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RESEARCH

Effect of long term treatment with antiepileptic drugs on carotid intima-media thickness as an indicator of atherosclerosis

Antiepileptik ilaçlarla uzun süreli tedavinin aterosklerozun bir göstergesi olarak karotis intima-media kalınlığı üzerine etkisi

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Abstract

Purpose: The aim of current study was to investigate the possible relation between antiepileptic drugs (AEDs) and atheosclerotic risk factors and carotid intima media thickness (IMT) as a marker of atherosclerosis.
Materials and Methods: Ninety-two patients, who had used carbamazepine (CBZ) and valproic acid (VPA) for three or more years and who had used a second AED (polytherapy) for two years in addition to CBZ or VPA monotherapy, were included in the study. The control group was composed of 31subjects with similiar demographics. Fasting blood glucose, liver and renal function tests, lipid profile, homocysteine, serum high sensitivity C-Reactive Protein (Hs-CRP), uric acid (UA), lipoprotein (a) (Lp (a)), folate and vitamine B12 levels were examined in both groups.
Results: Homocysteine levels were higher in the VPA, CBZ and politherapy groups compared to the control group. UA levels were higher in the VPA monotherapy group when compared to the CBZ monotherapy and polytherapy group. In the CBZ monotherapy group, Hs-CRP levels were higher than in the VPA monotherapy, polytherapy and control groups. Total cholesterol levels were higher in the CBZ monotherapy group when compared to the VPA monotherapy and control groups.
Conclusion: The findings showed no correlation between IMT values and duration of disease, duration of drug usage and dose, which suggests that long-term AED usage does not increase the development of atherosclerosis.
Keywords: Epilepsy, antiepileptic drugs, atherosclerosis, carotid intima media thickness

Öz

Amaç: Bu çalışmada, antiepileptik ilaç (AED) ile aterosklerotik risk faktörleri ve aterosklerozun bir belirteci olarak karotis intima media kalınlığı (IMT) arasındaki olası ilişkiyi araştırmayı amaçladık.
Gereç ve Yöntem: Üç yıl veya daha uzun süredir karbamazwpin (CBZ) ve valproik asit (VPA) kullanan ve CBZ veya VPA monoterapisine ek olarak iki yıl boyunca ikinci bir AEİ (politerapi) kullanan 92 hasta çalışmaya dahil edildi. Kontrol grubu benzer demografik özelliklere sahip 31 denekten oluşmuştur. Her iki grupta da açlık kan şekeri, karaciğer ve böbrek fonksiyon testleri, lipid profili, homosistein, serum yüksek hassasiyetli C-Reaktif Protein (Hs-CRP), ürik asit (UA), lipoprotein (a) (Lp (a)), folat ve vitamin B12 düzeyleri incelendi.
Bulgular: Homosistein düzeyleri VPA, CBZ ve politerapi gruplarında kontrol grubuna göre daha yüksekti. ÜA düzeyleri VPA monoterapi grubunda CBZ monoterapi ve politerapi grubuna kıyasla daha yüksekti. CBZ monoterapi grubunda Hs-CRP düzeyleri VPA monoterapi, politerapi ve kontrol gruplarına göre daha yüksekti. Total kolesterol düzeyleri CBZ monoterapi grubunda VPA monoterapi ve kontrol gruplarına kıyasla daha yüksekti.
Sonuç: Bulgular IMT değerleri ile hastalık süresi, ilaç kullanım süresi ve dozu arasında bir korelasyon olmadığını göstermiştir; bu da uzun süreli AEİ kullanımının ateroskleroz gelişimini artırmadığını düşündürmektedir.

Anahtar kelimeler: Epilepsi, antiepileptik ilaçlar, ateroskleroz, karotis intima media kalınlığı

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INTRODUCTION

Epilepsy affects around 65 million people worldwide. Antiepileptic drugs (AEDs), alone or in combination, form the basis of treatment. The primary goal of epilepsy treatment is to eliminate seizures while minimising the side effects of AEDs. The first generation of AEDs includes phenobarbitone, phenytoin (PHT), valproate (VPA) and carbamazepine (CBZ), while the second generation includes levetiracetam, lamotrigine and oxcarbazepine[1,2].

The risk of developing atherosclerosis is no longer concentrated in Western countries and now plays a role in most deaths worldwide. Atherosclerosis currently affects a younger population, more women and people from different ethnic backgrounds than ever before. It mostly affects large and medium-sized vessels and is caused by endothelial dysfunction, vascular inflammation and the accumulation of lipid, calcium and cellular debris in the intima layer of the vessel wall[3,4].

