Epilepsy Journal
ISSN: 2472-0895

Shaheen et al., Epilepsy J 2016, 2:3
DOI: 10.4172/2472-0895.1000112

Research Article Open Access

Early Atherosclerotic Changes in the Patients with Idiopathic Epilepsy: Egyptian Preliminary Study

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Received date: July 15, 2016; **Accepted date:** Aug 16, 2016; **Published date:** Aug 20, 2016

Abstract

Background: Patients with epilepsy are at higher risk for atherosclerosis which may be due to epilepsy or antiepileptic drugs. The frequency of atherosclerosis in patients with epilepsy was not previously studied in Egypt.

Objective of this study: This study aimed to detect the frequency of subclinical atherosclerosis and some vascular risk factors in patients with idiopathic epilepsy and to correlate it to clinical and laboratory data.

Patients and methods: Ninety patients with idiopathic epilepsy and 30 ages, sex matched healthy controls subjected to neurological examination, extra cranial carotid duplex, lipid profile, uric acid and CRP levels.

Results: The level of high density lipoprotein cholesterol was significantly lower in all patients with epilepsy and those treated with enzyme inducer antiepileptic drugs than the control subjects. Level of serum uric acid was statistically significantly higher in all patients with epilepsy including the untreated patients and those treated with non-enzyme inducer and poly antiepileptic drugs than control subjects. The Common Carotid Artery Intima Media Thickness (CCA IMT) was significantly higher in all patients with epilepsy including untreated and treated patients with enzyme inducer or non-inducer than control. There was a significant positive correlation between the CCA IMT and duration of illness as well as duration of the antiepileptic drugs.

Conclusion: Frequency of subclinical atherosclerosis in the patients with idiopathic epilepsy was 63.33%. The epilepsy itself could result in subclinical atherosclerotic changes in the patients with epilepsy, which could be exacerbated by the antiepileptic drugs, particularly the enzyme inducer drugs.

Keywords: Epilepsy; Antiepileptic drugs; Atherosclerotic risk factors; Carotid artery; Intima media thickness

Introduction

Epilepsy is considered one of the most common neurologic disorders worldwide [1], with prevalence ranging from 0.2–4.1% [2].

Some studies have found that the risk for heart disease and stroke are increased in patients with epilepsy [3,4].

The etiology of atherosclerosis-related vascular diseases in epileptic patients has not been fully clarified; it is possible that epilepsy itself might increase vascular risk, which might then be further exacerbated by enzymatically active Antiepileptic Drugs (AEDs) [5].

Noninvasive measurement of the Intima Media Thickness (IMT) by high resolution B-mode ultrasound is widely used in the previous studies and validated as a surrogate marker for early prediction of atherosclerosis [6,7].

This study aimed to detect the presence of subclinical atherosclerotic changes and some vascular risk factors in the patients with idiopathic epilepsy, and to find out if the atherosclerotic changes are due to the epilepsy itself as a disease or side effects of prolonged use of AEDs, and to correlate atherosclerosis in patients with epilepsy to clinical and laboratory data.

Patients and Methods

Patients

This study was a cross-sectional case-control study conducted on ninety Egyptian patients diagnosed as primary idiopathic epilepsy. The ethical committee of faculty of medicine, Fayoum University has approved the study. Written informed consent was obtained from all patients and control. The included patients were recruited in the period from May 2013 to July 2014 from Neurology outpatients' clinic, Fayoum University Hospital, Egypt. The age of the included patients ranged from 16 to 46 years. Thirty age and sex matched healthy volunteers were selected as controls; they had no neurological disorders or any vascular risk factor.

The patients had risk factors for atherosclerosis such as smoking, diabetes mellitus, hypertension, hyperuricemia or concomitant manifested atherosclerotic vascular disease such as myocardial infarction, cerebrovascular stroke or transient ischemic attacks, patients with family history of vascular disease or risk for vascular disease, or patients receiving contraceptive pills were excluded from the study.

Methods

All the patients underwent full medical and neurological examination including history taking that was obtained by interviewing the patients and their near relatives, with special emphasis on: Diagnosis of idiopathic epilepsy according to the recommendations of the International League Against Epilepsy [8] age of onset of seizures, duration of the illness, semiology of seizures, frequency of seizures (number of seizures per month), history of status epilepticus, family history of epilepsy, dosage and duration of the antiepileptic drugs received. Body Mass Index (BMI) was calculated for the patients and the controls. All patients underwent brain Magnetic Resonance Imaging (MRI) to rule out symptomatic epilepsy.

