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RESEARCH ARTICLE

COMPARATIVE EVALUATION OF SOME ANTIEPILEPTIC DRUGS ON LIPID PROFILE AND CAROTID INTIMA THICKNESS IN A SAMPLE OF EGYPTIAN CHILDREN: A ONE YEAR PROSPECTIVE STUDY.

Nahed Shehta[1], Takwa H. M. Elkhatib[1], Rasha M. Fahmi[1], Bothina M. Ramadan[1], Ahmed F. Elsaid[2], Samar M. Shehata[3].

1. Department of Neurology, Zagazig University; Egypt.
2. Department of Public Health and Community Medicine, Zagazig University; Egypt.
3. Department of Radiodiagnosis, Zagazig University; Egypt.

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Corresponding Author

Rasha M. Fahmi.

Abstract

Introduction:- This study aimed at detection of association between antiepileptic drugs and atherosclerosis in a sample of Egyptian children through evaluating lipid levels and carotid artery intima media thickness (CA-IMT).

Patients and methods:- 90 newly diagnosed epileptic children were administered a monotherapy with either carbamazepine (CBZ), valproate (VPA) or levetiracetam (LEV), from January 2014 to May 2015. 84 patients continued the study to the end. All subjects were clinically evaluated and followed up for 1 year. Basal and terminal (after 1 year) lipid profile and CA-IMT were assessed by biochemical and ultrasonography, respectively.

Results:- Although all drug groups didn't demonstrate any significant difference in the basal levels of lipid profile, CBZ and VPA drugs induced higher levels of TC, LDL, TG and lower levels of HDL compared to LEV after 1 year of treatment. Concomitantly, CBZ and VPA increased CA-IMT thickness more than LEV, but this difference was not statistically significant.

Conclusion:- LEV didn't perturb lipid profile and CA-IMT, whereas CBZ and VPA induced significantly higher levels of dyslipidemia and non-significant increased CA-IMT in children after one year of treatment.

Introduction:-

Epilepsy is a chronic neurologic problem which makes a lot of troubles for children and their families, however neurologists have little concern about the prevalence of vascular risk factors and their involvement in the development of atherosclerosis (AS) of epileptic patients. Nearly 3.5 million people worldwide develop epilepsy annually, about 40 percent of these are under 15 years of age. Interestingly more than 80% of them live in developing countries.[1]

The goal of epilepsy treatment is the achievement of complete seizure remission without any adverse events, nevertheless these drugs when given over a prolonged period can have several adverse effects.[2,3] Many studies have found that the epilepsy demonstrate high risk of cardiovascular disorders than the normal population. This might be associated with the long-term use of antiepileptic drugs (AEDs) that may cause AS especially the conventional antiepileptic drugs, whereas studies on the newer ones are deficient.[4]

Valporate (VPA) and carbamazepine (CBZ) are the most recognized conventional AEDs used for seizure control in children. As a result of its wide range of tolerability, sodium valporate is a first-line anticonvulsive agent used in epileptic children however weight gain, fatty liver disease, hematological and cardiovascular disorders are side effects of this widely prescribed medication.[5] Carbamazepine is another medication of decision for seizure control, although lipid profile changes, aplastic anemia, nausea and vomiting are among its frequent complications.[6]

Recently there has been an attention on the relationship between the epilepsy and AS. A few studies show that long treatment with AEDs is proatherogenic through change of serum lipids and apolipoprotein levels.[7,8] Unexpectedly numerous different studies report just negligible or transient changes in serum lipids in patients on AEDs.[9,10] The majority of this information originates from grown-ups[11,12] and there are just a couple studies assessing this relationship in children.[13,14]

On account of known harming impacts of older AEDs on atherosclerosis, new AEDs are frequently proposed as first line choice in the treatment of epilepsy. New AEDs are less inclined to induce hepatic enzymes so it appears to be conceivable that their consequences for vascular danger may be lower than more established AEDs[15], however constrained information are accessible to date, making their risky impacts on vascular danger are generally obscure.