Much data exist on some vascular determinants that may cause structural and functional alterations in the vessel wall, which tends to forming atherosclerosis in epilepsy patients[5]. This shows that long-term use of AEDs in epilepsy patients is associated with many risk factors that cause dysfunction and pathobiology of the vessel wall, which initiates atherogenesis with complex molecular mechanisms[6]. In the literature, switching patients from inducing AEDs to non-inducing AEDs leads to long-term improvement in serologic markers of vascular risk. Since inducing AEDs appears to be the culprit, patients receiving PHT and CBZ should be screened for vascular risk (through lipid and C Reactive Protein (CRP) studies and possibly stress tests or other measures). Many studies have demonstrated that long-term AED treatment may cause undesirable metabolic effects, such as an increase in plasma homocysteine level and changes in cholesterol, lipoprotein levels and uric acid (UA) levels[7-9].

These findings are related with vascular endothelial dysfunction and atherosclerosis. The most important reason for these studies is to realise the various atherogenic stimuli, endothelial dysfunction and oxidative stress that are important for complex inflammatory fibroproliferative changes known as atherosclerosis[10,11]. Similarly, an increase in serum lipoprotein (a) (Lp(a)) has been defined as a secondary risk factor for the development of atherosclerotic cardiovascular disease and an independent risk factor for myocardial infarction (MI) and cerebrovascular disease (CVD)[12-14].

Serum high sensitivity C-Reactive Protein (Hs-CRP) has been shown to be a useful marker of low-grade inflammation associated with atherosclerosis. The relationship between Hs-CRP and extracranial carotid artery atherosclerosis has been studied by various investigators, and Hs-CRP has been found to be significantly correlated with intima-media thickness (IMT) or plaque formation determined by ultrasound[15].

Carotid intima media thickness (IMT) has been associated with various vascular outcomes such as CVD and MI[16]. Noninvasive measurement of IMT with high-resolution B-mode ultrasound is frequently used in observational studies. It is considered to be an important marker in the early diagnosis of atherosclerosis[17,18]. Alterations in various vascular risk factors and an increase in carotid IMT may be associated with epilepsy and/or AED[6]. Since atherosclerosis is a disease that progresses slowly over time, the relationship between the duration of AED use and the risks of atherosclerosis is important. Epidemiological studies in adults with epilepsy have suggested that the risk of ischemic heart disease increased by 34% and the risk of foetal cardiovascular disease increased by 68%[19,20].

In this study, we aimed to show the risk markers of atherosclerosis in patients using long-term AEDs, and the relationship between AEDs and carotid IMT, which is an indicator of atherosclerosis. In addition, we screened patients at risk of atherosclerosis, especially those who were using first generation AEDs such as VPA and carbamazepine, to consider the possibility of switching to new generation antiepileptics if appropriate.

MATERIALS AND METHOD

Sample

Group sample sizes of 30 and 30 achieve 81% power to detect a difference of -0,3 between the null hypothesis that both group means are 1,9 and the alternative hypothesis that the mean of group 2 is 2,2 with estimated group standard deviations of 0,4 and 0,4 and with a significance level (alpha) of 0,05000 using a two-sided Mann-Whitney test assuming that the actual distribution is normal.

Patients admitted to the neurology outpatient clinic with a diagnosis of epilepsy were included. Our study included 92 patients (40 males, 52 females) aged 17-50 years who had received carbamazepine (CBZ) or valproic acid (VPA) monotherapy for three years or more and had been using another AED (polytherapy) in addition to CBZ or VPA for at least two years. Thirty-one cases (12 males, 19 females) whose age and gender were similar to the patient group were included in the study as the control group.

Procedure

This cross-sectional case-control study was conducted in strict aderence to the Declaration of Helsinki. The study protocol was approved by the Ankara Yıldırım Bayazıt Training and Research Hospital Ethics Committee at its meeting on May 28th, 2019 (Decision no: 117). Written informed consent was obtained from the subjects included in the study. Patient information was sourced from the unalterable hospital database.