Assessment of the Common Carotid Artery Intima Media Thickness (CCA IMT) including both right and left common carotid arteries of all patients and controls was performed by using a high-resolution 7.5 MHz linear transducer in B mode using (Logiq 7 ultrasound machine; GE Healthcare, Bethesda, USA) in the radiology department, Fayoum University Hospital. Measurements were carried out according to standardized protocol by an experienced ultrasound radiologist who was blinded to the clinical history of the participants. The CCA IMT measurement >0.68 mm was considered the cut-off value for atherosclerosis [9].

Routine biochemical tests as CBC, Erythrocyte Sedimentation Rate (ESR), liver functions, kidney functions, and blood sugar were done to exclude patients with systemic or metabolic disorders. Total cholesterol, Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C) and triglycerides levels were withdrawn from the patients and controls after fasting (at least 10 h) and sera were separated. Autoanalyser by colometric method applied for triglycerides and cholesterol measurements (NZOKIT Ranbaxy). AutoZyme High-Density Lipoprotein (HDL) cholesterol regent used for HDL determination while LDL calculated by Freidwald formula: LDL = TC - (HDL × 0.2 Triglycerides) [10]. Serum uric acid level was measured by the enzymatic colorimetric method using an automatic analyzer and Serum C Reactive Protein (CRP) level was measured using Enzyme Linked Immunosorbant Assay (ELISA).

Statistical Analysis

Statistical Package for Social Science (SPSS) version 16 was used for data management and analysis. The Mann-Whitney test was used for comparison of qualitative variables, while Spearman's test was used for correlations. Correlation analysis was used to evaluate the relationship between mean CCA IMT and variables in patients with epilepsy, including age, duration of AED therapy, seizure frequency, cholesterol-profile, triglyceride and uric acid concentration. The level $p \leq 0.05$ was considered the cut-off value for significance.

Results

The demographic data of the patients and controls were illustrated in Table 1. There was no significant difference in age, sex or BMI between them.

Clinical characteristics of the patients: Age of disease onset was 14.02 ± 4.3 years. Duration of illness was 7.08 ± 5.6 years. The timing of last seizure 42.9 ± 81.04 days. Frequency of seizures/month was 4.2 ± 2.4. Twenty nine patients were newly diagnosed has not received medications yet. The antiepileptic drugs used are illustrated in Figure 1.

Clinical data	All patients (n=90)	Controls (n=30)	P value
Age (years)	21.1 ± 7.3	22.2 ± 8.3	0.5
Sex (male: female)	46: 44	16: 14	0.9
Body mass index (kg/m^2)	23.9 ± 3	22.8 ± 3.4	0.08

Table 1: Demographic data of the patients with epilepsy and controls.

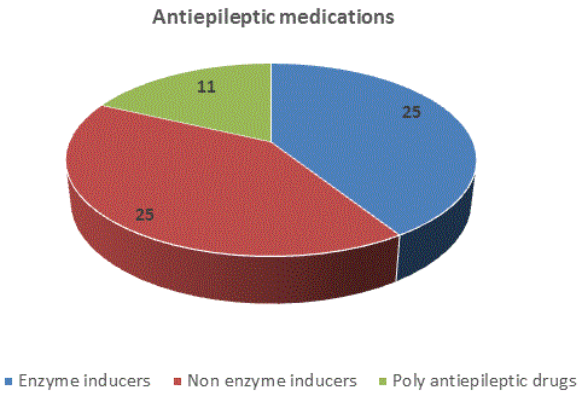

Figure 1: The distribution of the antiepileptic drugs among the epileptic patients.

Seventy five patients (63.33%) had subclinical atherosclerotic changes. Their mean CCA IMT was >0.68 mm as shown in Figure 2.

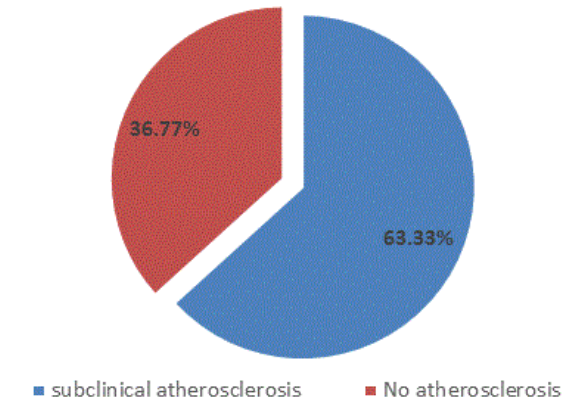

Figure 2: Atherosclerotic changes in the patients with idiopathic epilepsy.

