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Original Article

The Effect of the Ketogenic Diet on the Vascular Structure and Functions in Children With Intractable Epilepsy

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ABSTRACT

OBJECTIVE: We aimed to determine the midterm effect of a ketogenic diet on serum lipid levels, carotid intima-media thickness, and the elastic properties of the carotid artery and the aorta in patients with intractable epilepsy. **METHODS:** A total of 52 children aged between 12 months and 18 years with intractable epilepsy who started the ketogenic diet from September 2014 to September 2015 were included into this prospective study. Carotid intima-media thickness and the elastic properties of the carotid artery and the aorta were assessed by echocardiography in all cases before beginning of the ketogenic diet and after at least 12 months on the ketogenic diet. **RESULTS:** Twenty-one patients at the third month and 25 patients at the first year of the ketogenic diet were seizure free. A reduction of greater than 90% in the seizure frequency was achieved in three patients at the sixth month and in five patients at the first year of the treatment. The serum levels of total cholesterol, low-density lipoprotein, and triglyceride were increased significantly at a median of 12.6 months (range: 12 to 13.5 months) of the ketogenic diet treatment, whereas serum levels of high-density lipoprotein did not change. Carotid intima-media thickness, aortic and carotid strain, the stiffness index, distensibility, and elastic modulus did not change after 12 months of the ketogenic diet therapy. **CONCLUSION:** Olive oil–based ketogenic diet appears to have no disturbing effect on the carotid intima-media thickness and the elastic properties of the aorta and the carotid artery in epileptic children, although it may be associated with increased concentrations of serum lipids.

Keywords: epilepsy, ketogenic diet, children, vascular function, carotid intima-media thickness

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Introduction

The ketogenic diet (KD) is a promising option for children with drug-resistant epilepsy. It is not a benign therapy, however, being associated with a number of side effects including disturbances of metabolic, gastrointestinal, and renal functions. On the other hand, its effects on vascular structure and functions have not been well defined and are controversial.[1-3] The KD is a high-fat, low-carbohydrate diet that aims to achieve a metabolic state called ketosis. In this state, the body cells burn fats instead of glucose for energy. Since the diet contains a high percentage of fat, it may lead to dyslipidemia, which is a primary risk factor for the development of atherosclerosis.[2,4-6] A number of echocardiography-derived reliable parameters and indexes for the assessment of vascular structural change have been identified. Carotid intima-media thickness (cIMT) and some measures assessing the elastic properties of the carotid artery and the aorta, such as strain, stiffness index, distensibility, and elastic modulus, have been used as useful predictors of subclinical atherosclerosis and cardiovascular diseases.[2,7]

We aimed to determine the midterm effect of KD on serum lipid levels, cIMT, and the elastic properties of the

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carotid artery and the aorta in 52 patients with intractable epilepsy who received a KD for at least 12 months.

Materials and Methods

Patient cohort

A total of 65 children aged between 12 months and 18 years with intractable epilepsy who started a KD at the pediatric neurology clinic from September 2014 to September 2015 were included in the study. Patients who had a systemic and/or metabolic disease that had deleterious effects on cardiovascular functions were excluded from the study. Thirteen patients discontinued the KD because of lack of seizure control in six patients, gastrointestinal intolerance in four, and lack of compliance in three, and they were also excluded from the study. Thus, data of 52 patients who received the KD for at least 12 months were analyzed. Intractable epilepsy was defined as failure of adequate trials of at least two tolerated, appropriately chosen and used antiepileptic drugs to achieve sustained seizure control. Parents or caregivers were asked not to give patients any vasoactive drugs or products containing caffeine for 12 hours before follow-up visits.

The ketogenic diet: definition and details

All patients were started on a KD consisting of a 3:1 ratio of fat to carbohydrates plus protein with a nonfasting gradual initiation protocol. The ratio was 1:1 for the first day, gradually increased to 3:1 on the third day, and then adjusted according to the blood ketone levels, which were measured twice daily until a stable serum concentration of ketone was established at the desired levels (4-5 mmol/L). The recipes were prepared taking the children's tastes and their families and cultural preferences into consideration. Olive oil was used as the major polyunsaturated fat source because it has been shown to have positive effects on cardiovascular functions and is a common product in the region where the study was conducted. The caloric intake was adjusted according to the patients' baseline weights and heights, the recommended daily caloric intake for their ideal body weights, and their physical activity levels.