Physical and neurological examination were performed, and fasting blood glucose (FBG) levels, lipid profile (triglyceride (TG), total cholesterol (TC), High density lipoprotein cholesterol (HDL-c), Low densty lipoprotein (LDL-c)), homocysteine, Hs-CRP, UA, Lp(a), and vitamin B12 were measured. The carotid IMT level was determined using Doppler ultrasound. The cases diagnosed with idiopathic, cryptogenic and symptomatic epilepsy according to the ILAE-1989 seizure classification and taking CBZ or VPA monotherapy for three years or longer and another AED for at least two years in addition to CBZ or VPA (polytherapy) were included in the study.

Those who had a known atherosclerotic vascular disease (CVD, transient ischemic attack, MI); patients with hypertension, diabetes mellitus or another inflammatory disease; those taking drugs other than AEDs; patients undergoing drug therapy for obesity and participating in exercise programs, and those who had undergone brain imaging and demonstrated chemical injury were excluded from the study.

Antropometric measurements

Weights of all patients were measured by the same device in kgs. Height was recorded in centimetres by removing shoes and standing with a standard type stable height measuring device, model #ADE M320600-01 body mass index (BMI) height scale. The BMI of all patients including the control group was calculated with the formula of BMI=weight (kg)/height $(m)^2$.

Laboratory tests

Blood samples were drawn to measure blood glucose (FBG), lipid profile (TG, TC, HDL-c, LDL-c), Hs-CRP, UA, Lp(a) and vitamin B12 levels. Blood samples were taken between 7:30 and 8:30 a.m. after at least 10-12 hours of night fasting. The samples were studied immediately (FBG, lipid profile (TG, TC, HDL, LDL, Hs-CRP, UA, Lp(a), vitamin B12) after beomg transferred to the laboratory. Other samples (homocysteine, Lp(a)) were stored at -80 °C after separating their serum or plasma within one hour. Lp(a) was studied in serum and homocysteine was studied in plasma samples. To obtain plasma, blood samples taken into tubes containing 2.5 ml 1 mg/mL ethylenediamine tetraacetic acid (EDTA) were centrifuged at 2000 rpm for ten minutes. The separated plasma was placed in capped Eppendorf tubes and stored at -80 ºC until the time of analysis.

Homocysteine was measured using the chemulescence method with the Imulate 2000 commercial autoanalyser and expressed as μmol/L. Lp(a) was measured using the nephelometric method with a Beckman image commercial autoanalyser and expressed as mg/dl in our laboratuary.

Carotid artery intima media thickness

Measurements were performed in a supine position with the head slightly extended and turned to the left. Images were obtained from the posterior wall of the common carotid artery, 1 cm proximal to the carotid bifurcation, and two echogenic lines were detected. The outer line was accepted as the border of the medial adventitia and the inner line was accepted as the border of the luminal intima. The distance between the two parallel lines was accepted as intime media thickness (IMT). The IMT value was calculated by taking the arithmetic mean of three measurements in each case. B-mode USG measurements of all cases were performed by the same radiologist using a 6-12 MHz S6 linear probe on a General Electric color Doppler device in our radiology unit.

Statistical analysis

SPSS for Windows 11.5 software program was used to analyse data. The normally distributed measurement data in this study were expressed as the

mean ± standard deviation (x ± S) for continuous variables, and the number of cases and percentage for nominal variables. The significance of the difference between the groups was analysed using one-way ANOVA, and the significance of the difference in terms of median values was analysed using the Kruskal Wallis test, which was used to determine the situations that caused a significant difference in the multiple comparisons. Nominal variables were evaluated with Pearson's chi-square or Fisher's exact chi-square test. Spearman's correlation test was used to analyse a significant correlation between continuous variables. As a result of univariate statistical analysis, the combined effects of factors that may have an impact on carotid IMT or that were thought to be clinically effective were evaluated with multiple linear regression analysis. The regression coefficient, 95% confidence interval and significance levels for each variable were calculated. Since the carotid IMT was not normally distributed, logarithmic analysis was performed in the regression data. A probability of less than 0.05 was considered to be significant ($p<0.05$).

RESULTS

A total of 123 subjects (n: 92 patient study group; n: 31 patient control group) were included in the study. The mean age and gender were statistically similar between the groups ($p=0.648$, $p=0.662$, respectively). There was no statistically significant difference between the groups in terms of BMI mean levels ($p=0.638$) (Table 1).

There was a statistically significant difference in the mean age of onset of epilepsy among the patient groups, and it was observed that the disease had started earlier in the polytherapy group compared to the CBZ group ($p=0.040$). There was a statistically significant difference between the groups in terms of disease duration, and it was observed that the polytherapy group had a longer period of disease than the CBZ group and the VPA group ($p=0.009$ and $p=0.037$). The distribution of idiopathic and symptomatic epilepsy was similar between the groups ($p=0.470$).

