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ORIGINAL ARTICLE

Effects of Carbamazepine On Vascular Risk Factors and Atherosclerosis in Epileptic Children

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Abstract

Objectives: The aim of our study was to investigate the presence of increased cardiovascular risk in epileptic children treated with carbamazepine. This study was designed to evaluate the relation of carbamazepine and atherosclerosis by investigating the effect of carbamazepine on antioxidant capacity, lipid profile, oxidized low-density lipoprotein (LDL), and carotid artery intima-media thickness (C-IMT).

Methods: Twenty-one children aged between 2 and 16 years with epilepsy who were treated with carbamazepine were included in the study. Triglyceride, total cholesterol, high-density lipoprotein, LDL, lipid hydroperoxide, paraoxonase, arylesterase levels, and C-IMT were measured in all patients before the treatment, at the 3rd and 6th months of the treatment.

Results: Thirteen (61.9%) of the patients were male, and 8 (38.1%) were female. The mean age of the patients was 111.48±44.81 months. There was a significant increase in total cholesterol, arylesterase, and paraoxonase levels at the 6th months of the treatment compared with pre-treatment levels. No significant changes were observed in C-IMT values.

Conclusion: Our study is the first study in the literature in which the relation between arylesterase and paraoxonase levels and CIMT in pediatric patients before and after carbamazepine treatment was prospectively investigated. The exact mechanism of carbamazepine on atherosclerosis is not clearly understood. These results demonstrate that these patients could be at increased risk of the development of cardiovascular complications. In light of these findings, future studies in epileptic children should be to plan antioxidant capacity, cholesterol level, and measuring C-IMT with ultrasonography periodically in long term. We think that these findings enhance our understanding of the relationship between oxidative stress and antiepileptic drugs.

Keywords: Atherosclerosis; carbamazepine; carotid intima-media thickness; epilepsy.

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Introduction

Epilepsy is a common chronic disease characterized by recurrent convulsions.[1,2] The epilepsy incidence is 0.5–0.7% in general population.[3,4] Carbamazepine is a commonly prescribed agent for focal epilepsy and other non-epileptic conditions such as neuropathic pain, schizophrenia, and bipolar disorder in the pediatric and adult patients.[5] The atherosclerosis is defined as "accumulation of lipids, complex carbohydrates, blood and blood products; development of fibrous reactions; and deposition of calcium on media and intima layers of arteries" by the World Health Organization. Such lesions can lead to diseases such as cerebrovascular disease, coronary heart disease, and peripheral arterial obstructions, leading to a high risk for mortality and morbidity. Early signs of atherosclerosis can also be seen at childhood. In majority of the previous studies on sudden unexpected death in epilepsy, results suggest coronary artery-related causes.[6,7] In some studies, it has been reported that oxidative stress is also effective in the development of coronary artery disease and atherosclerosis. Although it is known that oxidative stress increases and facilitates the development of atherosclerosis in adults, pediatric studies are limited.[8,9]

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Karbamazepin Kullanan Çocuk Hastalarda Vasküler Risk Faktörleri ve Ateroskleroz

Öz

Amaç: Çalışmamızın amacı karbamazepin ile tedavi edilen epileptik çocuklarda artmış kardiyovasküler riskin varlığını araştırmaktır. Bu çalışma karbamazepin tedavisinin; paraoksonaz ve arilesteraz aktivitesi (antioksidan kapasite), lipid profili, oksitlenmiş LDL ve karotid arter intima-media kalınlığı (K-İMK) üzerine etkisini araştırmak ve ateroskleroz ile ilişkisini değerlendirmek için tasarlanmıştır.