Plasma proteins abnormalities are key for the event of atherosclerotic diseases including elevated concentration of total cholesterol (TC), low density lipoprotein (LDL) cholesterol, and triglycerides (TG).[16,17]

Management of atherosclerosis has become a primary focus of preventative care medicine. Sonographic assessment of the carotid arteries is the imaging modality of choice for screening, diagnosis, and monitoring of atherosclerotic disease of the extra-cranial carotid arteries. It is believed that thickening of the intima media thickness complex greater than 0.8 mm is abnormal and may represent the earliest changes of atherosclerotic disease. Thickening of intima goes before clinical cardiovascular occasions of AS by decades. CA-IMT could mirror the extensions and degrees of atherosclerotic injuries to some degree.[18]

Aim of the work:-

This study aimed at detection of association between antiepileptic medication and atherosclerotic danger variables. This will be accomplished through evaluating changes in serum lipid levels and CA-IMT, as markers of atherosclerosis after taking antiepileptic drugs which may be valuable to pick the most secure medication and counteractive action of cardiovascular hazard in later life.

Patients and methods:-

The current prospective study was initiated with 90 patients who were recruited from outpatient clinics of neurology department, Zagazig University Hospitals, Egypt from January 2014 to May 2015. We selected three drugs, among of the commonly prescribed ones, two of the traditional AED (VPA and CBZ) and one of the newer AED (LEV) as a noninducing drug and commonly prescribed in our locality. Patients were divided into 3 groups, 30 patients each, that were administered either CBZ, VPA or LEV. These drugs prescribed according to the type of epilepsy. All of patients received CBZ were of partial epilepsy while in the VPA group most of the patients were of generalized type. After 1 year, only 84 patients continued the study. Patients who dropped out included 2 patients refused to continue and 4 patients who travelled to another place and were not accessible.

The diagnosis as having idiopathic epilepsy was done through electroencephalogram (EEG) and imaging combined with clinical manifestation according to International League against Epilepsy.[19] Those patients started to get monotherapy with Leviteracetam, Carpamazepine, or valproate in light of clinician's choice. AED were controlled at a beginning dosage of 250 mg/day (LEV), 200 mg/day (CBZ), and 300 mg/day (VPA), and were then increased gradually to achieve the most tolerable dose that achieves great seizure control. The study was finished following a 12-month time of monotherapy with one of three AEDs. We informed all patients about details and goals of this study before the start. The local ethics committees approved this study, and parents of all participants gave informed consent.

Patients were excluded from the study in which other AEDs was included as polytherapy or initial AED was changed to another because of deficient seizure control or serious adverse effect. Patients who had not taken AED for >2 weeks during the study period were further excluded. We also excluded patients with secondary epilepsy,

other neurological or psychiatric disorder, medical or genetic disorder, patients taking other drugs that may alter lipid profile during our study period for >4 weeks, vasoactive medicines or folate or vitamin C intake in the past 4 weeks. We encouraged all our patients at the start of the study to avoid high caloric diet.

Blood sample was collected from the patients twice, the first one at baseline before starting treatment and the second after 1 year of AED treatment. 5ml of venous blood was collected under sterile conditions using a disposable syringe between 8.00 to 10.00 a.m. after overnight fasting and the sample was tested for TC, HDL-C, LDL-C and TG.

Intima media thickness (IMT) assessment:-

Instrumentation:-

All examinations were performed by a radiology professional using Philips clear view 650 ultrasound machine, with a 5 to 12-MHz high-frequency linear transducer, dependent on the patient body habitus.

Technique:- Imaging should be performed with the patient supine, arms down by their side, and the head turned about 45◦ away from the side being examined. A pillow can be placed under the shoulders of the patient to hyperextend the neck. Thorough gray scale examination of the right and left common carotid arteries was done for intima media thickness (CCA IMT) in longitudinal section, just proximal to the carotid bulb .A mean of two values was taken.

Intima-media thickness (IMT) is defined as the distance between the inner and the outer echogenic lines, as measured by a caliper placed at the level of the echogenic interface of the intima with the anechoic vessel lumen and a second caliper placed at the echogenic interface of the adventitia with the hypoechoic media.