However, the incidence of generalised and partial seizure types was statistically different between the groups ($p=0.015$). The generalised seizure type was less common in the CBZ group than in the VPA and polytherapy groups ($p=0.010$ and $p=0.031$). Moreover, it was seen that the polytherapy group had prominently more seizures than the CBZ and VPA groups, respectively ($p<0.001$ and $p=0.002$) (Table 1).

There was also a statistically significant difference between the groups in terms of TC levels ($p=0.020$), and the TC level of the CBZ group was found to be significantly higher than the control and VPA groups, respectively ($p=0.045$ and $p<0.001$) (Table 2). There was no statistically significant difference between the groups in terms of HDL-c, LDL-c and TG levels ($p=0.055$; $p=0.228$ and $p=0.515$) (Table 2). There was a statistically significant difference between the groups in terms of Lp(a) levels ($p=0.043$), and the median Lp(a) values of the VPA and polytherapy groups were significantly higher than the control group ($p=0.007$ and $p=0.025$) (Table 2).

The median values of Hs-CRP were statistically different between groups ($p=0.002$). The Hs-CRP level of the CBZ group was significantly higher than the control, VPA and polytherapy groups, respectively ($p=0.008$; $p<0.001$ and $p=0.037$). In addition, the Hs-CRP level was significantly higher in the polytherapy group than in the VPA group ($p=0.049$).

UA levels of the VPA group were found to be significantly higher than the CBZ and polytherapy groups ($p<0.001$ and $p=0.013$) (Table 2).

There was a statistically significant difference between the groups in terms of median homocysteine values ($p=0.010$). Homocysteine levels in the CBZ, VPA and polytherapy groups were found to be significantly higher, respectively, compared to the control group ($p=0.024$; $p=0.002$; $p=0.002$) (Table 2). There was no statistically significant difference between the groups in terms of vitamin B12 and FBG levels ($p=0.117$ and $p=0.329$). There was no statistically significant difference between the groups in terms of right, left and mean carotid IMT, respectively ($p=0.424$; $p=0.112$ and $p=0.197$) (Table 2).

In all cases, a significant positive correlation was found between age and BMI and carotid IMT ($p<0.001$). In addition, a significant positive correlation was found between TC, LDL-c, Hs-CRP, homocysteine and carotid IMT ($p<0.05$). No statistically significant correlation was determined between HDL-c, TG, Lp(a), UA, vitamin B12, FBG and carotid IMT ($p>0.05$) (Table 3).

Table 1. Demographic and clinical characteristics of the cases by groups

Variables	Control (n=31)	Carbamazepine (n=31)	Valproic acid (n=31)	Polytherapy (n=30)	p
Age (mean±SD)	30.7±8.5	32.2±10.2	29.2±11.2	29.9±8.6	0.648
Gender n (%)					0.662
Male	12 (%38.7)	11 (%35.5)	14 (%45.2)	15 (%50.0)	
Female	19 (%61.3)	20 (%64.5)	17 (%54.8)	15 (%50,0)	
BMI (kg/m2) (mean±SD)	24.4±3.7	24.9±3.8	24,0±4.5	23.6±3.8	0.638
Age of Onset (mean±SD)		20.0±10.3a	15.5±11.3	13.3±10.0a	0.045
Disease Duration Average (min-max)		10 (4-32)a	11 (3-45)b	15.5 (4-30)a,b	0.046
Etiology n (%)					0.470
Idiopathic		25 (%80.6)	28 (%90.3)	24 (%80.0)	
Symptomatic		6 (%19.4)	3 (%9.7)	6 (%20.0)	
Seizure Type					0.015
Generalized		18 (%58.1)a,b	27 (%87.1)a	25 (%8.3)b	
Generalized Tonic Clonic		18 (%100.0)	20 (%74.1)	24 (%96.0)	
Atonic		-	1 (%3.7)	1 (%4.0)	
Myoclonic		-	4 (%14.8)	-	
Absence		-	2 (%7.4)	-	
Partial		13 (%41.9)a,b	4 (%12.9)a	5 (%16.7)b	
Complex Partial		9 (%29.0)	3 (%9.7)	3 (%10.0)	
Secondary Generalized		4 (%12.9)	1 (%3.2)	2 (%6.7)	
Seizure Status n (%)					0.002
No Seizure		15 (%48.4)b	14 (%45.2)c	3 (%10.0)b,c	
With Seizure		16 (%51.6)b	17 (%54.8)c	27 (%90.0)b,c	

BMI: Body Mass Index

a The difference between the carbamazepine group and the valproic acid group was statistically significant. (p<0,05).

b The difference between the carbamazepine group and the Multidrug group was statistically significant. (p<0,05).

c The difference between the valproic acid group and the Multidrug group was statistically significant. (p<0,05).