Gereç ve Yöntem: Epilepsi tanısı konularak karbamazepin başlanan 2–16 yaş arasındaki 21 hasta çalışmaya dahil edildi. Tüm hastalardan başlangıç, üç ve altıncı aylarda trigliserid, total kolesterol, yüksek dansiteli lipoprotein (HDL), düşük dansiteli lipoprotein (LDL) ölçümleri, LOOH (lipid hidroperoksit), paraoksonaz (PON1), arilesteraz (ARE) düzeyi bakılmıştır. Hastaların K-İMK, sağ ve sol karotis arter bifurkasyonunun 1 cm proksimalinin posterior duvarından ölçülmüştür.

Bulgular: Hasta grubunun 13'ü (%61.9) erkek, 8'i (%38.1) kız idi. Grubun ay ortalaması 111.48±44.81 saptandı. Hasta grubunda başlangıçta bakılan total kolesterol değeri ile altıncı ayda bakılan total kolesterol değerleri arasında anlamlı farklılık saptandı (p=0.002). Hasta grubunun başlangıçta bakılan arilesteraz ve paraoksonaz değeri ile altıncı ayda bakılan değerleri arasında anlamlı farklılık saptandı (p=0.001) (p=0.004). Hasta grubunda başlangıçta bakılan sağ-sol K-İMK ile altıncı ayda bakılan değerleri arasında anlamlı farklılık gözlenmedi (p=0.966) (0.142).

Sonuç: Çalışmamız, pediatrik hastalarda karbamazepin tedavisi öncesi ve sonrası arilesteraz & paraoksonaz düzeyleri ile K-IMT arasındaki ilişkinin ileriye dönük olarak araştırıldığı literatürdeki ilk çalışmadır. Karbamazepinin ateroskleroz üzerindeki kesin mekanizması tam olarak anlaşılamamıştır. Bu sonuçlar, bu hastaların kardiyovasküler komplikasyonların gelişimi açısından risk altında olabileceğini göstermektedir. Bu bulgular ışığında, epileptik çocuklarda yapılacak çalışmalar ile uzun dönemde periyodik olarak antioksidan kapasite, kolesterol düzeyi ve K-IMT ölçümü yapılması, kardiyovasküler etkiler açısından takip edilmesi etki mekanizmasının anlaşılması açısından fayda sağlayacaktır.

Anahtar sözcükler: Ateroskleroz; epilepsi; karbamazepin; karotid arter intima media kalınlığı.

Serum paraoxonase-1 (PON1), an antioxidant enzyme with paraoxonase, arylesterase, and dyazoxonase activities, is a 45 kDa glycoprotein that is expressed in the liver. PON1 enzyme breaks down active lipids in LDL together with high-density lipoprotein (HDL) in its compound and thus acts protective by preventing the inflammatory response occurring in the vascular wall.[10] Lipid hydroperoxide (LOOH) causes disruption of membrane integrity and cell damage.[11]

In this study, it was aimed to discuss the effects of antiepileptic treatment on total antioxidant capacity, lipid profile, and carotid artery intima-media thickness (C-IMT) and its relationship between atherosclerosis in pediatric patients.

Materials and Methods

We recruited patients prospectively from epilepsy outpatient clinic of pediatric neurology department of Gaziantep University Faculty of Medicine. The study was approved by Ethics Committee of Gaziantep University Faculty of Medicine (approval number: 15/269). The study was also approved and supported by Scientific Research Projects Commission of Gaziantep University (project number: TF.UT.16.15).

Patients group– The study was conducted on 21 patients aged between 2 and 16 years newly diagnosed focal epilepsy and started carbamazepine as monotherapy, Patients had no infection at the time of blood sampling for study. In all patients, types of epilepsy were assigned using history and electroencephalography findings based on International League Against Epilepsy (ILAE) 2014 definition and 2017 classification.[12,13]

The patients having history of trauma, neurometabolic diseases, perinatal asphyxia, genetic syndromes or recurrent febrile convulsion; those receiving vitamin supplementation, medication other than AEDs affecting homocysteine or lipid metabolism; and those with clinical evidence of acute illness, renal dysfunction, thyroid dysfunction, metabolic disease, chronic inflammatory disease, cerebrovascular disease, or mental motor retardation with an unknown etiology were excluded from the study.

