Research Article

Estimation of Serum Level of Homocysteine and its Potential Cardiovascular Effect in Epileptic Children Receiving Antiepileptic Drugs

Samir T. Abdullah*, Doaa M. Mahrous*, Mahmoud M. Mounir and Tasneem M. Badawy***

* Department of Pediatrics at Minia University Hospital

** Department of Radiology at Minia University Hospital

Abstract

Introduction: Many studies have suggested that the plasma homocysteine level is increased as a side effect with prolonged use of some antiepileptic drugs, which is associated with increase Carotid intima media thickness; hence it increases the risk of atherosclerosis in young age. **Objectives:** To assess serum level of homocysteine in epileptic children on long standing antiepileptic drugs and its association with increased incidence of cardiovascular disease. **Patients and methods:** This study will include 85 children between 2-15 years (20 on one old generation antiepileptic drug, 20 on one new generation antiepileptic drug, 20 on polytherapy of antiepileptic drugs on antiepileptic drugs for at least 1 year and 25 apparently healthy children will be taken as a control group). All of them subject to careful history taken, clinical examination and anthropometric measures, laboratory investigation included (serum homocysteine) and radiological assessment included (carotid intima media thickness and carotid stiffness). **Results:** Our study revealed statically significant increase serum level of homocysteine, carotid intima media thickness and carotid stiffness in children on monotherapy of old generation antiepileptic drugs and poly therapy than that in children on monotherapy of new generation antiepileptic drugs and control. **Conclusion:** The old generation antiepileptic drugs and polytherapy antiepileptic drugs modalities increase the serum level of homocysteine in children. The new generation antiepileptic drugs have minimal effect on their serum level. Children who use the old generation antiepileptic drugs and polytherapy antiepileptic drugs have increasing in carotid intima media thickness and carotid stiffness than those who use the new generation antiepileptic drugs.

Key words: Antiepileptic drugs; carotid intima media thickness; Epilepsy; homocysteine

Introduction

Background: Epilepsy is a chronic disease of the brain affecting 3.5–5/1000 children in the developed countries with 41–187/100,000 new cases every year.[1]

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, which are caused by excessive discharges in the neurons.[2].epilepsy is diagnosed when an individual has: 1) at least two unprovoked or reflex seizures >24 h apart, 2) one unprovoked or reflex seizure and a probability of having another seizure similar to the general recurrence risk after two unprovoked seizures (≥60%) over the next 10 years, or 3) an epilepsy syndrome.[3]

Many effective antiepileptic drugs (AEDs) are currently available. These are generally subdivided into the first-generation AEDs (phenytoin, carbamazepine, phenobarbital, Primidone, valproate, ethosuximide, and the benzodiazepines), and the second-generation AEDs (felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, zonisamide, and pregabalin). Selection of the ideal drug for each individual patient should be based on a number of factors, including cost, spectrum of activity, potential for dose-related and serious side effects, drug interactions, and others.[4]

Homocysteine, a sulfhydryl-containing amino acid, is an intermediate product in the normal Biosynthesis of the amino acids methionine and cysteine.[5]

In children with epilepsy with long-term use of antiepileptic therapy, it is likely that vascular damage can be caused by metabolic, inflammatory, hormonal, and other effects on the vascular system.[6]

Over the past two decades, high tHcy levels, an independent risk factor for atherosclerosis, ADMA, lipoprotein (a), and impaired lipid profiles, have been documented in several studies with children on AEDs.[7]

Many studies have suggested that the plasma homocysteine (Hcy) level is increased as a side effect with prolonged use of some AEDs, which is associated with vascular endothelial injury; hence it increases the risk of atherosclerosis.[8]
Risk factors diagnosed in childhood can predict the development of preclinical carotid athero-sclerosis in adults. Thus; carotid artery intima-media thickness (CIMT) serves as a marker of preclinical atherosclerosis.[9]

Patients and Methods: In this work we tried to evaluate the effect of antiepileptics drugs and its types in pediatric on serum level of Homo-cysteine and its association with increase of CIMT and carotid stiffness .It was conducted upon 60 epileptic children who had regular follow up in The Pediatric neurology Outpatient Clinic, Minia University Children and Maternity Hospital, during the period from jaunary 2018 to march 2019; in addition to 25 apparently healthy children matching age & sex with diseased group were included as a control group, Their age ranged from 2-15 years and on regular antiepileptic drugs for at least 1 year, divided to 4 group according to type of treat-ment (old monotherapy, new monotherapy, polytherapy and control).

