

Assessment of carotid-intima media thickness in patients with epilepsy receiving antiepileptic drugs

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ABSTRACT

Aim: This study aims to investigate whether there is an increase in carotid-intima media thickness (C-IMT) in epilepsy patients using antiepileptic drugs when compared to the normal control group and whether there is a difference when we group them as monotherapy and polytherapy.

Material and Method: 68 people were included in the prospective cross-sectional study. 38 epilepsy and 30 healthy control groups that were matched in terms of demographic characteristics

Results: C-IMT was statistically higher in the epilepsy group ($p < 0.001$). When carotid USG results are analyzed as control, monotherapy, and polytherapy, there was no difference between control and monotherapy, there was statistical significance between the control group and polytherapy ($p < 0.001$), and between monotherapy and polytherapy ($p: 0.010$)

Conclusions: According to our study result, polytherapy should be avoided as much as possible, especially in patients with vascular risk factors.

Keywords: Carotid-intima media thickness, epilepsy, monotherapy-polytherapy

INTRODUCTION

Epilepsy affects 65 million people worldwide and is among the most common neurological diseases (1). Treatment is based on long-term anti-epileptic drugs (AEDs) and the use of these drugs is sometimes lifelong. Treatment aims to try to ensure seizure-freeness with drugs while minimizing the side effects of these drugs. Therefore, the physician should have a good knowledge of the side-effect profile of the drugs and know-how to manage the side-effects when they develop.

Long-term use of AEDs is associated with chronic adverse events such as metabolic and endocrine disorders, organ toxicity, cognitive dysfunction, and psychiatric problems (2-5). Studies have reported that patients with epilepsy have earlier deaths from stroke and ischemic heart disease compared to the general population (6,7). Although the reason for this relationship cannot be fully explained, it is thought that drugs may be responsible for this situation along with the disease itself. One of the reasons why mortality rates are higher than the general population may be susceptibility to atherosclerosis.

The impact of AEDs on the development of atherosclerosis has been discussed for a long time. The role of drugs in the pathogenesis of atherosclerosis has not been fully elucidated. Studies are showing that especially old generation antiepileptic drugs can cause dyslipidemia and hyperhomocysteinemia, which may lead to the development of atherosclerosis (8,9). In addition, inflammation marker CRP, which is closely related to atherosclerosis, and oxidative stress markers were detected in epilepsy patients using AED (10). There is also one opinion that atherosclerosis may be involved in the etiology of chronic cognitive dysfunction observed in epilepsy patients (11).

Carotid-intima media thickness (C-IMT) is an early marker of atherosclerosis and its increase is a predictor of future vascular events. Although they have controversial results, studies are showing that C-IMT increase in epilepsy patients (12,13). In this study, we aim to investigate whether there is an increase in C-IMT in epilepsy patients using antiepileptic drugs when compared to the normal control group and whether there is a difference when we group them as monotherapy and polytherapy.

MATERIAL AND METHOD

The study was approved by the Harran University Faculty of Medicine Ethics Committee (Date: 08.07.2019, Decision No: 07-13). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This cross-sectional study included 68 subjects, 38 epilepsy who were taking one or more antiepileptic drugs, and 30 healthy control. The study was conducted from June 2019 to September 2019 at the Neurology Department of Harran University Hospital. Exclusion criteria are including patients under 18 and over 50, body mass index above 35, hyperlipidemia, known heart disease, hypertension, diabetes mellitus, oral contraceptive usage, history of the previous stroke, multiple sclerosis, and inflammatory disease. Patients were also excluded from the study if the epilepsy was caused by metabolic or neurodegenerative diseases and taking any medication or vitamin preparations other than antiepileptic drugs. Patients were selected from those diagnosed as having epilepsy according to the International League Against Epilepsy (ILEA) 2017 criteria and who were using one or more antiepileptic drugs in treatment (14). The diagnosis of epilepsy made by an experienced neurologist (M.K.), was based on the clinical history, including the response to medication, seizure description, and electroencephalography, and magnetic resonance imaging result. The control group consisted of individuals of the same age, sex, and BMI without a history of epilepsy. The physical and neurological examinations of the control group were normal. Written informed consent was obtained from the patients before being included in the study. Body mass index (BMI) was calculated as weight (kg)/height (m²). Hypertension was defined as systolic blood pressure \geq 140 mmHg, diastolic blood pressure 90 mmHg, and/or taking antihypertensive medication, and/or a history of diagnosed hypertension. Diabetes mellitus was defined as fasting serum glucose \geq 126 mg/dL (7 mmol/L), non-fasting glucose \geq 200 mg/dL (11.1 mmol/L), use of diabetic medications, or a previously established diagnosis. Hyperlipidemia was defined as low-density lipoprotein > 160 mg/dL, and/or taking a lipid-lowering agent.

