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Original Article

The Short-Term Effects of Ketogenic Diet on Cardiac Ventricular Functions in Epileptic Children

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ABSTRACT

OBJECTIVE: Our primary aim was to determine the short-term effects of a ketogenic diet on cardiac ventricular function in patients with refractory epilepsy. **METHODS:** Thirty-eight drug-resistant epileptic patients who were treated with a ketogenic diet were enrolled in this prospective study. Echocardiography was performed on all patients before beginning the ketogenic diet and after the sixth month of therapy. Two-dimensional, M-mode, color flow, spectral Doppler, and pulsed-wave tissue Doppler imaging measurements were performed on all patients. **RESULTS:** The median age of the 32 patients was 45.5 months, and 22 (57.8%) of them were male. Body weight, height, and body mass index increased significantly at the sixth month of therapy when compared with baseline values ($P < 0.05$). Baseline variables assessed by conventional M-mode echocardiography showed no significant difference at month 6 ($P > 0.05$). Doppler flow indices of mitral annulus and tricuspid annulus velocity of patients at baseline and month 6 showed no significant differences ($P > 0.05$). Tricuspid annular E/A ratio was lower at month 6 ($P < 0.05$). Although mitral annulus tissue Doppler imaging studies showed no significant difference ($P > 0.05$), there was a decrease in Ea velocity and Ea/Aa ratio gathered from tricuspid annulus at month 6 compared with baseline ($P < 0.05$). **CONCLUSION:** A 6-month duration ketogenic diet does not impair left ventricular functions in children with refractory epilepsy; however, it may be associated with a right ventricular diastolic dysfunction.

Keywords: ketogenic diet, ventricular function, cardiac function, epilepsy, children

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Introduction

A ketogenic diet incorporates high-fat ratio with adequate protein and low carbohydrates and offers hope for improved seizure control in children with intractable epilepsy. Although a promising therapy option, a ketogenic diet has a number of side effects, including disturbances of metabolic, gastrointestinal, and renal functions. Known adverse effects include anorexia, constipation, renal stones, and dyslipidemia.[1-4] In a limited number of studies, several cardiac complications were reported including cardiac chamber enlargement in three patients with QT prolongation and sudden cardiac death in patients treated with a ketogenic diet.[5,6] There are reported cases of sudden cardiac death secondary to ketogenic diet-related selenium-deficiency cardiomyopathy.[7,8] In our previous study, we observed that a ketogenic diet of 6 months' duration has no significant effect on electrocardiography parameters, including P-wave duration, P-wave dispersion, maximum and minimum corrected QT interval, and QT dispersion in children.[9] However, prospective studies that evaluate

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cardiac ventricular systolic and diastolic functions in pediatric patients on ketogenic diet are lacking.

In this study, our primary aim was to determine the short-term effects of ketogenic diet on cardiac ventricular functions in patients with refractory epilepsy.

Materials and Methods

Study population

We prospectively enrolled 38 drug-resistant epileptic patients on a ketogenic diet between September 2012 and March 2014 from the pediatric neurology clinic at Behcet Uz Children's Research and Training Hospital, Izmir, Turkey. Patients older than one year of age with intractable epilepsy who were on the ketogenic diet for at least 6 months were included. Exclusion criteria were primary carnitine deficiency, selenium deficiency, dilated cardiomyopathy, ventricular failure, congenital heart disease, left ventricular hypertrophy, systemic hypertension, systemic or metabolic diseases affecting cardiac and vascular functions such as diabetes mellitus and obesity, corticosteroids or adrenocorticotropic hormone treatment, and evidence of persistent nonadherence to the ketogenic diet.

Ketogenic diet

All children were started on a standardized 3:1 ketogenic diet with a nonfasting gradual initiation protocol. Blood glucose and ketone concentrations were measured twice daily until blood ketone concentrations remained stabilized between 4 and 5 mmol/L. The diet ratio was adjusted according to blood ketone concentrations. All patients were given a multivitamin preparation from the beginning. Children were monitored at the first month after starting the diet and at every 3 months subsequently. At each visit, seizure frequency, adverse events, compliance with the diet, adherence, and the reason for ketogenic diet discontinuation were recorded. Before the initiation of ketogenic diet and at each visit, complete blood biochemistry, blood urea, serum creatinine, blood glucose, liver function tests (serum albumin, bilirubin, aspartate aminotransferase, and alanine aminotransferase), fasting serum lipid profile including low-density lipoprotein, high-density lipoprotein, total cholesterol and triglycerides, serum carnitine and selenium concentrations, and urine tests were performed.

