Seizure 23 (2014) 260–265

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

The impact of the ketogenic diet on arterial morphology and endothelial function in children and young adults with epilepsy: A case–control study

Giangennaro Coppola [a,*], Francesco Natale [b], Annarita Torino [a], Rosanna Capasso [c], Alfredo D'Aniello [a], Erica Pironti [a], Elena Santoro [a], Raffaele Calabrò [b], Alberto Verrotti [d]

[a] Child and Adolescent Neuropsychiatry, Medical School, University of Salerno, Italy
[b] Cardiology Department, Second University of Naples, Ospedale dei Colli, Naples, Italy
[c] Department of Biochemistry & Biophysics "F. Cedrangolo", Second University of Naples, Italy
[d] Alberto Verrotti, Department of Pediatrics, University of Perugia, Italy

ARTICLE INFO

Article history:
Received 14 May 2013
Received in revised form 3 December 2013
Accepted 4 December 2013

Keywords:
Ketogenic diet
Arterial morphology
Endothelial function
Carotid artery stiffness

ABSTRACT

Purpose: The present study aimed to assess the impact of the ketogenic diet on arterial morphology and endothelial function of the big vessels of the neck and on cardiac diastolic function, in a cohort of epileptic children and young adults treated with the ketogenic diet.
Methods: Patients were recruited based on the following inclusion criteria: (1) patients who were or had been on the ketogenic diet for a time period of at least six months. Each patient underwent measurement of carotid intima media thickness, carotid artery stiffness, echocardiography, and diastolic function assessment. Patients with drug resistant epilepsy, matched for number, age and sex and never treated with ketogenic diet, were recruited as controls.
Results: The population study was composed by 43 epilepsy patients (23 males), aged between 19 months and 31 years (mean 11 years). Twenty-three patients were or had been treated with ketogenic diet, and 20 had never been on it (control group). Subjects treated with the ketogenic diet had higher arterial stiffness parameters, including AIx and β-index and higher serum levels of cholesterol or triglycerides compared to those who had never been on the diet (control group) ($p < 0.001$).
Conclusions: Arterial stiffness is increased in children and young adults treated with the ketogenic diet, before the increase of the intima media thickness. This supports that arterial stiffness is an early marker of vascular damage.

1. Introduction

The ketogenic diet for the treatment of drug resistant epilepsy is composed of a high amount of lipids, an adequate intake of proteins and a very low percentage of carbohydrates.[1] It is well recognized that the ketogenic diet frequently leads to a wide range of adverse side effects, both early within the first days and late by the end of the first month and on.[2,3]

Among early and/or late adverse effects there is dyslipidemia, consisting of increased triglycerides and/or cholesterol,[3,4] which raises major concerns regarding the potential negative effects on macrocirculation, including the development of atheromasic plates, abnormalities in the vascular parietal elasticity mainly in the heart and brain, and a disorder of intraparenchymal microvascular resistance in the kidney.

Therefore, a relationship between the length of the ketogenic diet and the potential development of such cardiac and vascular adverse events, can be reasonably assumed. Studies on cardiovascular adverse effects arising major concerns upon the use of the ketogenic diet, are so far lacking. Recently, Patel et al.,[5] in a retrospective study on the long-term effects after the ketogenic diet had been discontinued in about one hundred patients, reported that lipids were normal at follow-up, despite most being abnormal while on the ketogenic diet.

On the other hand, Raitakari et al.,[6] found a positive relationship between the exposure to cardiovascular risk in pediatric age between 12 and 18 years, and an increased thickness of the intima and media layers of arterial vessels in adult age. These authors state indeed that exposure to cardiovascular risk factors early in life may induce changes in arteries that contribute to the development of atherosclerosis.

* Corresponding author. Tel.: +39 089 965014; Mobile: +39 3382747593.
E-mail address: gcoppola@unisa.it (G. Coppola).

1059-1311/$ – see front matter © 2013 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.seizure.2013.12.002

The present study aimed to assess the impact of the ketogenic diet on arterial morphology, specifically the development of atheromasic plates, on endothelial function of the big vessels of the neck as well as on cardiac diastolic function, in a cohort of children and young adults who were or had been fed the ketogenic diet.

2. Methods

All patients were followed as outpatients in the Epilepsy Unit of the Clinic of Child Neuropsychiatry of the Second University of Naples, and were recruited in the study in a time period comprised between January 2008 and October 2010.

Inclusion criteria were the following: (1) patients who were or had been on a classical (fat/protein + carbohydrate ratio 4:1) ketogenic diet for a time period of at least six months. This time interval was considered as the minimum treatment period to assess clinical responsiveness to the ketogenic diet. Exclusion criteria were: (1) patients with heart failure, systemic hypertension, diabetes mellitus, thyroid or parathyroid dysfunction; (2) poor compliance from parents/caregivers to participate in the study or from patients to undergo all examinations as requested by the study schedule. Patients with drug resistant epilepsy, matching for number, age and sex and never treated with ketogenic diet, were recruited as controls. The study protocol was approved by the local ethics committee; written informed consent was obtained by parents and, when possible, by patients.

