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Epilepsy and antiepileptic drugs: risk factors for atherosclerosis

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Introduction: Epilepsy is a chronic disease that affects metabolism either alone or through the antiepileptic drug (AED) treatment. A risk of atherosclerosis has been found in epileptic patients. *Aim* Prove the potential role of epilepsy and/or its treatment as atherosclerotic risk factors. *Subject and Methods:* Forty Egyptian patients with primary idiopathic epilepsy were compared to 20 healthy controls. B-mode ultrasound examination of the common carotid artery intima-media thickness (CCA IMT), measurement of serum lipid profile, fibrinogen and high sensitive C-reactive protein were performed to both groups. *Results:* Patients had significantly increased right and left CCA IMT ($p < 0.05$); elevated levels of HDL ($p < 0.01$) and hs-CRP ($p = 0.009$) in comparison to control subjects. Positive correlation was found between IMT and hs-CRP ($p < 0.05$) as well as fibrinogen level ($p < 0.05$). Carbamazepine level was positively correlated to triglycerides ($r = 0.748$, $p = 0.013$) and Valproate level was positively correlated to hs-CRP serum level ($r = 0.556$, $p = 0.032$). *Conclusion:* Epilepsy and AED's are potential risk factorsfor atherosclerosis. Weak relation between epilepsy and/or AED's and lipid profile was found. Hs-CRP may be implicated in atherosclerosis in epileptic patients.

KEYWORDS: epilepsy, atherosclerosis, serum lipids, hs-C reactive protein, fibrinogen

Introduction

Epilepsy is a chronic disease that, in the recent years, has been the center of attention trying to provide an effective chronic disease management (CDM) service [1,2]. With advance of age of epileptic patients special consideration should be taken toward medical conditions such as stroke, dementia, and metabolic disturbances [3].

Chronic use of conventional antiepileptic drugs (AEDs) (Phenytoin, Carbamazepine and Valproate) has been previously linked to higher incidence of strokes as well as other vascular pathologies among their users [4,5]. It was demonstrated that the longer duration of AED's therapy was significantly associated with the acceleration of atherosclerosis [6].

Older generation AED's (Valproate, Carbamazepine, Oxcarbazepine) were associated with a myriad of metabolic disorders that can lead to significant adverse health consequences [7]. Their chronic use was shown to be associated with a significant change of the lipid profile as well as C-reactive protein (a common marker of atherosclerosis). These changes were ameliorated by switching to new generation AED's [8–10].

Intima-media thickness (IMT), used as early markers for atherosclerosis, was studied in different age groups of epileptic patients on AED's. While studies of IMT in epileptic children treated with old generation AED's showed conflicting results [11–13], adults showed significant increase in IMT compared to controls [10,12]. Considering the lower prevalence of carotid atherosclerotic diseases [14] and higher prevalence of intracranial stenosis [15] among Egyptians, it was interesting to investigate for carotid changes among patients with epilepsy on chronic AED's treatment.

Our primary aim is to assess atherosclerotic biomarkers in patients on chronic old generation AED's treatment. Secondary aim is to assess common carotid artery intima-media thickness (CCA IMT) as an early indicator of atherosclerosis in these patients.

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Subject and Methods

This is a case control study which includes 40 patients with primary idiopathic generalized epilepsy (IGE) and 20 healthy age and sex matched control subjects. Patients were recruited from the outpatient epilepsy clinic of Faculty of Medicine, Cairo University. Healthy volunteers accompanying patients within neurology department were recruited as control. Verbal consent for unusual investigation (ultrasound imaging) was obtained from the patient or a family member if the patient was a minor. Laboratory investigations were done in the context of periodical checkup of patients at epilepsy clinic and verbal consent was obtained to use data and to further analyze blood sample.

The mean age of patients was 27.2 ± 7.51 years and control 29.95 ± 6.01 years ($p = 0.993$). Patients should have been on at least two years treatment with AEDs. We excluded patients and control subjects with known vascular risk factors (e.g. cardiac diseases, hypertension, diabetes and smokers).

Careful history taking included frequency of seizures upon which patients were divided into four groups: patients who experienced rare seizures (at interval more than 1 years), occasional seizures (at interval longer than 30 d but shorter than 1 year), frequent seizures (at interval longer than 7 d but shorter than 1 month), very frequent (intervals less than 7 d). Careful history included also number of AEDs taken, their types and compliance of the patient.