Statistical Analysis:-

Data were checked, entered and analyzed using IBM, SPSS Version Statistics 20.0 software package (special package for social science). Data were expressed as percentage for discrete variables and mean ±SD for continuous variables. Paired t-test was performed to determine within groups variation, whereas student t-tests and ANOVA were performed to determine between groups variation. $P<0.05$ was considered significant and $P<0.001$ was considered highly significant.

Sample size: Treatment of epileptic patients with CBZ was reported to induce total cholesterol level with an effect size of 0.32 compared to the control group.[17] To detect this size effect in the analysis of variance between the three examined drug groups with 2 repeated measurements (basal and 1 year after treatment) at 0.05 alpha level of significance, a sample size of 30 subjects per group was found to achieve more than 95% power. Sample size was calculated using G*Power software package (version 3.1.9.2, Franz Faul, Germany).

Results:-

The present study included children patients who were under treatment with AEDs for 1 year. This study provided evaluation of lipid profile and CA-IMT in these patients. The data were collected, summarized, and the results of the current study were tabulated and statistically analyzed and summarized as follows;

The clinical characteristics of patients are shown in Table (1). When compared the three groups there was no statistically significant difference as regard age, sex and body mass index.

Table 1:- Demographic data of the patients.

Variables	Carbamazepine	Valproate	Leviteracitam	P
Age (mean±SD)	10.25±2.86	11.00±2.84	11.53±2.39	0.44
Sex (M:F)	20:10	16:14	13:17	0.13
BMI (mean±SD)	26.13±4.31	25.27±3.45	24.47±2.92	0.14
Seizure type • Partial • generalized	 26 0	 2 26	 18 12	

With regard the lipid profile, ANOVA showed no statistically significant difference in lipid marker levels between groups at baseline values as shown in Table (2). However there were statistically significant differences after one year of monotherapy. TG (P=0.001), CHOl (P=0.04), LDL (P=0.003) and HDL (P=0.001) were increased in CBZ and VPA versus LEV treated patient (Table 3).

Table 2:- Comparison between the patients at the baseline regarding the lipid profile (before starting the ttt)

Variables	Carbamazepine	Valproate	Leviteracitam	P
TG	104.56± 15.36	107.34±13.68	103.44 ±20.43	0.77
TC	121.33±31.54	125.22±26.14	124.72±29.98	0.91
LDL-C	71.94±16.75	72.239±13.10	72.950±9.97	0.97
HDL-C	44.14±4.44	45.86±4.08	45.01±5.01	0.53

Table 3:- Comparison between the 3 groups at the follow up regarding the lipid profile (after 1 year of the ttt)

Variables	Carbamazepine	Valproate	Leviteracitam	P
TG	129.44±18.76	128.83 ±24.65	104.72 ±19.81	0.001
TC	152.39±37.81	157.06±36.05	128.67±31.37	0.04
LDL-C	93.39±20.31	90.61±19.03	73.98±11.68	0.003
HDL-C	41.00±3.59	40.99±4.60	46.44±4.86	0.001

Table (4) shows comparison of lipid and common carotid artery IMT change values within the groups before and after the treatment. There was statistically significant difference in the groups treated with CBZ and VPA regarding the lipid profile only, however there was no change in the group treated with LEV.

Table 4:- Comparison between the baseline and follow up lipid profile and common carotid artery IMT within the same group

Variables	Carbamazepine		Valproate		Leviteracitam	
	Change in variable	p-Value (within group)	Change in variable	p-Value (within group)	Change in variable	p-Value (within group)
TG	24.89±15.92	0.00	21.49±5.23	0.001	1.28±4.26	0.768
TC	31.06±15.44	0.00	31.83±8.68	0.002	3.94±2.94	0.198
LDL-C	21.44±15.74	0.00	18.37±3.69	0.000	1.03±2.38	0.392
HDL-C	-3.14±1.45	0.04	-4.86±169	0.01	-1.44±1.66	0.399
CA- IMT	0.04±0.03	0.20	0.04±0.02	0.08	0.02±0.01	0.24

As regard Carotid intima media thickness, when comparing between the three groups of patients at base line we found no statistically significant difference (P=0.64) between the patients (Table 5). However, there was an increase in thickness after one year in patients treated with CBZ and VPA more than the patients treated with LEV, but this difference was not statistically significant (Table 6).