Bilateral carotid arteries USG examination was done by the same neurologist (Ö.K. with 7 years of US experience and were blinded to epilepsy diagnosis and clinical data). The examinations were performed using the LOGIQ V5 (GE Medical Systems, Wuxi, China) with the same linear-array transducers. In the supine position, bilateral common and internal carotid arteries were examined for the presence of atherosclerotic plaques, using grayscale and color Doppler modes. C-IMT was defined as the thickness of the hyperechoic layer between the vessel

lumen and hyperechoic adventitia. C-IMT was measured in the posterior walls of both left and right CCA at 1 cm below the carotid bifurcation outside the areas of plaque and the average of two values (right wall and left wall) was recorded as C-IMT mean.

Statistical Analyses

The parameters were analyzed using SPSS for Windows ver. 23.0. Continuous variables are expressed as the mean \pm standard deviation and categorical variables as numbers and percentages. The Mann-Whitney U test was used to assess the differences between continuous variables in two groups. The Kruskal-Wallis test was used to compare more than two independent groups. Correlation between continuous variables was evaluated with the Spearman correlation test. The chi-square test was used to analyze categorical parameters and $p < 0.05$ was considered statistically significant.

RESULTS

This study compared healthy control (n=30; mean age 27.57 \pm 6.10 years) and epilepsy (n=38; mean age 25.58 \pm 7.61 years) groups. There were no significant intergroup differences in age, percentage of sex, serum lipid level, or BMI (**Table 1**).

Table 1. Demographic and clinical findings of the epilepsy patient and control groups

	Epilepsy n :38	Control n: 30	p
C-IMT	0.46 (\pm 0.08)	0.37 (\pm 0.04)	0.000
Age (years)	25.58 (\pm 7.61)	27.57 (\pm 6.10)	0.248
Female, n (%)	24 (55.8)	19 (44.2)	0.595
BMI (kg/m ²)	23.29 (\pm 4.38)	24.15 (\pm 3.52)	0.381
Epilepsy type (ILEA-2017)			
Focal onset	24 (63.2)		
Generalized onset	10 (26.3)		
Unknown Onset	4 (10.4)		
Seizure etiology, n (%)			
Structural	12 (31.6)		
Genetic	10 (26.3)		
Unknown	16 (42.1)		
Disease duration (years)	7.84 (\pm 5.82)		
Number of AED			
Monotherapy	16 (42.1%)		
Polytherapy	22 (57.9%)		
Serum lipid level (mg)			
LDL cholesterol	107.73 (\pm 16.45)	99.62 (\pm 14.20)	0.201
HDL cholesterol	60.39 (\pm 15.11)	53.82 (\pm 14.60)	0.074
Triglyceride	100.59 (\pm 36.55)	109.08 (33.28)	0.521
C-IMT: Carotid intima media thickness, BMI: Body Mass Index AED: Anti Epileptic Drug, LDL:Low Density Lipoprotein HDL: High Density Lipoprotein			

The patients were diagnosed as having focal epilepsy in 24 (63.2%), generalized epilepsy in 10 (26.3%) cases, and unknown in 4 (10.4%). Of the patients in the study group, 16 (42.1%) were receiving monotherapy and 22 (57.9%)

were receiving polytherapy. Eighteen of the patients in the polytherapy group were taking double antiepileptic, and 4 were taking triple antiepileptic. Considering the etiology of seizures, 12 (31.6%) patients are structural, 10 (16.3%) patients are genetic, and the etiology of 16(42.1%) patients is unknown.