Comparisons of the vascular risk factors and the mean CCA IMT between the patients groups and controls were illustrated in Tables 2-6. It showed that the level of HDL-cholesterol was significantly lower in the all epileptic patients, the all treated patients, the patients treated with enzyme inducer Antiepileptic Drugs (AEDs) and those treated with poly antiepileptic drugs than controls.

Vascular risk factors and mean IMT	All Patients (n=90)	Controls (n=30)	p value
HDL (mg/dL)	39.7 ± 11	46.9 ± 13.3	0.004
LDL (mg/dL)	96.3 ± 24.4	93.7 ± 23.8	0.6
Cholesterol (mg/dL)	160.4 ± 27	152.2 ± 25.1	0.1
Triglycerides (mg/dL)	122.7 ± 24.9	120.1 ± 20.6	0.6
Uric acid (mg/dL)	5 ± 0.8	4.5 ± 0.7	0.01
Mean IMT (mm)	0.621 ± 0.09	0.495 ± 0.08	0.001

Table 2: Comparisons of vascular risk factors and mean IMT between the all epileptic patients and controls. HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; IMT: Intima Media Thickness.

Vascular risk factors and mean IMT	Untreated patients (n=29)	Controls (n=30)	p value
HDL (mg/dL)	41.4 ± 14.7	47 ± 13.3	0.1
LDL (mg/dL)	98.8 ± 21.3	93.7 ± 23.8	0.4
Cholesterol (mg/dL)	61.7 ± 25	152.2 ± 25.1	0.2
Triglyceride (mg/dL)	122.8 ± 21.7	120.1 ± 20.6	0.6
Uric acid (mg/dL)	5.1 ± 0.63	4.5 ± 0.69	0.002
Mean IMT (mm)	0.601 ± 0.08	0.495 ± 0.08	>0.001

Table 3: Comparisons of the vascular risk factors and mean IMT between the untreated epileptic patients and controls. HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; IMT: Intima Media Thickness.

Vascular risk factors and mean IMT	Enzyme inducer treated patients (n=25)	Controls (n=30)	p value
DL (mg/dL)	39.7 ± 8.8	47 ± 13.3	0.02
LDL (mg/dL)	99.5 ± 18.5	93.7 ± 23.8	0.3
Cholesterol (mg/dL)	158 ± 23.4	152.2 ± 25.1	0.4
Triglyceride (mg/dL)	118.6 ± 17	120.1 ± 20.6	0.8
Uric acid (mg/dL)	4.6 ± 0.86	4.5 ± 0.69	0.8
Mean IMT (mm)	0.655 ± 0.1	0.495 ± 0.08	0.001

Table 4: Comparisons of the vascular risk factors and mean IMT between the enzyme inducer treated epileptic patients and controls. HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; IMT: Intima Media Thickness.

Moreover, the level of uric acid was significantly higher in the all epileptic patients, the untreated patients and the patients treated with non-enzyme inducer AEDs than controls.

The patients treated with poly antiepileptic drugs showed a significant higher, triglycerides, total cholesterol and uric acid levels and lower HDL level than controls.

The mean CCA intima media thickness was significantly higher in all patients groups than controls ($p<0.001$). There was no significant difference in ESR or CRP levels between patients groups and controls ($p>0.05$).

A statistically significant positive correlations were found between CCA IMT, duration of illness ($r=0.33$, $p=0.001$) as shown in Figure 3 and duration of antiepileptic drugs ($r= 0.26$, $p=0.04$) in the all epileptic patients.

Vascular risk factors and mean IMT	Non-enzyme inducer treated patients (n=25)	Controls (n=30)	p value
HDL (mg/dL)	39.2 ± 9.1	47 ± 13.3	0.2
LDL (mg/dL)	87.9 ± 26.6	93.7 ± 23.8	0.4
Cholesterol (mg/dL)	155.7 ± 30.9	152.2 ± 25.1	0.6
Triglyceride (mg/dL)	120.2 ± 30.5	120.1 ± 20.6	0.9
Uric acid (mg/dL)	5.1 ± 0.7	4.5 ± 0.69	0.004
Mean IMT (mm)	0.614 ± 0.1	0.495 ± 0.08	0.001

Table 5: Comparisons of the vascular risk factors and mean IMT between the non-enzyme inducer treated epileptic patients and controls. HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; IMT: Intima Media Thickness.