Table 5:- Comparison between baseline common carotid artery IMT in the 3 groups (before starting the ttt)

	Carbamazepine	Valproate	Leviteracitam	P
CA IMT	0.54±0.10	0.53±0.10	0.54±0.09	0.96

Table 6:- Comparison between baseline common carotid artery IMT in the 3 groups (after 1year of the ttt)

	Carbamazepine	Valproate	Leviteracitam	P
CA IMT	0.59±0.13	0.58±0.08	0.55±0.09	0.62

Discussion:-

In view of the fact that, information from diverse studies demonstrate the significance of long term utilization of AEDs and plasma lipoprotein abnormality for the event of atherosclerosis later in life. In the current study, we utilized a prospective study design, which has the advantage of revealing causal association compared to the cross-sectional study designs utilized in the majority of previous studies.

Recently, many new AEDs have been developed. Even though the efficacy of new AEDs is not stronger than that of old AEDs, there are advantages in using new AEDs. They have matchless or different mechanisms of action that enable the establishment of promising synergistic combinations. They have fewer or no pharmacokinetic drug interactions as well as fewer adverse effects including induction of congenital malformations. Moreover their effects

on lipid profile have been tested in few studies and the researchers has reported no change in serum lipids when compared to the older drugs.[20,21] This was supported by studies showed a promising results with the effect of newer AEDs like lamotrigine, levetiracetam and oxcarbazepine on lipid profile and carotid intimal thickness.[21] Other concerns about the long-term effects of established AEDs, such as bone health and development of atherosclerosis, may be alleviated by the use of new AEDs. To the best of our knowledge, this is the first prospective study conducted on epileptic children under monotherapy either old or new generation of AEDs to assess the risk of atherogenesis in Egypt.

As regard lipid profile, in our study children on CBZ had significantly higher values of TG, TC, LDL while lower values of HDL one year after starting the treatment compared to the baseline. This result was in agreement with several studies suggesting that enzyme inducers such as CBZ, PB, PHT, and PRM lead to increase serum cholesterol levels both in cross-sectional and prospective studies of children and adults with epilepsy[22-24] even in healthy adult male volunteers after the use CBZ, fortunately the increase in cholesterol could be reversible 1 year after cessation of treatment.[25] Our result was in disagreement with Erdemir et al.[14] who did not observe any differences in serum lipid profiles between epileptic and healthy children.

Unlike hepatic enzyme-inducing anti-epileptics, the effect of enzyme inhibitors like valproic acid on lipid profile remains unclear. In the present study we observed an elevation in the concentrations of serum lipids during valproic acid treatment. Numerous studies performed both on adults[26,27] and children[21,28,29] showed dyslipidemia after using valproate. In contrary to our results, Erdemier et al,[14] did not observe any change in the concentration of serum lipids during valproic acid treatment in epileptic children.

It was reported that valproic acid can cause insulin resistance with hyperinsulinemia which may also lead to atherosclerosis.[30] Moreover, valproic acid causes change in oxidant–anti-oxidant status On the other hand, through increase erythrocyte lipid peroxidation versus decrease erythrocyte glutathione peroxidase and superoxide dismutase activities which may lead to the development of atherosclerosis.[31,32]

As regard levetiracetam, we did not observe in our study any statistically significant difference among mean TC, HDL-C, LDL-C and TG levels in the group receiving levetiracetam treatment for 1 year. In concordance with our results, Manimekalai and colleagues[33] did not observe any statistically significant difference among TC, HDL-C, LDL-C and TG levels in the patients treated with levetiracetam. However, Kim and colleagues[34] reported that only LDL-C levels were increased in LEV after 6 months of monotherapy, while TC, HDL-C, TG, and non-HDL-C levels were unchanged. This was supported by other studies regarding levetiracetam where they observed a decline in total cholesterol levelwhen epileptic patients receiving an inducing AEDs like carbamazepine and phenytoin switched to the non-inducing AEDs lamotrigine and levetiracetam.[20,35]

