Epilepsy & Behavior 85 (2018) 110–114

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

The measurement of both carotid intima-media thickness and epicardial adipose tissue thickness in children with epilepsy receiving antiepileptic drug therapy

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ARTICLE INFO

Article history:
Received 9 April 2018
Revised 28 May 2018
Accepted 28 May 2018
Available online xxxx

Keywords:
Carotid intima-media thickness
Epicardial adipose tissue thickness
Epilepsy
Antiepileptic drug therapy
Cardiovascular complication
Children

ABSTRACT

Objective: The aim of this study was to evaluate the carotid intima-media thickness together with the thickness of the epicardial adipose tissue in patients receiving antiepileptic drug therapy and to investigate the presence of increased cardiovascular risk in these patients.
Methods: The study included a total of 52 patients comprising 32 males and 20 females who were diagnosed as having epilepsy and who were using one or more antiepileptic drugs. The control group consisted of 34 healthy individuals comprising 16 males and 18 females. The individuals selected for the study group were requested to go to the hospital after overnight fasting. After blood sampling for serum lipid value, the carotid intima-media thickness was measured with high resolution B-mode ultrasonography and epicardial adipose tissue thickness with echocardiography in the patients and the control group subjects.
Results: The carotid intima-media thickness was determined as 0.47 ± 0.05 mm in the patient group and 0.44 ± 0.04 mm in the control group ($p = 0.028$). The carotid intima-media thickness was measured as 0.45 ± 0.05 mm in patients with epilepsy taking monotherapy and 0.49 ± 0.04 mm in those taking polytherapy ($p = 0.003$). The epicardial adipose tissue thickness was determined as 3.42 ± 0.09 mm in the patient group and 1.72 ± 0.90 mm in the control group ($p = 0.000$). The epicardial adipose tissue thickness was measured as 3.16 ± 0.87 mm in patients with epilepsy taking monotherapy and 3.77 ± 0.83 mm in those taking polytherapy ($p = 0.041$).
Conclusions: It was determined that carotid intima-media thickness and epicardial adipose tissue thickness were significantly high in children with epilepsy taking long-term antiepileptic drugs. These results demonstrate that these patients could be at increased risk of the development of cardiovascular complications. There is a need for more extensive studies on this subject.

1. Introduction

Epilepsy is one of the most serious neurological conditions. It is accepted that at least 50 million people are affected worldwide, and the general prevalence in childhood has been reported to be approximately 3–11/1000 in developed countries including Turkey [1–3]. It is currently known that there are several potential side effects of the drugs that are used to start therapy and that must be continued by patients with epilepsy for a long time [4,5]. Similarly, several experimental and clinical studies have shown an increased oxidative stress level [6,7,9–11], vascular inflammation, and risk of vascular damage in long-term epilepsy therapy [8,12]. In children with epilepsy with long-term use of antiepileptic therapy, it is likely that vascular damage can be caused by metabolic, inflammatory, hormonal, and other effects on the vascular system [13,14].

The main reason for the emergence of cardiovascular disease in adults is atherosclerosis, which is a chronic inflammatory process characterized by atherosclerotic plaque in the vessel walls and intimal lesions extending towards the vessel lumen. There are many different lipid and nonlipid risk factors in the etiology [15,16]. Of the lipid risk factors, a positive relationship has been shown between serum low density lipoprotein (LDL) cholesterol and triglyceride (TG) levels and the incidence of atherosclerosis and coronary heart disease [17,18].

In recent years, in parallel with developments in technology, there has been an increase in studies oriented to the earlier determination

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https://doi.org/10.1016/j.yebeh.2018.05.042
1525-5050/

of atherosclerotic lesions. An increase in carotid intima-media thickness (CIMT), which is a finding of endothelial dysfunction and hardening in the vascular wall and can be determined on high resolution B-mode ultrasonography (USG), is used as the earliest indicator of preclinical vascular damage [19–21]. The epicardial adipose tissue (EAT) is a visceral fat that surrounds the heart and the coronary arteries and is located between the myocardium and the visceral layer of the pericardium [22]. In studies of obese adults, an increase in epicardial adipose tissue thickness (EATT) has been related to coronary heart disease, and it has been reported that a series of adipokines expressed from EAT contribute to this process [23–25]. However, there are few studies in literature related to EATT in children and adolescents. To the best of our knowledge, despite an evaluation of measurements of EATT in an obese pediatric patient group, it has not previously been evaluated in patients with epilepsy receiving antiepileptic drug therapy [26,27]. The aim of this study was to evaluate the CIMT together with the EATT in patients receiving antiepileptic drug therapy and to investigate whether there was increased cardiovascular risk in these patients.