There was a significant positive correlation between age, BMI, age of onset of disease and carotid IMT in the case group (p<0.001). In addition, a significant positive correlation was analysed between TC, LDL-c, TG, Hs-CRP, homocysteine and carotid IMT (p<0.05). No statistically significant correlation was found between disease duration, AED dose, AED duration, HDL-c, Lp(a), UA, Vitamin B12, FBG and carotid IMT (p>0.05) (Table 3).

Among all cases, carotid IMT was determined to be 0.54 (0.37-1.16) in females and 0.53 (0.36-1.38) in males. There was no statistically significant difference between gender (p=0.638). There was no statistically significant difference in carotid IMT between groups, according to etiology, seizure type and seizure status (p>0.05) (Table 4).

When the combined effects of all factors thought to affect carotid IMT were examined, no statistically significant difference was observed between the study and the control groups. After making adjustments for other risk factors, it was found that taking multiple drug therapy caused an increase in carotid IMT compared to the control group (p= 0.029) (Table 5).

In addition, the significant effects of BMI, TC, LDL-c, Hs-CRP and homocysteine, which had a significant correlation with carotid IMT, disappeared (p>0.05). The statistical significance of the enlargement of the carotid IMT continued only with advancing age (p<0.001) (Table 5).

When the combined effects of all factors thought to affect carotid IMT were examined in the study group, the significant effects of BMI, TC, LDL-c, TG, Hs-CRP and homocysteine, which had a significant correlation with carotid IMT, disappeared (p>0.05). The statistical significance of the enlargement of the carotid IMT continued only with advancing age (p<0.001) (Table 5).

Table 2. Evaluation of the laboratory measurements of the cases by groups

Variables Mean min-max)	Control	Carbamazepine	Valproic Acid	Multidrug	p
Total Cholesterol	172 (102-255)a	199 (115-267)a,b	158 (58-244)b	173 (110-350)	0.020
HDL Cholesterol	46 (26-87)	54 (31-93)	45 (29-73)	55.5 (28-89)	0.055
LDL Cholesterol	94 (27-147)	110 (60-181)	91 (17-172)	100.5 (36-211)	0.228
Triglyceride	122 (46-250)	135 (47-396)	125 (28-204)	95 (45-449)	0.515
Lipoprotein A	8 (2-48.9)c,d	8.4 (2-119)	17.4 (2-79.5)c	14.4 (0.1-112)d	0.043
HS-CRP	0.8 (0.1-6.7)a	2.6 (0.1-9.3)a,b,e	0.5 (0.1-12.5)b,f	1.1 (0.1-16)e,f	0.002
Uric acid	3.9 (1.6-6.8)	3.3 (1.8-6.2)b	4.3 (1,8-7.4)b,f	3.6 (1.6-6.7)f	0.009
Homocysteine	8 (4-21)a,c,d	10 (5-22.8)a	10.9 (5.6-29.6)c	10.6 (4.8-65.6)d	0.010
Vitamin B12	296 (115-4403)	241 (85-703)	305 (54.5-875)	316 (155.6-790)	0.117
FBG	86 (70-108)	86 (71-126)	82 (60-98)	82.5 (68-107)	0.329
Right Carotid IMT	0.49 (0.37-0.69)	0.55 (.,35-1.34)	0.52 (0.32-0.83)	0.54 (0.33-0.99)	0.424
Left Carotid IMT	0.49 (0.33-0.68)	0.58 (0.35-1.42)	0.53 (0.38-0.82)	0.57 (0.38-1.38)	0.112
Average IMT	0.52 (0.37-0.67)	0.56 (0.37-1.38)	0.52 (0.37-0.79)	0.56 (0.36-1.18)	0.197

HDL: High Dendity Lipoprotein LDL:Low Density Lipoprotein, HS-CRP:High Sensitve-C reaktive protein, FGB: Free Blood Glucose IMT :Intima Media Thickness

a The difference between the Control Group and the Carbamazepine Group was statistically significant. (p<0,05).

b The difference between the Carbamazepine Group and the Valproic acid Group was statistically significant. (p<0,001).

c The difference between the Control Group and the Valproic acid Group was statistically significant. (p<0,01).

d The difference between the Control Group and the Multi-Drug Group was statistically significant. (p<0,05).

e The difference between the Carbamazepine Group and the Multidrug Group was statistically significant. (p=0,037).

f The difference between the Valproic acid Group and the Multi-Drug Group was statistically significant. (p<0,05).