Both patients and controls underwent different serum laboratory tests including routine ones; total cholesterol level, triglycerides, low density lipoproteins, high density lipoproteins and uric acid.

Further inflammatory profile assessment included high sensitive C-reactive protein. Based on a study of an apparent normal population and established references a normal range for AcuuBind (hs) CRP ELISA microplate test system was established as follow; low risk <1 mg/L, moderate 1–3 mg/L, High risk >3 mg/L [16]4. Serum fibrinogen level were assessed after centrifugation (15 min at 2000–2500 g) and plasma stored 8 h at 20 ± 5°C. Normal range was estimated at 1.5–4.5 g/L [17].

CCA IMT was used as an early indicator of atherosclerosis. It was taken at three points at common carotid artery on both sides and an average value was obtained. It was measured in a B-mode image using Philips HDI 5000 machine using a high frequency (7 to 10 MHz) linear array transducer.

Statistical analysis

Descriptive data were expressed using mean and standard deviation (SD) for quantitative data, and the frequency distribution for qualitative data. Nonparametric tests were used to analyze nonparametric data. Qualitative variables were expressed as percentages and are compared using kruskal-wallis test. The comparison of mean values among the three groups is analyzed with one-way analysis of variance (ANOVA). Paired *t*-test is used to measure the difference between data in patient and control groups. The Pearson correlation test is used to estimates the correlation between given random variables. Two tailed probability test of p value < 0.05 was considered statistically significant.

Table 1. Comparison of different laboratory tests among patients and controls.

	Patients		Controls		
Serum level of (mg/dL)	Mean	SD	Mean	SD	p value
Total cholesterol	143.85	60.24	161.45	25.03	0.217
Triglycerides	99.65	51.05	111.90	60.77	0.415
LDL	116.22	41.36	100.15	27.69	0.122
HDL	68.82	18.50	50.90	12.6	<0.01*
Uric acid	4.68	1.55	4.49	1.14	0.626
Fibrinogen	279	83.30	272	63.67	0.720
hs-CRP**	4.44	4.36	1.74	1.34	0.009*

*p value <0.05 **hs-CRP = high sensitive C reactive protein.

Results

Distribution according to seizure frequency was as follows; rare 7.5%, occasional 27.5%, frequent57.5%, very frequent 7.5%. Thirty patients (75%) were on monotherapy with the following distribution; 33.3% on carbamazepine (CBZ), 50% on valproate (VPA) and 16.7% on phenytoin (PHT). Ten patients (25%) were on polytherapy. Mean dose of AED's among patients were as follows: carbamazepine 761 ± 283.81 mg, valproate 939.13 ± 372.69 mg and phenytoin 385.71 ± 145.68 mg.

Comparison of laboratory tests showed a statistically significant increase in HDL and hs-CRP in patients compared to control group ($p < 0.001$, $p = 0.009$ respectively). Other tests showed no difference as shown in Table 1.

IMT of right & left carotid arteries were significantly increased in patients compared to controls ($p = 0.002$, $p = 0.005$ respectively) as shown in Table 2.

Table 2. Comparison of IMT among patients and controls.

	Patients		Controls		
Average CCA IMT	Mean	SD	Mean	SD	p value
RT IMT	0.612	0.17	0.475	0.121	0.002*
LT IMT	0.605	0.17	0.480	0.115	0.005*

*p value < 0.05.

Table 3. Comparison of results among different groups of seizure frequency in epileptic patients.

