Evaluation of serum lipids and carotid artery intima media thickness in epileptic children treated with valproic acid

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Received 1 July 2008; received in revised form 1 October 2008; accepted 1 November 2008

Abstract

The aim of this study is to evaluate the carotid artery intima media thickness and serum lipids in pediatric patients with epilepsy treated with valproic acid. The study included 44 pediatric epileptic and 40 healthy children. Intima media thickness of left common carotid artery and fasting lipid profile (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol) were assessed. Although we did not observe any differences regarding serum lipid profiles, intima media thickness of common carotid artery was significantly higher in epileptic patients treated with valproic acid. We suggest that this increase in intima media thickness of common carotid artery may be due to epilepsy and/or valproic acid treatment.

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Keywords: Child; Epilepsy; Intima media thickness; Valproic acid

1. Introduction

It is estimated that 10.5 million children under 15 years have active epilepsy. This represents about 25% of the global epilepsy population [1]. Valproic acid is one of the most commonly administered drugs which are used for the treatment of childhood epilepsy. It is a very effective drug for treating partial and generalized seizures as a monotherapy and as a component of polytherapy. Beside its effectiveness, it also has many side effects including weight gain, tremor and hair loss [2]. Many studies including adult patients have showed that there is a significant effect of valproic acid treatment on total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and apoliporotein levels [3–6]. A few studies regarding the effects of valproic acid on serum lipids had been performed in children [7,8,4]. On the other hand, the relationship between the influence of valproic acid on serum lipids and the risk of atherosclerosis has not been understood. Death rates from heart disease are also slightly elevated in people with epilepsy [9]. It is also well known that increased intima media thickness is an early indicator of atherosclerosis.

In this study, we investigated the serum levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and carotid artery intima media thickness in epileptic children during chronic treatment with valproic acid.

2. Patients and methods

The study was conducted in the Department of Child Neurology and Cardiology of Dokuz Eylül University

Please cite this article in press as: Erdemir A et al., Evaluation of serum lipids and carotid artery intima media ..., Brain Dev (2008), doi:10.1016/j.braindev.2008.11.001
Medical Faculty. Forty four pediatric patients with primary epilepsy treated with valproic acid and 40 sex and age matched healthy controls were included in the study. All of the epileptic patients were taking valproic acid treatment as a monotherapy for at least one year and the patients had no history of seizures after treatment. Drug level in plasma was at the therapeutic concentration (valproic acid, 50–100 μg/ml). Patients with obesity, hypertension, mental retardation, symptomatic epilepsy, chronic illness other than epilepsy, previous use of any anti-epileptic drugs, or a family history of atherosclerosis were not included in the study.

Body weight was measured to the nearest 0.1 kg and height to the nearest 0.5 cm using a stadiometer. Weight for height is calculated for each patient.

Blood samples for total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were taken between 8:30 and 9:30 h after overnight fast. Total cholesterol, triglycerides, and high-density lipoprotein cholesterol levels were measured by enzymatic colorimetric method. Serum low-density lipoprotein cholesterol was estimated using Friedewald equation (LDL-C = Total cholesterol – HDL-C – TG/5) [10]. Hyperlipidemia was defined as serum lipids higher than 95% for age and sex [11].

Before ultrasound examination subjects are rested quietly in a temperature controlled dark room for 10–15 min. All the carotid artery ultrasound studies were performed by the same experienced radiologist who was blinded to the clinical and laboratory data of the patients. Ultrasonography examinations (ATL 5000-Philips, Bothell, WA) were performed with linear wide band 5–12 mHz transducer. Patients were in supine position, the head slightly extended and rotated to the other side during the ultrasound examination. Left common carotid artery was scanned according to a predetermined standard scanning protocol. The far wall was measured. Each imaging was recorded on digital system and was analyzed manually by the other radiologist blinded to the clinical data. Due to poor imaging quality of proximal, distal wall measurements were performed. Intima media thickness was defined as the mean of three distinct measurements from each of the left common carotid artery.

Statistical analysis was performed using the Statistical Package of Social Science (SPSS), Version 11.0 (SPSS, Inc., Chicago, IL). Data were expressed as mean ± standard deviation. Student t test and chi square test were used for comparing group averages. A p value less than 0.05 was considered as statistically significant.

### 3. Results

A total of 84 subjects were included in the study. The mean age of patients, weight for height values and distribution of sexes did not differ between the groups (Table 1).

The epilepsy types of the patients were generalized tonic clonic (29 patients), absence (9 patients), atonic (1 patient) and simple partial (5 patients), respectively. Mean duration of epilepsy was 29.11 ± 16.02 (12–65) months.

Differences in the mean levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol among groups were not significant (Table 2). Triglyceride values of two patients (one in the epilepsy group and one in the control group) were above 95% for age and sex.

Intima media thickness of the common carotid artery was significantly higher in the epilepsy group when compared to the control group (Table 3; Fig. 1).