Electrocardiography

Heart rate, maximum and minimum P-wave durations, P-wave dispersion, maximum and minimum corrected QT durations, and QT dispersion were manually measured from the 12-lead surface electrocardiographs. A standard 12-lead electrocardiograph (Nihon Kohden electrocardiograph, Cardiofax GEM, Model 9022K, Tokyo, Japan) was obtained simultaneously using a recorder set at 25 mm/second paper speed and calibration of 10 mV/mm in a comfortable supine position.

Echocardiographic examination

Each patient was examined with a Vivid S6 Echocardiography System (General Electric Healthcare, Milwaukee, WI) equipped with a M4S-RS broadband transducer (General Electric Healthcare Japan Corporation, Hino-shi, Tokyo) with a second harmonic capability.

Echocardiography was performed on all patients at the beginning of the ketogenic diet and after sixths month of therapy. Echocardiographic measurements were done using a Vivid S6 (General Electric Healthcare) with 4S-RS (1.7-4 MHz, General Electric Healthcare Japan Corporation) probe incorporating two-dimensional, color flow, spectral Doppler, and pulsed wave tissue Doppler imaging. Echocardiographic measurements were done while the patients were at rest and in supine position. Images were recorded digitally. Measurements were performed by a pediatric cardiologist. Conventional echocardiographic measurements were obtained according to the guidelines of the American Society of Echocardiography.[10]

Pulsed-wave tissue Doppler imaging studies

Pulsed-wave tissue Doppler imaging was performed using a special software package available on the Vivid S6 by adjusting the spectral pulsed Doppler signal filters to obtain a Nyquist limit of 15 to 20 cm/second and using the minimal optimal gain. High-frame-rate (>150 frames/s) images were acquired in the tissue Doppler mode. This method is capable of providing ventricular wall motion velocity measurements by positioning the sample volume at the lateral margin of the mitral and tricuspid valve annuli.[12] Care was taken to obtain an ultrasound beam parallel to the direction of the annular motion. Three consecutive images were recorded. The mean values of these measurements were used for statistical analysis. All recordings were made using a sweep speed of 100 mm/second, with a simultaneous electrocardiograph (lead II) at these locations and stored digitally for subsequent analysis.

Statistical analyses

Statistical analyses were performed using SPSS, release18.0 (SPSS, Chicago, IL, USA). The variables were checked to assess the distribution using graphical and analytical. We used mean ± standard deviation for normally distributed data and median (interquartile range) for normally distributed data and median for nonnormally distributed data. One-way analysis of variance was used to compare the means of normally distributed parameters among the groups. Homogeneity of variances was assessed with Levene test. Post hoc tests were performed using Tukey's method when an overall significance was observed. Kruskal-Wallis tests were conducted to compare not normally distributed variables among groups. Mann-Whitney *U* test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons. Significance for these analyses was set at $P < 0.05$.

Results

During the study period, ketogenic diet treatment was initiated in 52 children with refractory epilepsy; of these, 10 patients were excluded from the study because of cessation of the ketogenic diet because of a lack of seizure control and four patients because of poor compliance in undergoing all the examinations requested by the study schedule. A total of 38 patients (22 boys, 16 girls) with a median age of 45.5 months ranging from 13 to 158 months were included in the study. Of the 38 patients, six were diagnosed with hypoxic-ischemic encephalopathy, six with West syndrome, five with tuberous sclerosis, three with cortical dysplasia, three with Dravet syndrome, three with Lennox-Gastaut syndrome, two with glucose transporter 1 deficiency, one with myoclonic-astatic epilepsy, one with electrical status epilepticus in slow wave sleep, and one with malignant migrating epilepsy of infancy. Etiology could not be determined in five patients. All patients were taking antiepileptic drugs in combination (median, three drugs) including phenobarbital, valproic acid, carbamazepine, oxcarbazepine, levetiracetam, topiramate, benzodiazepines, clobazam, primidone, and zonisamide. The number of antiepileptic drugs was reduced as seizure control was achieved; the median drug number was two at the first and third months and one at the sixth month.

Table 1 presents age, height, body weight, body mass index, heart rate, and M-mode echocardiographic