All patients underwent central nervous system magnetic resonance imaging to exclude potential comorbid conditions.

Carbamazepine, used in the treatment of partial onset epilepsy, was started in eligible patients as monotherapy. In all patients, paraoxonase, arylesterase, LOOH, triglyceride, total cholesterol, HDL, and LDL levels were measured at baseline and on months 3 and 6 after initiation of treatment. Carbamazepine was given at a dose of 15 mg/kg in all patients. No recurrent convulsion was observed after initiation of carbamazepine therapy. The blood carbamazepine level was measured with an interval of 3 months and maintained between 4 and 12 mg/L.

All participants gave written informed consent before participation.

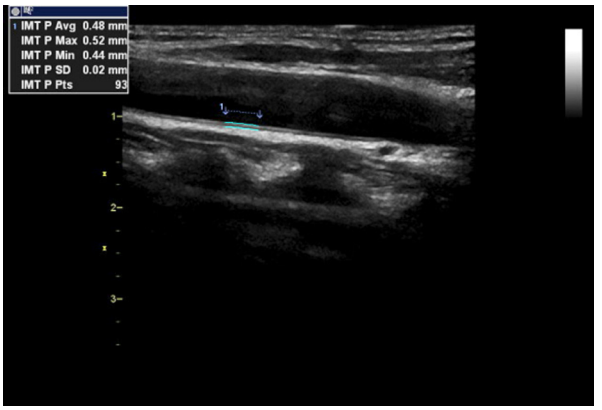

Fig. 1. C-IMT measurement. C-IMT: Carotid artery intima-media thickness.

Biochemical methods– Fasting venous blood samples were taken into tubes with and without anticoagulants. All samples were centrifuged at 4000 rpm for 10 min to obtain serum and plasma. Serum glucose, triglyceride, total cholesterol, HDL, and low-density lipoprotein (LDL) levels were measured by an automated analyzer (Beckman Coulter Chemistry Analyzer AU480). Serum paraoxonase, arylesterase, and LOOH levels were measured by an automated analyzer using commercial kits (Rel Assay DC, Gaziantep, Turkey).

Ultrasound methods– The C-IMT was measured by Vivid 9 4D system using 11 Hz linear probe at baseline and on months 3 and 6. The C-IMT was assessed by pediatric cardiology department. In all patients, intima-media thickness was measured from posterior wall images obtained at 1 cm proximal to carotid artery bifurcation by automatic contour detection technique (Fig. 1).

Statistical analysis– The normal distribution of continuous variables was assessed using Shapiro–Wilk test. In data with skewed, Mann–Whitney U-test was used to compare two independent groups. In data with normal distribution, paired t-test was used to compare two dependent groups. In data with skewed, Wilcoxon test was used to compare two dependent groups. In the comparison of the measurements obtained at different time points, variance analysis with repeated measures was used for variables with normal distribution while Freidman test for variables with skewed distribution.

Statistical analyses were performed using SPSS for Windows version 22.0. P<0.05 was considered as statistically significant.

Results

The study included 21 children with a diagnosis of epilepsy. Of the patients, 13 (61.9%) were boys whereas 8 were girls (38.1%). The mean age was 111.48±44.81 months.

No significant difference was found between HDL, LDL, and triglyceride values measured at the baseline and on months 3 and 6 (p=0.164, p=0.104, and p=0.717, respectively). Although there was an increase in LDL and triglyceride levels on months 3 and 6 after initiation of carbamazepine therapy when compared to baseline, the difference did not reach statistical significance (Table 1).

In the patient group, a significant difference was found between total cholesterol values measured at baseline and on month 6 (p=0.002) (Table 1).