Table 3. Correlation coefficients and significance levels between factors that may be associated with carotid intima media thickness means in all cases and case groups

Variables	All Cases (n=123) r	All Cases (n=123) p	Case Group (n=92) r	Case Group (n=92) p
Age	0.421	<0.001*	0.528	<0.001*
BMI	0.250	0.006*	0.300	0.004*
Total Cholesterol	0.205	0.024*	0.262	0.012*
HDL Cholesterol	-0.142	0.118	-0.196	0.063
LDL Cholesterol	0.277	0.002*	0.310	0.003*
Triglyceride	0.172	0.058	0.274	0.009
Lipoprotein A	0.036	0.694	0.002	0.984
Hs-CRP	0.293	<0.001*	0.335	<0.001*
Uric acid	0.033	0.720	0.163	0.122
Homocysteine	0.251	0.005	0.208	0.048*
Vitamin B12	0.022	0.809	0.048	0.652
FBG	0.084	0.360	0.161	0.127
Age of onset			0.346	<0.001
Disease Duration			0.115	0.278
AED Dose			0.145	0.171
AED Duration			0.029	0.785

HDL: High Density Lipoprotein LDL: Low Density Lipoprotein, HS-CRP: High Sensitve-C reaktive protein, FGB: IMT: Intima Media Thickness, AED: Antiepileptic drug

Table 4. Investigation of carotid intima media thickness according to gender, etiology, seizure type and seizure status within the case group

Variables	Carotid Intima Media Thickness	p
Gender		0.168
Male	0.57 (0.36-1.38)	
Female	0.53 (0.37-1.18)	
Etiology		0.822
Idiopathic	0.55 (0.36-1.38)	
Symptomatic	0.56 (0.42-0.75)	
Seizure Type		0.499
Generalized	0.55 (0.36-1.38)	
Partial	0.52 (0.42-0.71)	
Seizure Status		0.977
No Seizure	0.53 (0.40-1.38)	
With Seizure	0.55 (0.36-1.18)	

Table 5. Investigation of the effects of all factors considered to be effective on carotid intima media thickness in all cases and case groups according to multiple linear regression analysis

Variables	Regression coefficient All Cases (n=123)	p value All Cases (n=123)	95% Confidence Interval All Cases (n=123)		Regression coefficient Case Group (n=92)	p value Case Group (n=92)	95% Confidence Interval Case Group (n=92)	
			Lower Bound	Upper Bound			Lower Bound	Upper Bound
Carbamazepine	0.0910	0.083	-0.0121	0.1941				
Valproic acid	0.0852	0.097	-0.0158	0.1863				
Polytherapy	0.1162	0.029	0.0124	0.2200				
Age	0.0074	<0.001	0.0033	0.0116	0.0089	<0,001	0.0040	0.0138
Gender	0.0446	0.276	-0.0362	0.1254	0.0385	0.494	-0.0731	0.1502
BMI	0.0063	0.202	-0.0034	0.0160	0.0047	0.433	-0.0072	0.0166
Total Cholesterol	-0.0012	0.352	-0.0037	0.0013	-0.0001	0.930	-0.0035	0.0032
HDL	-0.0014	0.454	-0.0050	0.0023	-0.0020	0.385	-0.0066	0.0026
LDL	0.0013	0.348	-0.0014	0.0039	0.0003	0.881	-0.0033	0.0039
Triglyceride	0.0004	0.350	-0.0004	0.0012	0.0004	0.484	-0.0006	0.0014
Hs-CRP	0.0023	0.750	-0.0118	0.0164	0.0066	0.416	-0.0095	0.0228
Uric acid					0.0260	0.222	-0.0161	0.0681
Homocysteine	0.0033	0.189	-0.0016	0.0082	0.0034	0.232	-0.0022	0.0090
Disease Duration					-0.0035	0.330	-0.0106	0.0036
AED Dose					0.0000	0.528	-0.0001	0.0002
AED Duration					0.0046	0.366	-0.0055	0.0147