Vascular risk factors and mean IMT	Polytherapy treated patients (n=11)	Controls (n=30)	p value
HDL (mg/dL)	36.6 ± 7.1	46.9 ± 13.2	0.01
LDL (mg/dL)	101.5 ± 35.9	93.7 ± 23.8	0.4
Cholesterol (mg/dL)	173 ± 30	152.2 ± 25.1	0.03
Triglyceride (mg/dL)	137.9 ± 31.2	120.1 ± 20.6	0.04
Uric acid (mg/dL)	5.1 ± 1.2	4.5 ± 0.69	0.04
Mean IMT (mm)	0.61 ± 0.1	0.495 ± 0.08	0.001

Table 6: Comparisons of the vascular risk factors and mean IMT between the polytherapy treated epileptic patients and controls. HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; IMT: Intima Media Thickness.

Discussion

In the last decade, some data are available about the vascular markers that are critically implicated in the structural and functional changes of the vessel wall predisposing to atherosclerosis in patients with epilepsy. In this study atherosclerosis was found in 63.7% of the patients. Up to our knowledge no previous Egyptian study mentioned the prevalence of atherosclerosis in patients with epilepsy to compare our results to it. In the epilepsy cohort patients exhibited a 3-fold increased stroke risk, compared with their control [11].

Epilepsy and prolonged antiepileptic drug treatment, particularly enzyme inducer AEDs have been found to induce hypercholesterolemia/dyslipidemia [12,13] and hyperuricemia [14].

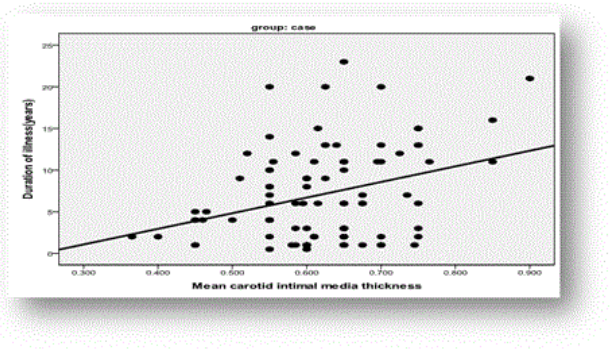

Figure 3: Correlation between CCA IMT and duration of illness among patients with epilepsy.

It was found in this study that the level of HDL was significantly lower in the patients with epilepsy compared to the control group. There were different studies having the same results [14-16]. Hamed et al. [17] attributed the low levels of HDL-c to the altered metabolism of the major HDL-apolipoprotein A-I, and/or the effect of endogenous total cholesterol and LDL metabolism on HDL-c level in the epileptic patients.

Moreover, the present study showed that the levels of total cholesterol and triglycerides were significantly higher in the patients treated with poly antiepileptic drugs and lower HDL cholesterol level especially in those treated with enzyme inducer AEDs compared to the control group. Hamed [18] reported that *lipid abnormalities* have been commonly found in the patients with epilepsy on enzyme inducer AEDs. The effect of AEDs on the serum level of lipids and lipoproteins could be explained on the basis of different biotransformation pathways of AEDs. It was found that Cytochrome P450 enzyme induction might reduce the feedback inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the rate-limiting step of cholesterol synthesis, and subsequently resulted in increasing the level of cholesterol [19].

On the contrary, Talaat et al. [20] found that the HDL level was significantly elevated in the patients with epilepsy especially those were treated with enzyme inducer AEDs. Talaat et al. assumed that the alterations occurring in HDL composition and metabolism resulting from inflammation can make HDL actually having a pro-inflammatory and pro-oxidant role through promoting LDL oxidation.

In this study, the mean common carotid artery intima media thickness was significantly higher in the epileptic patients compared to the control group which could be attributed to the effect of epilepsy itself, decreased HDL levels and increased uric acid level. This result was in agreement with other studies [14,17,20,21]. The antiepileptic drugs are thought to cause increase in the CCA IMT through alterations in lipid profile and lipoproteins [22,23]. It has been reported that chronic treatment with AEDs was found to compete with cholesterol in the utilization of hepatic microsomal enzymes P-450 system which leads to reduction in the transformation of cholesterol in bile acids with increased serum cholesterol [24]. Hypercholesterolemia is known to result in increased endothelial permeability, retention of lipoproteins within the arterial intima, inflammatory cell recruitment and foam cell formation filled with oxidized-LDL, increase lipid peroxidation, induce vasoconstriction and enhance muscle wall proliferation and thrombotic properties [25].