Parameters*	Rare	Occasional	Frequent	Very frequent	*p* value
Cholesterol(mg/dL)	111.33 ± 47.42	163.81 ± 61.27	134.26 ± 61.41	176.66 ± 42.44	0.322
Triglycerides(mg/dL)	81.66 ± 34.03	93.27 ± 46.61	107.43 ± 56.16	81.33 ± 46.91	0.760
LDL(mg/dL)	97.66 ± 73.07	124.00 ± 47.60	111.65 ± 35.41	141.33 ± 29.50	0.513
HDL(mg/dL)	89.00 ± 6.00	74.54 ± 13.20	64.43 ± 20.48	61.33 ± 7.57	0.088
Uric acid(mg/dL)	4.86 ± 1.47	5.14 ± 1.51	4.31 ± 1.24	5.66 ± 3.48	0.330
Fibrinogen(mg/dL)	306.00 ± 18.73	285.18 ± 52.46	267.30 ± 97.53	328.33 ± 100.20	0.615
hs-CRP (mg/dL)	4.53 ± 2.15	3.22 ± 3.11	4.81 ± 5.04	6.03 ± 4.95	0.717
RT CCA IMT(cm)	0.53 ± 0.32	0.55 ± 0.16	0.61 ± 0.12	0.86 ± 0.15	0.030**
LT CCA IMT(cm)	0.50 ± 0.17	0.53 ± 0.18	0.61 ± 0.14	0.86 ± 0.15	0.014**

*Values were expressed as mean ± SD **statistically significant $p < 0.05$.

Comparison of different epilepsy frequency groups (rare, occasional, frequent, very frequent) showed a statistically significant increase of right & left carotid IMT in patients with higher epilepsy frequency ($p = 0.03$, $p = 0.014$ respectively). Laboratory tests did not show any statistically significant difference among different seizure frequency groups (Table 3).

Comparison of laboratory results among patients on different AED's showed only statistically significant higher hs-CRP in patients on CBZ and PHT compared to VPA (Table 4).

Comparison of patients on monotherapy and polytherapy showed a statistically increased LDL level in monotherapy group ($p = 0.02$). Otherwise, other laboratory tests and IMT showed no significant difference.

No correlation was found between age, duration of disease, duration of treatment and laboratory tests or IMT on both sides (Table 5).

Lipid profile and uric acid was not correlated to IMT in our patients' group. Fibrinogen and hs-CRP showed a positive correlation with IMT (Table 6).

Carbamazepine dose was positively correlated to triglyceride serum level ($r = 0.748$, $p = 0.013$) and Valproate level was positively correlated to hs-CRP serum level ($r = 0.556$, $p = 0.032$).

Table 5. Correlation between age, duration of disease, duration of treatment and different parameters in epileptic patients.

	Age		Duration of disease		Duration of treatment	
	r	*p*	*r*	*p*	*r*	*p*
Cholesterol	0.096	0.554	0.104	0.523	0.136	0.409
Triglycerides	−0.032	0.844	−0.159	0.327	−0.113	0.493
LDL	0.207	0.199	0.074	0.649	0.193	0.239
HDL	0.100	0.541	0.082	0.616	0.089	0.589
Uric acid	0.169	0.296	−0.051	0.754	0.011	0.948
Fibrinogen	0.197	0.223	−0.044	0.788	0.014	0.932
CRP	0.418	0.363	0.050	0.760	0.162	0.325
RT CCA IMT	−0.037	0.825	0.056	0.737	0.004	0.979
LT CCA IMT	−0.1360	0.411	–0.033	0.844	–0.09	0.590

Table 6. Positive correlation between fibrinogen, hs-CRP and CCA IMT.

	RT CCA IMT		LT CCA IMT	
	r	*p*	*r*	*p*
Fibrinogen	0.386	0.015*	0.369	0.021*
hs-CRP**	0.034	0.032*	0.226	0.167

*p value < 0.05 **hs-CRP = high sensitive C reactive protein

Table 4. Comparison of results among epileptic patients using different antiepileptic drugs.

Parameters*	Carbamazepine	Valproate	Phenytoin	*p* value
CRP(mg/dl)	5.38 ± 2.90	2.32 ± 2.09	6.04 ± 4.70	0.015**
Fibrinogen(mg/dl)	305.30 ± 71.83	264.93 ± 73.31	311.00 ± 88.18	0.319
Cholesterol(mg/dl)	155.30 ± 58.71	128.13 ± 60.07	128.4 ± 87.0994	0.561
Triglycerides(mg/dl)	119.20 ± 74.21	98.73 ± 45.46	105.6 ± 50.85	0.685
LDL(mg/dl)	136.90 ± 47.87	110.20 ± 35.32	144.80 ± 41.31	0.155
HDL(mg/dl)	73.80 ± 22.12	65.66 ± 19.24	78.80 ± 13.02	0.362
Uric acid(mg/dl)	5.32 ± 2.00	4.60 ± 0.92	4.68 ± 1.47	0.467
LTCCA IMT(cm)	0.58 ± 0.19	0.62 ± 0.14	0.54 ± 0.16	0.595
RTCCA IMT(cm)	0.60 ± 0.21	0.62 ± 0.12	0.54 ± 0.1673	0.598

*Values were expressed as mean ± SD

Discussion

The current study showed that chronic use of old generation AED s (Phenytoin, Carbamazepine and Valproate) and high frequency of seizures significantly increase IMT. Only hs-CRP seems to be a potential cause of elevated IMT in our patients.