BMI: Body Mass Index, HDL: High Density Lipoprotein LDL: Low Density Lipoprotein, HS-CRP: High Sensitve-C reaktive protein, FGB: Free Blood Glucose, IMT: Intima Media Thickness, AED: Antiepileptic drug

DISCUSSION

Epilepsy is a common chronic neurological disease affecting 1% to 3% of the population[21]. It is a chronic disease that affects metabolism, either alone or through antiepileptic drug (AED) therapy[22]. Although many dose-dependent effects and hypersensitivity reactions that occur with the use of AEDs are known, the metabolic adaptation of these drugs and the metabolic effects they will cause in long-term use are not fully understood.

In some epidemiological studies in the literature, a slight increase in atherosclerosis-related cardiovascular disease prevalence and death rate was found in epilepsy patients using AEDs[23,24]. However, the results obtained in other studies showed that the mortality rate from ischemic heart diseases was lower in patients with epilepsy who were treated, in contrast

to studies that made comparisons to the normal population[25,26]. The most important feature of recent studies is the realisation that various atherogenic stimuli, endothelial dysfunction and oxidative stress are important for complex nonadaptive inflammatory fibroproliferative changes known collectively as atherosclerosis[10,11].

Elevated homocysteine levels in epilepsy patients can cause long-term deterioration in cognitive functions, CVD, cardiovascular disease, and death[27]. In a study conducted by Ono et al. among 81 pediatric and adult patients taking AEDs, they found high homocysteine levels in the blood in 13.8% of the patients[28]. Tümer et al., 111 examined epilepsy patients and a control group of 46 people, and plasma homocysteine levels were found to be significantly higher in the patient group compared to the control group[13]. Another study conducted by Verotti et al., determined that homocysteine levels were found to be significantly higher after fasting homocysteine and methionine loading in patients receiving VPA and CBZ[29]. In our study, homocysteine levels were found to be statistically significantly higher in epilepsy patients who received AEDs either as monotherapy or as polytherapy, which is similar to the abovementioned studies.

In the studies conducted by Hamed and Abdellah in 2005, Ayçiçek and Akın in 2007, and Teng-Yeow et al. in 2009, UA levels were found to be high in the VPA monotherapy group[6,9,18,30]. In the present study, we found higher UA levels in the VPA monotherapy group compared to the CBZ monotherapy and polytherapy groups, which supports previous studies.

The literature has reported that long-term use of CBZ especially increases TC and LDL-c, TG, while VPA decreases TC, LDL-c, TG. In other studies, VPA does not affect LDL-c[8,30-36]. In our study, when the CBZ monotherapy group was compared with the control group and the VPA monotherapy group, we found that the TC levels were significantly higher in favour of the CBZ group. However, we did not find any significant difference between the groups in terms of HDL-c, LDL-c and TG levels. While these findings support the effect of CBZ on TC increase, no effect on LDL-c was detected, and VPA's increasing effect on lipid profile was not demonstrated. In this respect, our findings partially support the literature data. In light of these data, our study shows that enzyme-inducing AEDs (CBZ) increase dyslipidemia, and enzyme-inhibiting AEDs (VPA) increase UA metabolism.

Various studies have been conducted on serum Lp(a) levels of epilepsy patients using AEDs. Sönmez et al. in 2006, reported an increase in Lp(a) in all 64 children in three groups who had epilepsy and were using CBZ, VPA and phenobarbital. While a higher increase was found in those using CBZ, this was not statistically significant when compared with VPA[37]. In a study conducted by Tümer et al. in 2002, 111 children undergoing treatment with CBZ, VPA and phenobarbital were compared with healthy controls; LP(a) levels were found to be significantly higher than the controls[13]. Research conducted by Voudris et al. in 2006 on epilepsy patients using VPA and CBZ found that the serum concentration of LP(a) increased at 6-, 12- and 24-month follow-ups[14]. Similarly, the study by Schwaninger et al. on adult epilepsy patients using VPA, CBZ, phenytoin or phenobarbital, showed that the serum Lp(a) level of the patient group was higher when compared to the control group[12]. In our study, there was a statistically significant difference between the groups in terms of Lp(a) levels, and we determined that the median Lp(a) values of the VPA and polytherapy groups were significantly higher than the control group.