Both patients and control groups were subjected to full history taking, thorough clinical examination, laboratory investigations (including homocysteine) and radiological assessment to CIMT and carotid stiffness.

Inclusion criteria:
1. Age ranged from 2 -15 years.
2. Idiopathic epileptic children.
3. on regular antiepileptic drugs for at least 1year.

Exclusion criteria:
1- Secondary epilepsy.
2- Use antiepileptic drugs for short duration less than 1 year.
3- Any vascular disease may affect elasticity or thickness of vessels example: hypertension.
4- Any metabolic disease may affect lipid profile.
5- Obesity

Results:

Table (I): Demographic data of the study groups (n=85)

	Group A N= 20	Group B N=20	Group C N=20	Group D N=25	P value
Age (year)					
Mean±SD	7.3±2.7	6.5±3.7	5.1±2.9	7.1±3.4	**0.06**
Median	7	4.7	4.5	6	
Interquartile range	6-9	3.5-10	2.6-6	4.5-10	
Duration of treatment(year)					
Mean±SD	3±1.8	2.4±2	3.5±2.4		0.08
Median	2.5	2	3	———	
Interquartile range	2-3.8	1-3	2-4		
Sex					
Male	10 (50%)	9(45%)	12 (60%)	13 (52%)	0.8
Female	10 (50%)	11 (55%)	8 (40%)	12 (48%)	

P value calculated by Kruskal-Wallis test for quantitative data and by Chi-square test for qualitative data (<0.05 is considered significant).
Group A: children received monotherapy of old generation antiepileptic drugs.
Group B: children received monotherapy of new generation antiepileptic drugs.
Group C: children received Polytherapy antiepileptic drugs.
Group D: Control group. SD: standard deviation.
GASE: Global Assessment of Severity of Epilepsy Scale BMI: Body Mass Index
CIMT: Carotid intima media thickness

Table (II): Comparison between the study groups in laboratory and radiological investigations.

	Group A N= 20	Group B N=20	Group C N=20	Group D N=25	P value
Homocysteine(µmol/L)					
Mean±SD	17.2±5.2	3.4±3.4	20.2±14.1	2.8±2.3	0.0001*
Median	16	2.3	17	1.7	
Interquartile range	15-18.7	0.8-5.8	11.5-20.7	1.2-4	
CIMT (mm)					
Mean±SD	0.46±0.03	0.36±0.08	0.43±0.1	0.38±0.08	0.0001*
Median	0.46	0.38	0.45	0.4	
Interquartile range	0.43-0.49	0.28-0.4	0.35-0.49	0.31-0.43	
Carotid stiffness (cm/sec)					
Mean±SD					
Median	4.5±0.8	3.5±0.8	4±1.1	4.2±0.8	0.03*
Interquartile range	4.8	3.2	3.5	4.5	
	4.1-5	2.9-4	2.9-5.5	3.1-4.9	

P value calculated by Kruskal-Wallis test for all quantitative data except for CIMT calculated by one way anova test (<0.05 is considered significant).