Assessment of the carotid intima-media thickness

The cIMT is a reliable marker of generalized atherosclerosis.[8] Assessment of cIMT was performed according to the recommendations of Urbina et al.[7] The patients were allowed a resting period of 10 minutes before the ultrasonographic examination. Then bilateral carotid arteries were scanned longitudinally, while the patients' head turned 45° away from the examination side, using a Vivid S6 echocardiography system (General Electric's Healthcare, Milwaukee, WI) equipped with a high-frequency 12L-RS linear array scan head (General Electric's Healthcare, Japan Corporation, Hino-shi, Tokyo, Japan). Three images obtained from both sides of the head were stored for offline analyses. The cIMT was defined as the distance from the line between the echolucent lumen and the echogenic intima to the line between the echolucent media and the echogenic adventitia. The images were taken from the distal portion of the common carotid artery, 1-2 cm proximal to the carotid bulb. The mean of the cIMT values obtained from both carotid arteries were used for further analyses.

Assessment of the elastic properties of the carotid artery and the aorta

Blood pressure measurement was performed 5 minutes before the ultrasonographic evaluation by an experienced nurse who was blinded to the study. B-mode–guided M-mode images of the carotid artery and the ascending aorta were obtained using a Vivid S6 echocardiography system equipped with a high-frequency M4S-RS transducer with second harmonic capability (General Electric's Healthcare, Japan Corporation, Hino-shi, Tokyo, Japan). The ascending aorta diameter was obtained from 3 cm distal to the aortic valve on a parasternal long axis plane. The changing diameters of the aorta and the carotid artery throughout the cardiac cycle were measured offline on still frames by a pediatric cardiologist who was blinded to the patients' clinical status. The values were measured at the systole and diastole along averaged three consecutive cardiac cycles and used for further analyses. The Aortic and carotid strain, distensibility, stiffness index, and elastic modulus were calculated using a number of formulas presented previously.[7,9]

Follow-up protocol

Blood ketone and glucose levels were measured daily during the initial period and weekly thereafter by the children's parents or caregivers. Clinical examinations and laboratory investigations including concentrations of blood urea; serum creatinine; blood glucose; serum albumin; bilirubin; aspartate aminotransferase; alanine aminotransferase; fasting serum lipid profile, including low-density lipoprotein (LDL); high-density lipoprotein (HDL); total cholesterol and triglycerides; serum carnitine; and selenium, urine tests, electrocardiographic and echocardiographic examinations were performed at baseline and at 1, 3, 6, and 12 months of the KD. Seizure frequency, adverse events, compliance with the diet, and the reason for KD discontinuation were questioned at each visit. Patients who developed carnitine deficiency during the treatment were given carnitine supplementation. All patients received multivitamin supplements once a day during the duration of the KD.

Statistical analysis

SPSS 22.0 (IBM Corporation, Armonk, NY) was used to analyze the data. The Shapiro-Wilk test was performed to determine the conformity of the univariate data to normal distribution, and the Leneve test was conducted to ascertain variance homogeneity. Independent-samples T and Mann-Whitney U tests were carried out to compare the two independent groups. A paired sample T test was employed to calculate the difference between each before-and-after pair of measurements. Pearson χ^2 and Fisher exact tests were conducted to compare the categorical data. The quantitative data were expressed as mean ± S.D. and median range (minimum-maximum) values. The categorical values were stated in units of numbers (n) and percentages. The data were analyzed at a 95% confidence level and considered significant at a P value of less than 0.05.

Results

The mean age of patients was 60.1 ± 41.2 months (range: 13 months-19 years) at the beginning of the study. Demographic characteristics, heart rate, blood pressure, fasting serum lipid levels, and fasting glucose levels of the patients at baseline and at month 12 are shown in Table 1. Blood pressure levels and percentiles were within normal range at baseline and at month 12. Blood pressure levels at month 12 were not statistically different compared with baseline (Table 1). Of the 52 patients (27 male, 25 female) enrolled in the study, the initial diagnoses were hypoxic-ischemic encephalopathy in 15 patients, West syndrome in seven, tuberous sclerosis in six, Dravet syndrome in three, Lennox-Gastaut syndrome in two, cortical dysplasia in eight, glucose transporter type 1 deficiency in two, electrical status epilepticus in slow wave sleep in two, and Landau-Kleffner syndrome in one. Etiology could not be identified in six patients.

All patients were receiving antiepileptic medication, including valproic acid, phenobarbital, carbamazepine, oxcarbazepine, topiramate, levetiracetam, benzodiazepines, and zonisamide, at the beginning of the treatment. The number of epileptic drugs was reduced from a median of