There was a significant increase in arylesterase value on months 3 and 6 when compared to baseline (p=0.001 and

Table 1. Evaluation of average of all parameters by months

Variables	Month 0 (n=21)	Month 3 (n=21)	Month 6 (n=21)	p-value
HDL (mg/dL)	51.14±2.41	52.62±15.07	57.33±14.73	0.163
Total cholesterol (mg/dL)	160.95±30.60	172.62±33.58	184.04±30.50[a]	0.002
Triglyceride (mg/dL)	138.14±94.17	120.47±57.04	152.28±77.87	0.717
LDL (mg/dL)	88.12±54.32	92.32±55.73	98.09±43.21	0.104
C-IMT right (cm)	0.47±0.05	0.47±0.06	0,47±0.06	0.962
C-IMT left (cm)	0.47±0.04	0.47±0.04	0.49±0.04	0.142
Paraoxonase (u/L)	193.38±116.96	236.76±136.15[b]	241.85±132.7[c]	0.021, 0.004
Arylesterase (u/mL)	834.42±149.48	934.95±142.08[d]	947.47±186.6[e]	0.001, 0.002
LOOH (nmol/mL)	20.66±18.16	17.91±13.15	17.93±12.22	0.897

[a]Significant difference at a level of p<0.05 between baseline and month 6 values (p=0.002). [b]Significant difference at a level of p<0.05 between baseline and month 3 values (p=0.021). [c]Significant difference at a level of p<0.05 between baseline and month 6 values (p=0.004). [d]Significant difference at a level of p<0.05 between baseline and month 3 values (p=0.001). [e]Significant difference at a level of p<0.05 between baseline and month 6 values (p=0.002). HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LOOH: Lipid hydroperoxide; C-IMT: Carotid artery intima-media thickness.

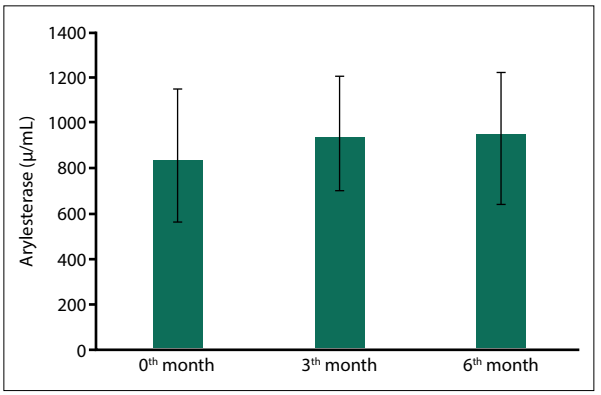

Fig. 2. Arylesteraze levels at baseline, 3th and 6th months of treatment.

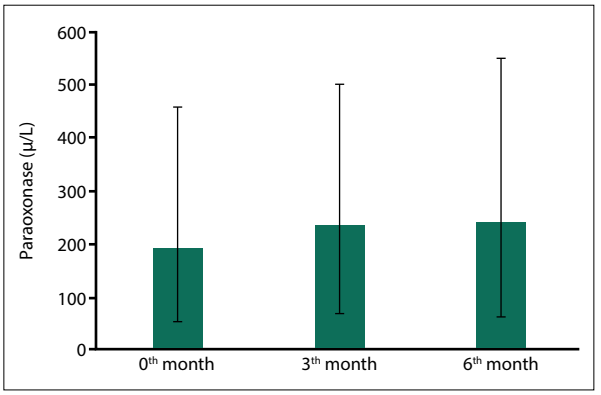

Fig. 3. Paraoxonase levels at baseline, 3th and 6th months of treatment.

p=0.002, respectively). No significant difference was detected between arylesterase values measured on months 3 and 6 (p=0.540) (Table 1, Fig. 2).

In the patient group, a significant increase was found between the paraoxonase value measured in the initial month and the paraoxonase values measured at the 3th and 6th month (p=0.001 and p=0.004, respectively) (Table 1, Fig. 3). In the patient group, there was no significant difference between LOOH levels measured at the beginning and the 3rd and 6th months (p=0.897) (Table 1).

