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Original article

Does ketogenic diet have any negative effect on cardiac systolic and diastolic functions in children with intractable epilepsy?: One-year follow-up results

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Abstract

Objective: The ketogenic diet (KD) has been referred to as an "effective therapy with side effects" for children with intractable epilepsy. Among the most recognized adverse effects, there are cardiac conduction abnormalities, vascular and myocardial dysfunction. However, very limited and controversial data are available regarding the effects of the KD on cardiac functions. We sought to analyze the mid-term effect of ketogenic diet on cardiac functions in patients with intractable epilepsy who received a ketogenic diet for at least 12 months using conventional and relatively new imaging techniques.

Methods: This prospective study included 61 patients with intractable epilepsy who received ketogenic diet for at least 12 months. Clinical examinations, serum carnitine and selenium levels as well as electrocardiographic and echocardiographic examinations were scheduled prior to the procedure and at 1, 3, 6 and 12 months. We utilized two-dimensional, M-mode, colored Doppler, spectral Doppler and pulsed wave tissue Doppler imaging techniques to investigate ventricular systolic and diastolic functions of this subgroup of patients.

Results: In our study, there was no significant difference after 1 year of KD therapy compared to baseline values—except a significantly decreased A wave velocity—in terms of pulse wave Doppler echocardiographic measurements of the diastolic function. The tissue Doppler measurements obtained from the lateral wall of tricuspide and mitral annuli were not different at baseline and at month 12 of the treatment, as well.

Conclusion: The ketogenic diet appears to have no disturbing effect on ventricular functions in epileptic children in the midterm.

Keywords: Ketogenic diet; Epilepsy; Children; Systolic function; Diastolic function

1. Introduction

The ketogenic diet (KD) is a well-known effective treatment option in children with intractable epilepsy [1–4]. However it may be associated with many side effects, including gastrointestinal disturbances, dyslipidemia, electrolyte imbalance, hypoglycemia, infectious diseases, hepatitis, acute pancreatitis and persistent

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metabolic acidosis [2]. Theoretically, KD may disturb cardiovascular functions due to the dyslipidemia induced by high-fat diet. However very limited and conflicting data are available regarding the effects of the KD on cardiac functions [5–7,11,12,19]. In several reports, the KD was found to be associated with left ventricular dilation and systolic dysfunction, which seemed mostly to be related with selenium deficiency [5,11,12]. On the other hand, a recent report from our hospital has shown that the KD had no deleterious effect on systolic and diastolic ventricular functions of the left ventricle in patients with refractory epilepsy in the short term [6].

Ventricular systolic and diastolic functions can be accurately assessed echocardiographically using two-dimensional, M-mode, colored Doppler, spectral Doppler and, a recently introduced imaging modality called pulsed wave (PW) tissue Doppler imaging techniques [8–10]. In this study, we evaluated the mid-term effect of the ketogenic diet (KD) on cardiac functions using conventional and relatively new imaging techniques in 61 patients with intractable epilepsy, who received a ketogenic diet for at least 12 months.

2. Methods

2.1. Patient cohort

Between September 2014 and September 2015, a ketogenic diet therapy was initiated in 68 patients with intractable epilepsy. Seven patients were excluded from the study due to unsatisfactory seizure control in 3, gastrointestinal intolerance in 2 and a lack of compliance to the treatment and follow-up in 2. Thus, the final sample consisted of 61 patients who met the inclusion criteria for the study. The inclusion criteria were: (1) to be between 1 year and 18 years of age with intractable epilepsy and to have been receiving at least two antiepileptic medications for a minimum of 2 months prior to the initiation of the KD; and (2) to have a minimum of four seizures per month. Patients who already had a congenital or acquired heart disease, or systemic and/or metabolic disease, that had a deleterious effect on cardiovascular functions were excluded from the study.

2.2. The ketogenic diet: definition and details

The KD is a high-fat, low-carbohydrate diet that aims to achieve a metabolic state of ketosis. In this state, the body cells burn fats, instead of glucose for energy. All patients were placed on a KD consisting of a 3:1 ratio of fat to carbohydrates plus protein. All patients were on antiepileptic medication at the beginning of treatment, including valproic acid, phenobarbital, carbamazepine, oxcarbazepine, topiramate, levetiracetam, benzodiazepines, and zonisamide. The diet was initiated without a prior fasting period and with a lipid to non-lipid ratio of 1:1 for the first day. The ratio of fat was gradually increased to 3:1 on the third day and then adjusted according to the blood ketone levels, which were measured daily during the initial period and weekly thereafter by the children's parents or caregivers. Blood ketone measurements were performed until the serum concentration of ketone remained stable at the desired levels (4–5 mmol/L). Olive oil was the major polyunsaturated fat source of the diet since it has been shown to have positive effects on cardiovascular functions [13–15] and is a common product in the region where the study was conducted. The caloric intake was adjusted to the weight, height, and physical activity levels of the patients. Clinical examinations, serum carnitine, selenium levels as well as electrocardiographic and echocardiographic examinations were scheduled prior to the procedure and at 1, 3, 6 and 12 months. Seizure frequency, adverse events, and compliance with the diet, including the reason for KD discontinuation, were recorded at each visit. All patients received multivitamin supplements once a day for the duration of the study. Additionally, patients who had carnitine or selenium deficiency also received carnitine or selenium supplementation, respectively.

2.3. Examination of systolic and diastolic functions

We utilized two-dimensional, M-mode, colored Doppler, spectral Doppler and pulsed wave tissue Doppler imaging techniques to investigate ventricular systolic and diastolic functions in this subgroup of patients. For this purpose, a Vivid S6 echocardiography system (General Electric's Healthcare, Milwaukee, Wisconsin) equipped with a high-frequency M4S-RS transducer with a second harmonic capability (General Electric's Healthcare, Japan Corporation, Hino-shi, Tokyo) was employed. All echocardiographic examinations were performed following the guidelines of the American Society of Echocardiography and European Society of Cardiology [16–18]. Ejection fraction (EF), fractional shortening (FS), left ventricle end diastolic diameter (LVEDd), left ventricle end systolic diameter (LVEDs) and left ventricular mass index (LVMI) were obtained from M-mode echocardiographic measurements. Peak late atrial filling velocity (A), peak early left and right ventricle filling velocity (E) and E/A ratio (E/A), which are PW Doppler recordings of the mitral and tricuspide velocities that indicate the dynamics of ventricular filling and help to evaluate diastolic function [18], were acquired from spectral Doppler measurements. Late diastolic myocardial velocity (Am), early diastolic myocardial velocity (Em), Em/Am ratio (Em/Am), systolic myocardial velocity (Sm) and myocardial performance index (MPI), which are relatively new and better measures introduced for the assessment of ventricular systolic and diastolic functions [9], were