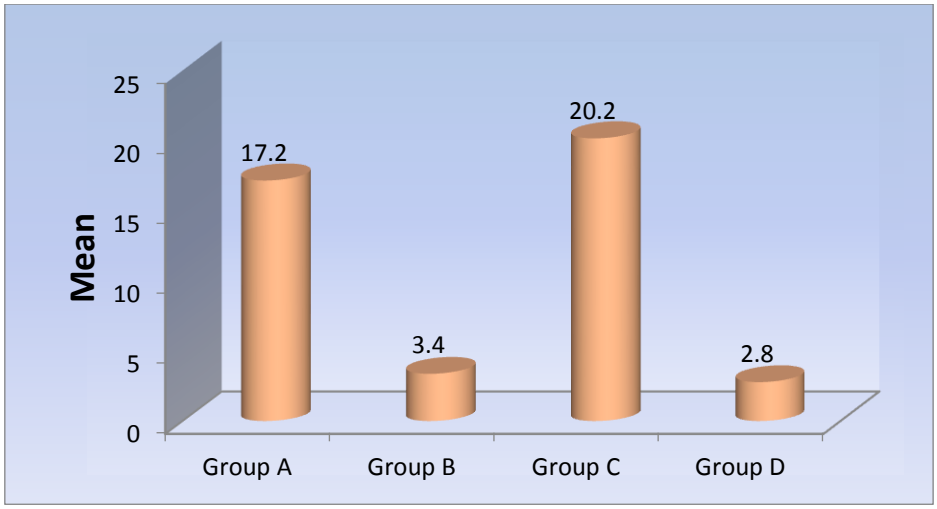

Figure (1) Homocysteine of the study groups

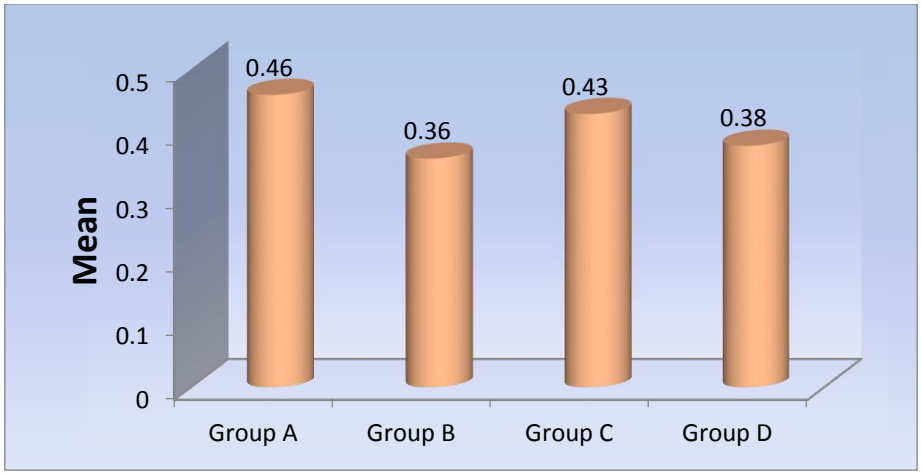

Figure (2) CIMT of the study groups

Table (III): Comparison between the study groups with each other as regard the investigations which have done.

	Group A N= 20	Group B N=20	Group C N=20	Group D N=25	P value
Homocysteine (µmol/L)					1 0.0001* 2 0.9
Mean±SD	17.2±5.2	3.4±3.4	20.2±14.1	2.8±2.3	3 0.0001*
Median	16	2.3	17	1.7	4 0.8
Interquartile range	15-18.7	0.8-5.8	11.5-20.7	1.2-4	5 0.0001* 6 0.0001*
CIMT(mm)					1 0.0001* 2 0.3
Mean±SD	0.46±0.03	0.36±0.08	0.43±0.1	0.38±0.08	3 0.0001*
Median	0.46	0.38	0.45	0.4	4 0.4
Interquartile range	0.43-0.49	0.28-0.4	0.35-0.49	0.31-0.43	5 0.04* 6 0.01*
Carotid stiffness(cm/sec)					1 0.003* 2 0.2
Mean±SD	4.5±0.8	3.5±0.8	4±1.1	4.2±0.8	3 0.1
Median	4.8	3.2	3.5	4.5	4 0.02*
Interquartile range	4.1-5	2.9-4	2.9-5.5	3.1-4.9	5 0.6 6 0.4

P value calculated by Mann-Whitney test for all quantitative data except for CIMT calculated by independent sample t-test (<0.05 is considered significant).
P value 1 (group A and B), p value 2 (group A and C), p value 3 (group A and D), p value 4 (group B and D), p value 5 (group C and D) and p value 6 (group B and C).

In table (I) there is group A (50% male, 50% female, group B 45% male, 55% female, group C 60% male and 40% female and group D 52% male, 48% female. there is no significance difference between groups in duration of treatment .

In table (II) there is significant difference in the level of homocysteine, CIMT and carotid stiffness between groups.

Discussion

This study was conducted on 60 children from age of 2 to 15 years old who diagnosed as idiopathic epilepsy receiving different types of modalities anti-epileptic drugs for at least one year without any apparent disease can affect level of serum homocysteine ,elasticity or thickness of vessels to evaluate the effect of the administration of the antiepileptic drugs for long time on homocysteine and vessels elasticity and thickness and If that will change according to the type of antiepileptic drugs.

