49)	(31.5-48.3)	
VLDL	*Median*	34.6 [a]	35.6 [a]	17.9 [b]	19.8 [b]	***0.004****
	IQR	(29.8-60.8)	(30.4-68.8)	(17.6-25.6)	(15.6-51.1)	

- Kruskal Wallis test for non-parametric quantitative data (expressed as median and IQR) between the four groups followed by Mann Whitney test between each two groups
- Superscripts with same small letter indicate insignificant difference between each two groups, otherwise there was significant difference between each two groups
- *: Significant level at P value < 0.05

In this study we found that TG is significantly higher in epileptic children receiving VPA, CBZ while TC and LDL have no significant difference between groups , higher HDL is reported to be present between epileptic children receiving LEV and OXC and VPA, as regard VLDL it was higher in epileptic children receiving VPA and CBZ .

Discussion

This study was designed to evaluate the difference between the effect of monotherapy antiepileptic drugs on lipid profile parameter of epileptic children.

In this study we found a significant higher BMI in epileptic children receiving treatment with old antiepileptic drugs (VAP&CBZ) than control group.

This result was in accordance with Gungor et al., who found that some drugs such as VPA, and to some extend carbamazepine cause weight gain and increase BMI. (Gungor et al., 2007)

In dis agreement with this result Pickrell et al., who found that LEV was associated with significant weight gain while CBZ was not associated with significant weight gain. (Pickrell et al., 2013).

In this study we found no significant difference between studied groups in lipid profile except there are significant higher TC and LDL in group III than other groups with p value among groups = (<0.001) for each, also we found that TG is significantly higher in epileptic children receiving VPA, CBZ while TC and LDL have no significant difference between groups

In accordance with us was Nishiyama et al., who found there were no significant changes in total cholesterol, LDL in patient before starting Carbamazepine (as old antiepileptic drug) by 1m and after staring them by 6m (Nishiyama et al., 2019)

In accordance with us was Yamamoto et al., who found that epileptic patients on VPA or CBZ were associated with a higher non-HDL-C, but he found that an elevated non-HDL-C level was associated with increasing age, increasing BMI, and male gender, and use of inducer drugs, Treatment with levetiracetam had little influence on the lipid profile and he recommend routine monitoring of the non-HDL-C level when using VPA and inducers, especially CBZ (Yamamoto et al., 2016)

In disagreement with us was El-Farahaty et al., who study the metabolic and atherogenic effects of long-term antiepileptic drugs in a group of adult Egyptian epileptic patients. He found Significant higher LDL and significantly larger diameter of common carotid artery intima-media thickness in each drug-treated group (old AEDs) versus control group .and he conclude that long-term monotherapy treatment with valproate, carbamazepine had altered markers of vascular risk that might enhance atherosclerosis, whereas levetiracetam exerted minimal effect (El-Farahaty et al., 2015).

Also in disagreement with us was Płonka-Półtorak et al., found that no significant difference between patients on the valproate (VPA) treatment and controls for total cholesterol (CHOL), low-density-lipo-protein cholesterol (LDL) (Płonka-Półtorak et al., 2016),

We also found that significantly higher HDL is reported to be present between epileptic children receiving LEV and OXC and VPA, as regard VLDL it was higher in epileptic children receiving VPA and CBZ.

Attilakos et al., also found that LEV increase HDL and the LDL-C/HDL-C ratio was significantly decreased at 12 months of LEV treatment in children and considered LEV as a safer alternative drug for the prevention of antiepileptic drug-induced cardiovascular complications in adult life. (Attilakos et al., 2019)

In disagreement with us Kim et al., who found that patient treated with (LEV and OXC) after 6-month period of monotherapy not significantly change, HDL-C levels. (Kim et al., 2013b)

We found that there is no significant difference in lipid porofile between newly diagnosed epileptic children and control except in significantly higher LDL serum level than control with p value (=0.030)

This result was in accordance with the result of (Arend et al., 2018) how found that higher lipid profile levels were observed in the patients with epilepsy than controls

Conclusion

From the present study we can conclude that old generation antiepileptic drugs like VAP and CBZ are strongly associated with dyslipidemia whereas OXC and LEV associated with minimal changes in lipid profile and increase HDL which is a protective factor against atherosclerosis. Therefore, the serum lipid profile level should be regularly monitored in patients undergoing therapy with antiepileptic medicines and we recommend selection new AEDs (OXC & VPA) in treatment of epileptic children to overcome dyslipidemia occurs with AEDs.

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