When epileptic patients were grouped according to the duration of valproic acid treatment (12–24 months; >24 months), no differences were observed regarding the intima media thickness of the left common carotid artery (Table 4).

### Table 1

<table>
<thead>
<tr>
<th>Age, gender and weight for height values of epileptic cases and controls.</th>
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<tbody>
<tr>
<td><strong>Epilepsy group (n = 44)</strong></td>
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<tr>
<td>Age (year)</td>
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<tr>
<td>Gender (male/female)</td>
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<tr>
<td>Weight for height</td>
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### Table 2

<table>
<thead>
<tr>
<th>Serum lipid values of epileptic cases and controls.</th>
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<tbody>
<tr>
<td><strong>Epilepsy group (n = 44)</strong></td>
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<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
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<tr>
<td>HDL cholesterol (mg/dl)</td>
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<td>LDL cholesterol (mg/dl)</td>
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4. Discussion

Plasma lipoprotein abnormalities are essential for the occurrence of atherosclerotic vascular diseases. These abnormalities include elevated concentrations of total cholesterol, triglycerides, low-density lipoprotein cholesterol and reduced concentrations of high-density lipoprotein cholesterol [12]. Although the effects of hepatic enzyme-inducing anti-epileptics, such as phenobarbital and carbamazepine are well established, the effect of valproic acid on lipid profile remains unclear [3,13,14]. Total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels were all increased in children on long-term therapy with carbamazepine or phenobarbital. On the other hand, some articles found no effect of valproic acid on plasma concentration of total cholesterol, high-density lipoprotein cholesterol, or its components, whereas others demonstrated significant changes in lipids, lipoproteins and apolipoproteins [3,4,15–17]. We did not observe any alterations in the concentrations of serum lipids during valproic acid treatment.

The most interesting finding in the study was increased intima media thickness of carotid artery in epileptic patients treated with valproic acid. Atherosclerosis is reversible with early detection. High resolution B mode ultrasonography is used as an early predictor of pre-clinic atherosclerosis. The changes observed in high resolution B mode ultrasonography include increase in intima media thickness, arterial stiffness and endothelial dysfunction at carotid artery. We also used high resolution B mode ultrasonography in our study. To our knowledge, this is the first study evaluating intima media thickness of carotid artery in epileptic children. There is only one study in adult epileptic patients and the investigators showed that intima media thickness of carotid artery significantly increased in the treated group of epileptics more than the untreated group and healthy control group [18]. Patients treated with carbamazepine demonstrated more increase in intima media thickness of carotid artery than those treated with valproic acid [18]. Since we did not find any increase in serum lipids in our study, the reason for increased in intima media thickness could not be alterations in serum lipid concentrations. Although we did not measure plasma lipoprotein (a) levels, some studies showed significant increase in lipoprotein (a) levels during valproic acid treatment [8,16,19]. It was reported that increased lipoprotein (a) levels were highly associated with atherosclerosis [20]. Valproic acid can also cause insulin resistance with hyperinsulinemia which may also lead to atherosclerosis [21]. On the other hand, erythrocyte lipid peroxidation increases while erythrocyte glutathione peroxidase and superoxide dismutase activities decrease during valproic acid treatment [22,23]. The change in oxidant–anti-oxidant status may also lead to the development of atherosclerosis. If valproic acid causes intima media thickness, this seems unrelated to the duration of treatment.

The other fact is that beside anti-epileptic treatment, epilepsy itself may also lead to development of early atherosclerosis. Hamed et al. showed that intima media thickness of the common carotid artery in untreated epileptic patients was higher than healthy control subjects [18]. In one study including pediatric epileptic patients, the authors showed that serum lipid peroxidation before starting anti-epileptic treatment was significantly higher when compared to healthy children [24]. This finding

Table 3

<table>
<thead>
<tr>
<th>Epilepsy group (n = 44)</th>
<th>Control group (n = 40)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Intima media thickness of the common carotid artery (mm)</td>
<td>0.480 ± 0.064 (0.35–0.63)</td>
<td>0.430 ± 0.063 (0.30–0.55)</td>
</tr>
</tbody>
</table>

Table 4

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<tr>
<th>Duration of valproic acid treatment</th>
<th>12–24 months</th>
<th>&gt;24 months</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Intima media thickness of the common carotid artery (mm)</td>
<td>0.486 ± 0.068</td>
<td>0.474 ± 0.060</td>
<td>0.611</td>
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Fig. 1. Intima media thickness versus age in control and epilepsy groups.


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suggests that epilepsy itself may also lead to increased intima media thickness by increasing lipid peroxidation.

In conclusion, this study indicates that pediatric epileptic patients have increased vulnerability to develop increased intima media thickness of common carotid artery. The reason for that may be epilepsy itself and/or valproic acid treatment. More prospective studies before and after anti-epileptic treatment are needed to confirm these findings.

References