In table (III) the mean serum level of homocysteine was significant high in group A and group C than that in group B and group D with no significant difference between group A and group C.

There is significance increasing in CIMT and carotid stiffness in group A and group C than that in group B and group D with no significant difference between group A and group C.

The results of our study revealed that 50% male, 50% female in children receiving mono therapy (old generation antiepileptic drugs), 45% male, 55% female in children receiving monotherapy (new generation antiepileptic drugs) and 60% male and 40%female receiving polytherapy. Table I

Our results revealed that mean duration of treatment in monotherapy of old AEDs was 2.5year, monotherapy of new AEDs users 2 years and polytherapy users 3 years which no significance difference between them. Table I

In our study the mean serum level of homocysteine was significant high in children on monotherapy of old generation AEDs and polytherapy than that in children on monotherapy of new generation AEDs and control with no significant difference between monotherapy of old generation and polytherapy. table III

Who consistent with our finding in the study was (Verrotti et al., 2000) who state that a significant increase in p-tHcy levels when compared to baseline data and control values in pediatric patients treated with either CBZ or VPA (both are old generation).[10] Also(Linnebank et al., 2011) who state that a deficiency of folate, an important cofactor in the metabolism of Hcy, induced by older antiepileptic drugs (AEDs), such as carbamazepine, phenytoin, phenobarbital and Primidone.[11] on the other hand (Belcastro et al., 2010) state that Topiramate TPM and oxcarba-zepine OXC among of the recent AEDs can cause hyper-tHcy, hereas lamotrigine (LTG) and levetiracetam (LEV) are devoid of this effect.[12] (Huemer et al., 2005)found that High plasma -tHcy levels in pediatric patients receiving AEDs were predo-minantly associated with multidrug treatment.[13]

On the contrary (Emeksiz et al., 2013), (Belcastro et al., 2010) who state that There was no significant difference in tHcy levels among the VPA (old generation), OXC (new generation), and control groups and that new generation antiepileptic may cause increasing in serum homocysteine level.[7][12]

Also against our finding was (Sener et al., 2006) who state that plasma tHcy levels were not significantly different between patients on AED polytherapy versus monotherapy.[14]

In our study we found that there is significance increasing in CIMT and carotid stiffness in children received monotherapy of old generation AEDs and polytherapy than children received monotherapy of new generation AEDs and control with no significant difference between monotherapy of old generation and polytherapy. Table III

This is in agreement with (Luo et al., 2015)who states that The average CIMT of the epileptic patients treated with VPA (old generation) was higher than that of healthy people also The average CIMT of the patients with VPA administration duration >1 year was higher than that of the patients with VPA-administration duration < year while the difference was not statistically significant (P = 0.196).[15]

Also (Chuang et al., 2012) State that Long-term monotherapy with older-generation AEDs, including CBZ, PHT, and VPA, caused significantly increased CCA IMT in patients with epilepsy with no significant alterations in the CCA IMT were observed in patients who received long-term LTG monotherapy (new generation) and Oxcarbazepine treatment also did not cause any alteration in carotid intima media thickness when compared with the healthy group according to (Yiş and Doğan, 2012).[6][16] Also (Calik et al., 2018) demonstrate that there is significant increase found in CIMT in patients using long-term multiple drug therapy could be an indication that these patients are at risk of the development of vascular damage and other cardiovascular complications.[17]

On the contrary was (Lai et al., 2017) who state that there is no significant difference in CIMT was observed in children using antiepileptic drugs (MD=0.03 mm, 95% CI=0.00–0.07 mm).[18] (Keenan et al., 2014) also state that there is no differences were apparent in mean CIMT (p = 0.152), between controls, children using AEDs.[19]

Conclusion

Antiepileptics represent one of the largest and most diverse therapeutic medication classes that may cause serious metabolic and cardiovascular effect with long term use in children so we recommend:

- Routine follow up to serum level of homocysteine in children receiving AEDs for long term especial the old generation and polytherapy.

- Routine follow up to CIMT and carotid stiffness in children receiving AEDs for long term especial the old generation and polytherapy.

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