Carotid atherosclerosis is a major risk factor for both stroke and myocardial infarction. The importance of CA-IMT assessment as an early surrogate measure for atherosclerosis, which has been strongly correlated with risk of both stroke and myocardial infarction, were reported in many studies.[36,37]

In the present study, there was increased intima media thickness of carotid artery in epileptic patients treated with carbamazepine and valproic acid which was demonstrated more in patients treated with carbamazepine than those treated with valproic acid. However, in patients treated with levetiracetam there was no change in intima media thickness. Our result was in accordance with other studies found that CBZ-treated patients had higher CA-IMT than VPA-treated patients.[38] However our results were not significant which was inconsistent with other studies found significantly higher CA-IMT in epileptic treated children without a difference in serum lipids.[18,39] This could be a consequence of difference in the design of our study which most properly is the follow up time. In addition, El farahaty et al,[21] established that long-term monotherapy treatment with valproate, carbamazepine, lamotrigine, and topiramate had altered vascular risk markers that might augment atherosclerosis, whereas patient treated with levetiracetam showed minimal effect on lipid profile and CA-IMT.

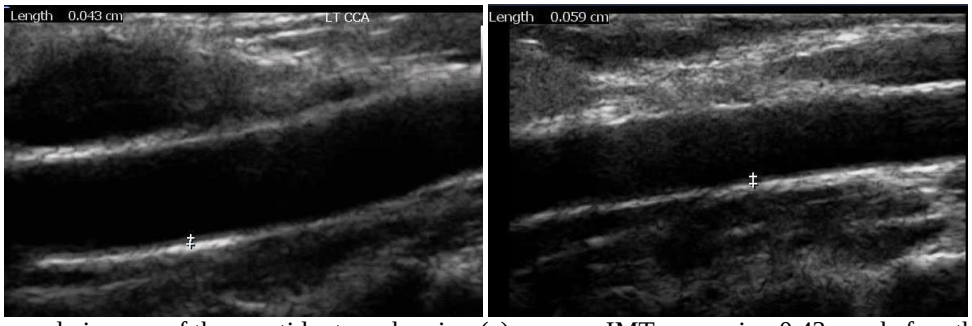

Fig 1:- Grayscale images of the carotid artery showing (a) average IMT measuring 0.43 mm before therapy; (b) abnormal thickening of the IMT measuring 0.59 mm thick in a patient who treated with CBZ for 1 year.

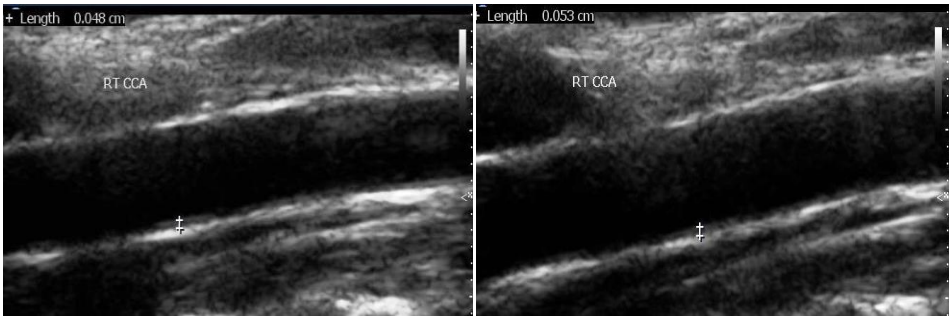

Fig 2:- Grayscale images of the carotid artery showing (a) average IMT measuring 0.48 mm before therapy; (b) abnormal thickening of the IMT measuring 0.53 mm thick in a patient who treated with VPA for 1 year.

Conclusion:-

This study shows that LEV didn't perturb lipid profile and CA-IMT, whereas CBZ and VPA induced significantly higher levels of dyslipidemia. Ultrasonographic imaging of the carotid arteries plays a key noninvasive role in the clinical evaluation for atherosclerosis.

Recommendation:-

We recommended regular checking for all children under treatment of antiepileptic drugs especially for lipid profile and CA-IMT. Also, further prospective studies for longer time are needed to verify the effect of monotherapy with antiepileptic drugs on CA-IMT.

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