2. Methods

The study included 52 patients diagnosed as having epilepsy who were taking one or more antiepileptic drugs and were being followed-up in the Pediatric Neurology Department of Harran University Medical Faculty Hospital. The control group consisted of 34 age- and gender-matched healthy subjects with no history of disease or medication who presented at the polyclinic with nonspecific complaints and were evaluated as healthy in physical and neurological examinations. The individuals selected for the study group were requested to go to the hospital after overnight fasting. Height and body weight measurements were taken. Body mass index (BMI) was calculated as weight (kg)/height (m^2). The BMI and standard deviation score were evaluated using the percentile charts prepared for Turkish children according to age and gender [28]. Blood samples were taken for routine biochemistry examinations. After the blood sampling, CIMT was measured with USG and EATT with echocardiography in the patients and the control group subjects.

2.1. Patient selection

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 [29].

Diagnosis of the patients was made from the findings of clinical seizure semiology, electroencephalography, and high resolution brain magnetic resonance imaging (MRI). All families were informed about the study, and consent was obtained from the patients and their parents or legal guardians for the blood sampling.

2.2. Exclusion criteria

Patients were excluded from the study if the epilepsy was caused by metabolic or neurodegenerative diseases. Those who were obese or taking any medication or vitamin preparates other than antiepileptic drugs were also excluded.

2.3. Blood samples

For all the children in the patient and control groups, full blood counts were made using an automatic blood count device (Abbott Celldyn 3500, IL, USA). The fasting blood samples taken from all the cases in the study were centrifuged at 3500 rpm for 10 min then the formed elements were discarded with the tube. From the remaining serum samples, electrolytes, lipid profile [high density lipoprotein (HDL) cholesterol, TG, LDL cholesterol], and kidney and liver function tests (Abbott Aeroset, Abbott Diagnostics, Abbott Park, IL, USA) were measured on the same day using colorimetric methods.

2.4. CIMT measurement

Carotid intima-media thickness measurements were taken using a USG device with a broadband, high resolution 12-MHz probe (General Electrics, Logiq 7, Milwaukee, USA). All the measurements were performed on the same device by the same radiologist who was blinded to the clinical diagnoses. The right and left main carotid arteries were used in the measurements. All measurements were performed with the patient in supine position, neck in mild extension, and head turned to the opposite side. Three measurements were taken, and the average was recorded for use in the analyses.

2.5. EATT measurement

The echocardiographic examination was performed using a General Electric Medical Systems USA Vivid S6 device with a 4-MHz phase transducer. Epicardial adipose tissue thickness was measured on the free wall of the right ventricle, perpendicular to the wall, and from the parasternal long axis view at end-diastole for three cardiac cycles.

2.6. Statistical analysis

Statistical analyses of the data obtained were applied using SPSS ver 22 software (Statistical Package for the Social Sciences, version 22 for Windows, SPSS® Inc., Chicago, IL, USA). In the comparison of the patient and control groups, the independent samples *t*-test was used. In the comparisons of the monotherapy and polytherapy groups with the control group, one way analysis of variance (ANOVA) and the post hoc Tukey test were applied. Results were evaluated at a 95% confidence interval. A value of $p < 0.05$ was accepted as statistically significant.

3. Results

The study group of 52 patients comprised 32 males and 20 females with a mean age of 8.92 ± 4.09 years. The control group consisted of 34 subjects comprising 16 males and 18 females with a mean age of 8.58 ± 4.49 years. No statistically significant difference was determined between the patient and control groups with respect to mean age and gender distribution ($p = 0.645$) (Table 1).

The patients were diagnosed as having generalized epilepsy in 26 (50%) cases, focal epilepsy in 17 (32.7%), and unknown in 9 (17.3%). The brain MRI examinations demonstrated abnormality in 29 of 52 patients. The abnormalities included periventricular leukomalacia ($n = 6$), porencephalic cyst ($n = 3$), multicystic encephalomalacia ($n = 5$), arachnoid cyst ($n = 2$), focal cortical dysplasia ($n = 5$), hemimegalencephaly ($n = 1$), nonspecific gliosis ($n = 3$), vascular malformation ($n = 1$), cortical tubers ($n = 2$), and neoplasm ($n = 1$).

Monotherapy was being taken by 22 (42.3%) patients and polytherapy by 30 (57.7%) patients. Of those taking polytherapy, 21 (40.3%) patients had started 2 antiepileptic drugs, 6 (11.5%) were taking 3 antiepileptic drugs, and 3 (5.7%) were taking 4 antiepileptic drugs. The mean duration of drug use was 3.23 ± 2.45 years. Body mass index was calculated as mean 17.95 ± 2.33 kg/m^2 in the patient group and 17.04 ± 2.49 kg/m^2 in the control group. No statistically significant difference was observed between the patient and control groups with respect to BMI ($p = 0.259$) (Table 1).

The fasting serum HDL cholesterol, LDL cholesterol, and TG levels were determined as 42.96 ± 8.33 mg/dl, 85.32 ± 16.13 mg/dl, and 123.71 ± 42.62 mg/dl, respectively, in the patient group and 44.54 ± 15.39 mg/dl, 82.06 ± 19.06 mg/dl, and 86.02 ± 34.44 mg/dl, respectively, in the control group ($p = 0.219$, $p = 0.041$, $p = 0.000$, respectively) (Table 1).