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Evaluation ofserum free carnitine/acylcarnitine levels and left ventricular systolic functions in children with idiopathic epilepsy receiving valproic acid

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ABSTRACT

Objectives: In the study, the effect of valproic acid on serum free/acylcarnitine levels and left ventricular systolic function in pediatric patients with idiopathic epilepsy receiving valproic acid was investigated.
Patients and Methods: Patients receiving valproic acid treatment for six months between January 2012 and December 2012 were evaluated. Blood samples were obtained from the participants twice (pretreatment and the sixth month of treatment) and serum-free and acylcarnitine levels (from C2 to C18:1-OH) were measured using tandem mass spectrometry. Cardiac functions (ejection fraction, shortening fraction, cardiac output, left ventricular systolic and diastolic diameters, left atrial diameter, aortic diameter, cardiac output, and myocardial performance index) were evaluated by echocardiography simultaneously.
Results: A total of fourty patients, 23 female (57.5%) and 17 male (42.5%), with the diagnosis of idiopathic epilepsy and receiving valproic acid monotherapy were studied. Comparison of serum-free and acylcarnitine levels measured pretreatment and sixth month of treatment revealed a decrease in average C0 and C5:1 (respectively $p < 0.001$, $p = 0.013$) and an increase in C2, C3, C5-OH, C8:1 and C4-DC levels (respectively $p < 0.001$, $p < 0.001$, $p = 0.019$, $p = 0.013$, $p < 0.001$). Other serum acylcarnitine levels did not change significantly ($p > 0.05$). No difference was observed in concurrent echocardiographic measurements of left ventricular systolic function ($p > 0.05$).
Conclusion: The study demonstrated that valproic acid treatment results in low levels of free carnitine and changes in some acylcarnitine subgroups but has no influence on left ventricular systolic function.

1. Introduction

Valproic acid (VPA) is widely used in the treatment of partial and generalized seizures [1]. Although life-threatening and VPA-induced liver failure, Reye-like liver failure and hyperamoniemic encephalopathy have been rarely identified, VPA is often well tolerated [2].

Some studies in the literature have shown that the use of VPA in mono or poly treatment leads to reduction in blood carnitine levels [3–6]. Several mechanisms related to VPA-induced carnitine deficiency have been proposed in the literature. In fatty acid chain, VPA combines with carnitine and constitutes valproilcarnitine and is excreted from kidney and reduces carnitine storage in the body. VPA metabolites indirectly reduce alpha-ketoglutarate, butyrobetaine enzyme cofactor, and thus decreasing carnitine biosynthesis [7]. Valproic acid affects adversely tubular reabsorption of free carnitine and acylcarnitine [8,9]. It reduces the availability of valproil-coenzyme A (CoA) and valproil carnitine formation chain CoA and inhibits carnitine uptake at transport level. In addition, decreased free-CoA in mitochondria deteriorates the production of adenosine triphosphate (ATP) and beta-oxidation of fatty acid, and thus negatively affecting ATP-dependent membrane carnitine transport [10].

Carnitine (β -hydroxy-γ- trimethylaminobutyric acid) serves as a cofactor which is necessary for the transport of long chain fatty acid across the mitochondrial membrane for beta- oxidation. This process takes places through specific enzymes (carnitine palmitoyltransferase CPT-I and CPT-II) and shuttle system in mitochondrial membrane (carnitine acylcarnitine translocase). Long-chain fatty acids are transported across mitochondria membrane as carnitine esters activated by

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acyl coenzyme A synthase. Long chain acylcarnitine esters activated in carnitine esters with CPT-I are enclosed in the mitochondria through carnitine acylcarnitine translocase shuttle. Long chain acylcarnitine esters are transesterified into long-chain acylcarnitine and free CoA with CPT-II enzyme. At this stage, fatty acylcarnitine is oxidized and free CoA is reacted as pyruvate oxidation and ß –oxidation [11]. Carnitines, serving as a carrier, play a role in the oxidation of all metabolic fuels. Maintenance of cardiac function and production of ATP require fatty acid oxidation [12] and metabolic and contractile needs of myocardium are met with carnitine. Lipid storage myopathy, muscle weakness and left ventricular dysfunction are common consequences of carnitine deficiency syndromes [13]. In addition to its critical role in fatty acid metabolism, carnitine binds to acetyl groups in cytosol and regulates mitochondrial acetyl CoA / CoA ratio [14,15]. This reduces the intramitochondrial level of acetyl CoA and adversely affects inhibition of the pyruvate dehydrogenase, rate- limiting enzyme of glucose metabolism. Consequently, carnitine indirectly stimulates glucose oxidation and plays an important role in supplying ATP to myocardium [15].

Although it is known that valproic acid treatment may lead to carnitine deficiency and some toxic effects, its influence on myocardial function is not clear. To our knowledge, this is the first study investigating acylcarnitine levels and left ventricular systolic functions in epileptic children receiving valproic acid treatment.