Patients included were either on mono- or polytherapy of old generation AED's. Although Valproate is the drug of choice for IGE [18], choice of Phenytoin and Carbamazepine for treating IGE was made upon lack of sufficient resources to treat patients who are not candidate to Valproate (Obesity, childbearing period, intolerable side effects, etc.). Carbamazepine has been proved to be a good alternative to Valproate in such condition [19]. Our guide to treatment was control of seizures with minimal or accepted side effects.

Common carotid artery intima media thickness (CCA IMT) was increased in patients compared to the control group ($p = 0.002$ and 0.005 on right and left side respectively). CCA IMT was increased with increasing frequency of fits (p value 0.030, 0.014 of right and left CCA IMT respectively). This may confirm the findings of Tan et al. [6] who reported that patients with refractory epilepsy appeared to manifest thicker CCA IMT than patients who were seizure free even though the difference did not exhibit statistical significance ($p = 0.09$) [10]. Although no correlation between duration of treatment and IMT thickness was found, this finding can be related to the narrow range of age of our patients (27.2 ± 5.1 years). Mehrpour and colleagues, who found similar results, worked on almost the same range of age (27.7 ± 8.1) [20].

Our findings also showed a significant increase in hs-CRP in patients compared to controls ($p = 0.009$). Positive correlation found between hs-CRP and IMT in our patients' group can deduce that elevated IMT can be partly due to increased serum level of hs-CRP, yet this causative relation is to be further investigated. These findings agrees with relation previously described between hs-CRP levels and subclinical atherosclerosis [21] yet this relation was to be proved as a cause, a consequence or having a common origin [22].

Although we did not find any relation between fibrinogen level and epilepsy frequency or its drugs yet it was positively correlated with IMT in our patients' group. This can lead us to a third axis of causality of elevated IMT in our patients like for instance common pathology. This is supported by the fact that elevated fibrinogen was proved to be related to carotid IMT independent of confounding variables [23]

Examination of the lipid profile showed a significantly elevated HDL level in patients' group compared to control group ($p < 0.01$). Verrotti et al. [24] showed this later finding in patients on Carbamazepine [24]. Our finding may be explained by the fact that about third of our patients were on Carbamazepine. Other studies on the contrary failed to prove such results [6,25] likely due to different methodology either due to shorter duration of CBZ intake [25] or due to larger number of patients recruited ($n = 195$) compared to our sample ($n = 40$) [6].

Although HDL has been known to be protective on endothelium through different complex mechanisms [26] not all HDL are referred to as "good cholesterol" [27]. Alterations occurring in HDL composition and metabolism resulting from inflammation can make HDL not only ineffective as an anti-inflammatory and antioxidant but actually having a pro-inflammatory and pro-oxidant role through promoting LDL oxidation [28]. Yet role of HDL in atherosclerosis in epileptic patients still have to be proved.

Possible role of AEDs inducing atherosclerosis may be dose dependent. Triglyceride serum level was positively correlated to Carbamazepine level. A previous study proved this finding even in children showing that change in lipid profile could potentially facilitate the development of atherosclerosis in such children [29]. Similarly, valproate dose was positively correlated tohs-CRP serum level. We suggest that this was due to increased incidence of developing metabolic syndrome and insulin resistance with valproate intake. Obesity or increased body mass index occurring as a part of the metabolic syndrome is associated with low grade systemic inflammation with high concentrations of hs-CRP [30].

Conclusion

Chronic epilepsy and AED's treatment has been shown to be a potential risk factor for Carotid artery atherosclerosis. Lipid profile didn't seem to be the causative factor for atherosclerosis. Elevated hs-CRP was found to be associated with increased IMT, yet, this relation whether a causative, consequence or rooting from a common origin is not clear and needs further investigations.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. AQ2

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