When the study population was analyzed as monotherapy (n=16; mean age 23.88 ± 7.32 years), polytherapy (n=22; mean age 26.82 ± 7.73 years), and control groups (n=30; mean age 27.57 ± 6.10 years), there was no difference between the groups in terms of age, gender, BMI and serum lipid levels (**Table 2**).

When carotid ultrasound findings were compared between epilepsy and control groups, C-IMT was statistically higher in the epilepsy group ($p < 0.001$) (**Table 1**). When carotid USG results are analyzed as control, monotherapy, and polytherapy, there was no difference between control and monotherapy, there was statistical significance between the control group and polytherapy ($p < 0.001$), and between monotherapy and polytherapy ($p: 0.010$) (**Table 2**). Distribution of antiepileptic drugs used by the patients were showed in **Table 3**. **Figure 1** showed that there was no relationship between the duration of epilepsy and the increase in C-IMT.

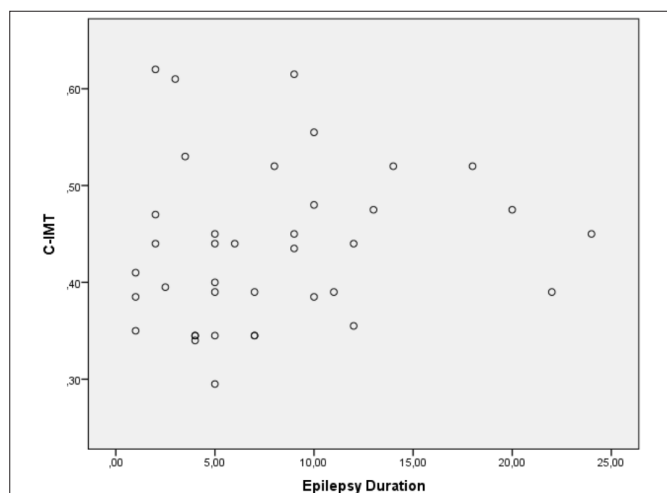


Figure 1. Correlation between epilepsy duration and C-IMT ($p: 0.217$). C-IMT: Carotid-intima-media thickness

	Monotherapy (n)	Polytherapy (n)	Total (n)
Levetirecetam	6	13	19
Lamotrigine	2	11	13
Valproic acid	5	9	14
Carbamazepine	3	10	13
Topiramate	-	2	2

DISCUSSION

C-IMT measurement is a noninvasive ultrasonographic method and is applied easily and inexpensively (12). Its increase is indicative of subclinical atherosclerosis and is associated with many vascular events, including cardiovascular and cerebrovascular accidents (15). Although there are studies evaluating whether there is an increase in C-IMT in epilepsy patients using antiepileptic drugs, according to our knowledge, there is no study evaluating the increase in C-IMT in adult patients according to polytherapy-monotherapy groups. In this study, we planned to investigate whether the use of polytherapy has an effect on the increase in C-IMT and we obtained statistically significant results. In our study, we examined whether there was a significant difference in C-IMT between 30 healthy controls and 38 epilepsy patients, who were matched in terms of age, sex, and BMI. As a result, it was seen that there was a statistically significant C-IMT increase in the patient group compared to the control group (**Table 1**).