No significant difference was observed between C-IMT measurements obtained at baseline and on months 3 and 6 at right side (p=0.966). Again, no significant difference was observed between C-IMT measurements obtained at baseline and on months 3 and 6 at the left side (p=0.142) (Table 1).

Discussion

In our study, we have prospectively investigated the effect of carbamazepine on lipid profile, arylesterase, paraoxonase levels, and C-IMT values in children with newly diagnosed focal epilepsy. The finding that chronic use of antiepileptic drugs predisposes to atherosclerosis has led studies investigating lipid profile in patients with epilepsy. In literature, there are several retrospective studies and data regarding the effect of carbamazepine on the lipid profile. In their study, Sözüer et al.[14] investigated serum lipid profile in pediatric epilepsy patients who received long-term valproic acid and carbamazepine. Authors found a significant increase in serum lipid levels in the group that received carbamazepine but not in the group that received valproate. They concluded that, owing deterioration in the lipid, carbamazepine use was associated with higher risk for atherosclerotic diseases compared to valproate use in long term. In the study on cardiovascular risk factors in epileptic children who were receiving carbamazepine or valproate monotherapy, Harit et al.[15] detected no significant alteration in lipid profile measured during treatment and 3 months after treatment discontinuation. Based on their findings, authors concluded that antiepileptic drugs and associated cardiovascular risks should be monitored at long-term regarding reversible or permanent effects.

El-Farahaty et al.,[16] in a cross-sectional comparative study, they conducted to examine the effect of long-term old and new-generation antiepileptic monotherapy on atherosclerosis, found a high level of LDL in particular, and showed that dyslipidemia developed in these patients. They concluded that since LDL is an important risk factor for atherosclerosis by increasing endothelial permeability, these patients should be followed closely in terms of cardiovascular diseases in connection with the selected antiepileptic type.

In our study, among the lipid parameters measured prospectively at baseline and at month 6, a significant increase was detected in total cholesterol value as well as insignificant increases in triglyceride and LDL values. In addition, no significant change was observed in HDL. In the early period when antioxidant capacity is high, the first parameter to increase is total cholesterol, and the insignificant increase in LDL and triglyceride values suggests that these parameters should be closely monitored in the future.

In a study on children receiving valproate and carbamazepine monotherapy, Gerstner et al.[17] found that microcirculation changes occurring in terminal vascular bed in both groups caused degeneration in endothelium and indicated that this may lead to atherosclerotic diseases. In parallel with technological advances, studies aiming to detect atherosclerotic lesions earlier have gained momentum. The

demonstration of increased C-IMT, stiffness in vascular wall, and endothelium dysfunction by high-resolution B-mode sonography is used as the earliest marker of preclinical atherosclerosis.[18,19] There is limited number of published studies involving the pediatric epilepsy patients and measuring C-IMT. In a study on etiology and effects of atherosclerosis in epilepsy, Hamed[20] found a significant increase in C-IMT in patients receiving antiepileptic treatment when compared to controls.

It is known that the increase in CIMT is a marker of atherosclerosis before onset of clinical manifestations of atherosclerosis. In a study conducted by Chuang et al.,[21] in which vascular risk factors and effects of long-term antiepileptic usage on atherosclerosis were examined retrospectively, C-IMT was found to be increased in all patient groups including carbamazepine monotherapy. In that study, it was concluded that antiepileptic type, duration of use, age, and sex are important determinants for C-IMT in atherosclerotic process since the results appeared to be more prominent in male patients and in those who received antiepileptic treatment for a long time. In our study, it was failed to found a significant increase in C-IMT. Many studies involved comparisons between the patients using carbamazepine and the control group. However, in our study, we measured C-IMT at baseline and on month 6. The lack of difference in our study suggested that the atherosclerotic process does not begin in the first 6 months and develops after a longer period of use. The possible reason that we could not find a difference between CIMT values in our study may be the short follow-up period in our study.