2. Patients and methods

2.1. Patient selection

Patients s who were admitted to Ondokuz Mayıs University Faculty of Medicine, Pediatric Neurology outpatient clinic with the complaints of seizure and then diagnosed with idiopathic epilepsy between January 2012 and December 2012 were included in the study. All of the patients in our study were received valproic acid monotherapy and were not used any other antiepileptic drug during the study period. Two non-compliance patients and one whose medication was changed due to failure in seizure control were excluded from the study.

Exclusion criteria were following: 1) mental motor retardation; 2) liver and cardiac disease; 3) muscle weakness or elevated muscle enzyme ; 4) ketogenic and / or vegetarian diet; 5) endocrine disease (diabetes mellitus); 6) chronic gastroenteritis and/or other gastrointestinal disease ;7) suspected metabolic disease in physical examination and laboratory findings; 8) malnutrition and/or not orally fed ; 9) patients who were used any antiepileptic drugs including valproic acid before the diagnosis of epilepsy 10) patients who were used carnitine 11) patients who were received antibiotics containing pivalic acid during study and/or within at least 3 weeks before starting the study.

Epilepsy was classified according to The International League Against Epilepsy (ILAE) 1989 criteria, and the patients diagnosed with idiopathic generalized and focal epilepsy were included. Clinical and electroencephalographic characteristics were used for diagnosing idiopathic epilepsy. All of the patients had no underlying cause.

Pretreatment values of the patients were used as a control group and then compared with those obtained in the sixth months of the treatment.

2.2. Drug selection

The patients diagnosed with idiopathic generalized and focal epilepsy were initiated 10 mg/kg/day VPA treatment (divided into two equal doses) and the dose was increased to 20 mg/kg/day after a week.

2.3. Collection of blood samples

Blood samples were obtained from all patients before valproic acid treatment for complete blood count, serum electrolytes, aspartate amino transferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, creatine kinase (CK), glucose, ammonia and blood carnitine levels. In addition, this was repeated in the sixth month of valproic acid treatment to determine serum electrolytes, AST, ALT, BUN, creatinine, CK, glucose, ammonia, blood carnitine and VPA levels. Samples were taken after an overnight fast at least 10–12 h at 08:30 - 09:30 in the morning. Blood samples obtained in the sixth month of treatment for blood VPA and carnitine levels were taken 10 to 12 h after the last drug dose. For serum carnitine levels, venous blood samples were taken on Guthrie cards and stored in envelopes at + 4 °C so as to avoid light exposure.

2.4. Study of blood samples

Aspartate and alanine amino transferase, CK, fasting blood glucose and plasma ammonia levels were studied with Spectrophotometer using a Cobas Integra 2000 System device. Valproic acid levels were studied via immunoassay method using ADVIA Centaur CP device whereas free / acylcarnitine values were studied via Tandem Mass Spectrophotometer from samples taken on Guthrie cards.

2.5. Electrocardiographic examination

All patients underwent electrocardiogram (ECG) twice (pretreatment and sixth month of treatment). Electrocardiographic examinations were performed using a Cardifax device at recording speed of 25 mm/sec in 12 diversions. Heart rate and rhythm, QRS axis, PR- QRS - QT-QTc intervals and left ventricular hypertrophy were investigated.

2.6. Echocardiographic examination

All patients underwent echocardiographic (ECHO) twice (e pretreatment and sixth month of treatment) by the same researcher who is blind to the information about the clinical condition of the patient. Echocardiographic examination was performed in the supine position using a Hewlett-Packard device with 3 and 5 MHz probes. Systolic and diastolic left ventricular posterior wall thickness, interventricular septum thickness, left ventricular end-diastolic and end-systolic diameter, the aorta and left atrium diameter and cardiac output were measured in parasternal long-axis with M-mode echocardiography and left ventricular hypertrophy (LVH) and left ventricular dilatation has been investigated. Left ventricular ejection fraction (LVEF) and shortening fraction were calculated by the same method.

Myocardial performance index (MPI) of all patients is calculated simultaneously. For this purpose, pulsed wave doppler echocardiography (PWDE) techniques were used in Hewlett-Packard model device and cardiac time intervals were obtained. Myocardial performance index is calculated as numerical value by using cardiac time intervals. This numerical value is calculated as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time. All these measurements were calculated as left ventricular MPI.

2.7. Statistical analysis

Data analysis was performed using the Statistical package for the Social Sciences (SPSS, Inc., Chicago, IL, USA) version 15.0. Numeric variables were expressed as mean ± standard deviation, median and range. Non-parametric Kruskal-Wallis variance analysis was used for the non-normally distributed data. Correlation between paired variables was analyzed using Spearman's correlation analysis, Pearson correlation analysis and two proportion test. A p value < 0.05 was considered as statistically significant.

2.8. Ethical aspects

The study was performed according to the Declaration of Helsinki