When we divided epilepsy patients as monotherapy and polytherapy, the increase in CIMT in the polytherapy group was statistically significant compared to the monotherapy group. However, when monotherapy and healthy control groups were compared, the result did not reach statistical significance (**Table 2**). In our study, the disease duration did not affect CIMT (**Figure 1**)

The results of C-IMT studies in epilepsy patients are controversial due to the diversity of patient groups (age, therapy, comparison vb.). In one study, while an increase in CIMT was observed in epilepsy patients compared to the healthy control group, the same study did not find a significant difference between patients taking valproic acid

Table 2. C-IMT, Age, BMI, LDL, HDL, Triglyceride mean values \pm standard deviation of Control, Monotherapy and Polytherapy groups.

	Control (n:30)	Monotherapy (n:16)	Polytherapy (n:22)	P values	P1	P2	P3
C-IMT	0.37 (± 0.04)	0.40 (± 0.08)	0.46 (± 0.08)	<0.001	0.35	<0.001	0.01
Age (years)	27.57 (± 6.09)	23.88 (± 7.32)	26.82 (± 7.73)	0.227	-	-	-
Female, n (%)	19 (63.3%)	10 (62.5%)	14 (63.6%)	0.997	-	-	-
BMI (kg/m ²)	24.16 (± 3.52)	22.44 (± 4.28)	23.91 (± 4.44)	0.371	-	-	-
Serum lipid level (mg)							
LDL cholesterol	99.62 (± 14.20)	103.06 (± 30.51)	111.18 (± 30.64)	0.275	-	-	-
HDL cholesterol	53.82 (± 14.46)	58.44 (± 13.92)	58.44 (± 13.93)	0.162	-	-	-
Triglyceride	109.08 (33.28)	93.00 (± 33.23)	105.9 (± 35.83)	0.629	-	-	-
Disease duration (years)		5.71 (± 5.29)	9.39 (± 5.80)	0.054			

P: within groups, P1: significance between control-monotherapy, P2: significance between control-polytherapy, P3: significance between monotherapy and polytherapy.

and enzyme-inducing drugs (16). In a meta-analysis of 15 studies involving 1175 epileptic patients, the majority of epilepsy patients using AEDs had increased C-IMT (15).

Among AEDs, especially CBZ and VA were more significantly associated with the increase in C-IMT. While phenytoin had no significant effect on C-IMT, studies about LMT were inconclusive. The results of phenytoin were attributed to study group smallness and heterogeneity. In our study, there was no difference between the groups in terms of lipid profile, and the increase in C-IMT was independent of lipid level. In the literature, some studies are compatible with this study (10,17), as well as studies that correlate with lipid increase (18). The effect of treatment duration on CIMT is controversial. While studies are stating that the duration is independently effective on the increase in C-IMT (18,19), there are also studies stating that it does not have any effect (10,16,20). We could not evaluate the duration of treatment because we had polytherapy patients in the study group. We looked at the duration of epilepsy in our patients. In our study, the duration of epilepsy did not affect C-IMT.

When evaluating the increase in C-IMT in epilepsy patients, most of the studies included patients receiving monotherapy and analyses were made on specific drug groups. On the other hand, we divided the patients into monotherapy and polytherapy instead of a group using a certain drug. Similar to our study, Çalık et al. (18) made a distinction between monotherapy and polytherapy in pediatric patients and found the increase in C-IMT compatible in our study.

In addition, since epilepsy patients who did not use drugs were not included in the studies, it was interpreted that it could not be determined whether atherosclerosis was caused by the disease itself or the drugs used (16). When we separate and evaluate our patients as monotherapy and polytherapy, there is no difference between the monotherapy group and the control group in terms of C-IMT increase, but the fact that the polytherapy group is significant compared to the monotherapy group may highlight the effect of drugs rather than the disease. There is a need to work with larger patient groups for stronger comments on this issue. The limitations of our study are its cross-sectional nature and heterogeneous drug use in our patients.

CONCLUSION

According to our study results, it may be recommended to closely monitor atherosclerotic risk factors to prevent future vascular events, especially in epilepsy patients receiving polytherapy, however, more research is needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Harran University Faculty of Medicine Ethics Committee (Date: 08.07.2019, Decision No: 07-13)

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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