PON1 is a protein of 354 amino acids with a molecular mass of 43 kDa. In serum, it is almost exclusively located on HDL. Serum PON1 is an antioxidant enzyme with paraoxonase, arylesterase, and dazoxonase activities. Experiments with transgenic PON1 knockout mice indicate the potential for PON1 to protect against atherogenesis. This protective effect of HDL against LDL lipid peroxidation is maintained longer than is the protective effect of antioxidant vitamins and could thus be more important. There is evidence that the genetic polymorphisms of PON1 least able to protect LDL against lipid peroxidation (LOOH; a sign of high oxidative stress) are overrepresented in coronary heart disease.[10]

Viktorinova et al.,[22] in their study examining cardiovascular disease risk factors in adult patients, found that significant abnormalities of lipid parameters, oxidative stress markers, and the relationship between PON1 and HDL were associated with antioxidant capacity. In this study, it was concluded that lipid profile and oxidative stress markers can be used in the early diagnosis of atherosclerotic diseases in asymptomatic population. Although increased oxidative stress and oxidative modification of lipoproteins have been reported in adults, data on serum paraoxonase, arylesterase, and LOOH activity in children are limited. In a study on antioxidant capacity in adult epilepsy patients receiving antiepileptic monotherapy, Işık et al.[23] found that serum paraoxonase level was lower in the group receiving carbamazepine when compared with the group receiving valproate. This finding emphasizes that the selection of antiepileptic agent is an important factor for the development of atherosclerosis. Varoglu et al.[24] in their study found that serum paraoxonase and arylesterase values were significantly lower in patient groups receiving monotherapy and combined therapy. They thought that oxidative damage did not differ between the patient receiving monotherapy and combined therapy while oxidative damage is only related with antiepileptic type and duration of use. In our study, a significant increase in paraoxonase and arylesterase levels was found while an insignificant decrease in LOOH levels was detected. The significant increase in paraoxonase and arylesterase levels during the development of atherosclerotic process was interpreted as an indicator of the early onset of the protective defense mechanism against atherosclerosis that may develop without C-IMT changes.

Conclusion– Our study is the first study in the literature in which the relationship between arylesterase and paraoxonase levels and CIMT in pediatric patients before and after carbamazepine treatment was prospectively investigated. No significant difference was found between C-IMT measured may be due to the fact that our patients were in the pediatric age group or that CIMT was evaluated after a relatively short period of 6 months. In our patients, the increase in total cholesterol in terms of atherogenic dyslipidemia in our patients also indicates a risk for atherosclerosis in the future and suggests that close follow-up is required. Oxidative stress is a biological condition in which oxidant capacity increases and antioxidant capacity decreases or both seen together. In cases where oxygen radicals are increased chronically, they exceed the antioxidant capacity and begin to represent a risk for the development of atherosclerosis. In our study, epileptic children receiving carbamazepine monotherapy, the antioxidant capacity increases as a protective agent in the early period, and it is thought that the paraoxonase and arylesterase enzyme reaction neutralizes the atherogenic effects of lipid peroxides and protects the cell membranes. Further long-term studies with larger sample size are needed to evaluate carotid thickness, lipid panel disorder, and antioxidant capacity in patients prescribed carbamazepine monotherapy.

Informed Consent– Written informed consent was obtained from patients who participated in this study.

Ethics Committee Approval– This study approved by the Gaziantep University Faculty of Medicine Ethics Committee (Date: 12.02.2015, Number: 15/269).

Peer-review– Externally peer-reviewed.

Authorship Contributions– Concept: A.A.O., A.I.Y.; Design: A.A.O.; Data collection &/or processing: A.A.O., A.I.Y., O.B.; Analysis and/or interpretation: A.A.O., A.I.Y., S.T.; Literature search: A.I.Y.; Writing: A.I.Y., A.A.O.; Critical review: A.I.Y., A.A.O.

Conflict of interest– The authors declare that they have no conflict of interest.

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