Biton stated in his study in 2003 that clinically significant changes in body weight are a well-known side effect of AEDs[38]. De Michele et al. in 2002, found carotid IMT to be associated with obesity and an increase in BMI[39]. Research conducted by Teng-Yeow et al. reported that the main mechanism of atherogenesis in obese or people with increased BMI was a low-grade systemic inflammation resulting from high concentrations of Hs-CRP[18]. Accordingly, in our study, there was a statistically significant difference in the median values of Hs-CRP between the groups that had been receiving AED treatment for a long time. In addition, the Hs-CRP level was found to be statistically significantly higher in the polytherapy group than in the group using VPA. These results also support that Hs-CRP contributes to atherosclerosis through inflammation in epilepsy patients using CBZ.

The early determining radiological feature of atherosclerosis is IMT measurement with Doppler ultrasound (US). Teng-Yeow et al. measured IMT with B-mode US in 195 epilepsy patients using AEDs and in a control group of 195 people of the same age and gender. The results showed that atherosclerosis was associated with the duration of drug use independent of age, gender and oxidative stress causing atherosclerosis. The same study observed that IMT thickness was higher in males[18]. In a study

by Hamed et al. in 2007, with 225 adults undertaking AED treatment and 60 people in a control group, it was found that carotid artery IMT and various vascular risk factors were significantly increased in epilepsy patients, both for those receiving and not receiving AED treatment, compared to the control group[6]. In the study by Schwaninger et al. with an adult patient group, carotid IMT was found to be higher among those taking long-term medication compared to the control group; it was further indicated that VPA posed a risk for atherosclerosis [12]. In our study, although IMT tended to increase in the patient group, we did not find a significant difference between the patient and control groups in terms of right, left and mean IMT values. We did not find a statistically significant difference between men and women in terms of mean carotid IMT among all cases, which may have been caused by the relatively small size of the patient group and the inability to match the age and gender of the control group. A significant correlation can be established between the use of AEDs and IMT by matching the age and gender of the larger patient groups and the control group.

In the present study, when all cases were evaluated together, a significant positive correlation was found between age and IMT values. It was also reported in the studies of Sun et al. in 2002 and Homma et al. in 2001 that the increase in carotid IMT may be associated with ageing[40,41]. This conclusion was consistent with those of previous studies. Again, when all the cases evaluated together, a significant positive correlation was found between BMI and IMT values. When only the cases taking AEDs were evaluated, a significant positive correlation was more evident between BMI and IMT values. In addition, a positive and significant correlation was found between TC, LDL-c, TG, Hs-CRP, homocysteine and carotid IMT. This suggests that risk factors for atherosclerosis, including impaired homocysteine metabolism and increases in TC, LDL-c, TG, BMI or Hs-CRP, may contribute to the atherosclerotic process as a cumulative effect in those receiving AED treatment, and may be important for understanding the pathogenesis of atherosclerosis in epilepsy.

In our study, no correlation was found between carotid IMT and disease duration, AED dose, AED duration, HDL-c, Lp(a), UA, vitamin B12 and FBG levels of epilepsy patients.

When the effects of all factors thought to affect carotid IMT were examined together, there was no statistically significant difference between the case groups and the control group, but when adjustments were made for other risk factors, it was found that taking multiple drugs compared to the control group caused an increase in carotid IMT.

Limitations of our study include the relatively small sample size, possible confounding factors or cross-sectional design, lack of measurements of inflammatory cytokines or other novel markers of atherosclerosis and the lack of controls for lifestyle factors.

In order to detect clinical signs and symptoms of atherosclerosis, lesions should be in the middle or advanced stage, while increased arterial IMT is generally considered as an early sign of atherosclerosis. In the early phase of atherosclerosis, the increase in IMT of the vessels can be evaluated from peripheral arteries, especially the carotid artery, with B-mode US. While we observed an increase in IMT proportional to age in our study, we could not detect an increase in IMT in long-term use of AEDs. However, when the effects of taking multidrug therapy together with all factors were examined, we determined that it may cause an increase in carotid IMT. Our results do not fully demonstrate the significant effect of AED treatment on the atherosclerotic process, since the factors known to cause atherosclerosis (BMI, TC, LDL-c, TG, Hs-CRP, and homocysteine) had a more significant correlation in the group using AED, especially in epilepsy patients receiving polytherapy. However, a cumulative effect of the atherosclerotic process was supported. This may shed light on the development of new strategies to reduce morbidity and mortality due to atherosclerosis, especially among the elderly and high-risk epilepsy patients using long-term AEDs.

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