The uric acid was thought to be implicated in the pathogenesis of epilepsy. Oxidative stress and mitochondrial dysfunction are increasingly being recognized as having important roles in the pathophysiology of epilepsy, so uric acid could be increased in the epileptic patients to counteract this oxidative stress [26,27].

It was found in this study that the level of uric acid was significantly higher in the epileptic patients who have not received AEDs yet in comparison to controls which could be related to the role of uric acid in epilepsy itself, in which it could be a compensatory mechanism trying to counteract oxidative stress encountered in epilepsy [28].

Moreover, the level of uric acid was significantly higher in the all epileptic patients as well as the patients treated with poly antiepileptic drugs especially the non-enzyme inducer AEDs compared to the control group. These results were in agreement with these studies [14,17]. It was reported that hyperuricemia in the treated patients with epilepsy could be a compensatory mechanism trying to counteract oxidative stress encountered in epilepsy itself. Also it may be related to alteration of the renal excretion of the uric acid by the AEDs [29].

It was postulated that uric acid act as an antioxidant in the early stages of the atherosclerotic process. During progression of the atherosclerotic process, uric acid can undergo paradoxical antioxidant–prooxidant switch or the urate redox shuttle due to consumption of the naturally occurring local antioxidants by oxidative stress. In the presence of atherosclerotic progression, uric acid interacts with other substrate toxicities and increases reactive oxygen species, depletes local antioxidants, increases oxidation of LDLs, induces endothelial cell damage, decreases endothelial nitric oxide bioavailability, and accelerates atherosclerosis [28,30]. So the antiepileptic drugs especially the non-enzyme inducer AEDs could result in increased carotid IMT through alteration of the uric acid metabolism in the epileptic patients.

This study could not find any statistically significant difference between CRP level in the patients groups and the control group. This result could be attributed to measurement of low-sensitivity CRP in the patients of this study, this could not be sufficiently sensitive to measure blood levels of CRP within the normal range (<10 mg/L); however, the development of high-sensitivity assays for CRP had permitted detection of even mild elevation of CRP, even within the normal range [31]. As Talaat et al. [20] reported that high sensitivity CRP showed significant elevation the patients with patients than controls and was positively correlated with CCA-IMT.

There was a significant positive correlation between the common carotid artery intima media thickness and duration of illness which could be attributed to the role of epilepsy itself through the oxidative stress and the effect of epileptic seizures on the production of interleukin-6 (IL-6) promoting atherosclerosis [17,32].

In this study, there was a significant positive correlation between the CCA IMT and duration of the antiepileptic drugs. The chronic use of conventional antiepileptic drugs has been previously linked to higher incidence of strokes as well as other vascular pathologies among their users [33,34]. Thus, subclinical atherosclerotic changes could be exacerbated by the antiepileptic drugs, particularly enzyme inducer drugs in the patients with idiopathic epilepsy. It was demonstrated that the longer duration of AEDs therapy was significantly associated with the acceleration of atherosclerosis [21].

Nevertheless, the present study presented several limitations. First, the measurement of low-sensitivity CRP in the patients of this study, that was not be sufficiently sensitive to measure blood levels of CRP within the normal range (<10 mg/L); we could not use the high-sensitivity assays for CRP. Secondly we did not measure interleukin that promote atherosclerosis. Thirdly, the sample is hospital based not a community one, so these results could not be generalized.

Early identification of atherosclerosis in patients with epilepsy and its proper management could serve to reduce the hazards of cerebrovascular and cardiovascular complications in these patients.

Conclusion

Frequency of subclinical atherosclerosis in the patients with idiopathic epilepsy was 63.33%. The common carotid artery intima media thickness was positively correlated with duration of the illness and duration of the antiepileptic drugs. Thus, subclinical atherosclerotic changes are common in the patients with idiopathic epilepsy. It could be due to epilepsy itself and antiepileptic drugs, particularly enzyme inducer drugs.

Recommendations

Carotid duplex and inquire about vascular risk factors are recommended in patients with epilepsy for early detection and management of atherosclerosis in these patients.

Further studies in epileptic patients with and without treatment are still needed to rule out or to prove the role of the epilepsy itself in atherosclerosis.

Large community based sample are needed to find out the prevalence of atherosclerosis in patients with epilepsy.

Conflict of Interest

The authors have no conflicts of interest to declare in relation to this study. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgment

The contribution of the laboratory and radiology departments is gratefully acknowledged.

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