Each patient underwent the following examinations on admission: (1) a blood sample was taken to evaluate white and red cell blood count, alanine and aspartate transaminases, gamma-glutamyltransferase, serum calcium, sodium and potassium, urea, serum creatinine, blood glucose, total and free acylcarnitine, total serum proteins, serum iron, and lipid profile (total cholesterol, high-density (HDL) and low-density (LDL) lipoprotein-cholesterol and triglycerides).

Age at study entry, length of diet treatment, number and type of anticonvulsant drugs, blood levels of each anticonvulsant drug, familial dyslipidemic risk factors, and maximal blood values of lipid profile throughout the diet, were the other parameters considered in all patients.

Serum levels of total cholesterol, triglycerides and lipoprotein fractions were considered in normal, borderline or high range, following Daniels and Greer,[7] In all subjects, anthropometric parameters (height and weight) were measured and body mass index (BMI) was calculated. Furthermore, each patient underwent on admission blood pressure assessment, measurement of carotid intima thickness (IMT), echotracking of the common carotid for the assessment of arterial stiffness, echocardiography and diastolic function assessment by means of standard methodology. Blood pressure was measured after a 5-min rest in supine position, by a digital oscillometric device (Omron model 705 IT; Omron Corporation – Healthcare, Kyoto, Japan) validated for use in children and adolescents. Brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated as the mean of three blood pressure measurements at rest. Pulse pressure (PP) was calculated as (SBP–DBP). Subjects with abnormal blood pressure values were consequently excluded from the study.

2.1. Measurement of carotid IMT

Measurement of carotid intima media thickness (IMT) and arterial stiffness high-resolution B-mode ultrasound images (Aloka alfa 10; Tokyo, Japan) with a 7–10 MHz linear array transducer were used to measure IMT. Carotid arteries were examined bilaterally in the areas of common carotid (1 cm proximal to the carotid bulb), carotid bifurcation (1 cm proximal to the flow divider) and internal carotid artery (1 cm distal to the flow divider). All measurements were determined manually on the far wall in longitudinal and transverse planes with anterior, lateral and posterior approaches.[8] Two different readings were acquired for each projection. From B-mode images, single video frames were selected for IMT measurements. Intima media thickness (IMT) was defined as the distance between lumen/intima and media/adventitia interfaces. The mean value was calculated for each parameter. Two independent readers, who were blinded with respect to patients' clinical and laboratory profile, made the measurements. The inter- and intra-observer variability was assessed for each measurement from all subjects participating in the study. The inter-observer variability of IMT measurements, evaluated by comparing the values obtained by two sets of scans performed by each reader, was 0 ± 03 mm (coefficient of variation $3 \pm 59\%$). The intra-observer variability was 0 ± 02 mm (coefficient of variation $2 \pm 15\%$).

2.2. Carotid artery stiffness

Subjects were studied after resting supine for 15 min in a temperature-controlled environment. The stiffness parameter β was calculated according to the formula: $\beta = \ln(Ps/Pd)/(Ds - Dd/Dd)$; Ep (pressure-strain elasticity modulus): $Ep = (Ps - Pd)/[(Ds - Dd)/Dd]$; AC (arterial compliance) ($AC = \pi(Ds \times Ds - Dd \times Dd)/[4(Ps - Pd)]$) where Ps and Pd are systolic and diastolic blood pressure in the brachial artery measured by an automated sphygmomanometer (Omron 705CP, Tokyo, Japan), and Ds and Dd are the maximal and minimal diameters of the right common carotid artery measured by e-tracking (ultrasonic high resolution wall tracking Aloka 10, Tokyo, Japan; 7.5 MHz linear array probe). Adjustable gates were positioned at the junctions of the intima and media, and diameter was calculated and displayed in real time as the difference between the displacement waveforms of the anterior and posterior walls. Measurements were taken as a mean of five beats; b was log transformed for analyses, because its distribution was skew. Arterial stiffness was automatically assessed at the common carotid artery 2 cm before the bifurcation by Echo-tracking software (ALOKA Prosound alpha 10 ultrasound machine, Mitakashi, Tokyo, Japan). Echo-tracking system implemented in the ultrasound machine allows accurate measurements of carotid diameter changes, based on radio frequencies (RF) signals, able to detect variations of the arterial diameters with a strictness of 0 ± 01 mm. Arterial pressure waveforms were derived noninvasively by echo tracking from change in carotid diameter over time, and calibrated using SBP and DBP (the software used needs to insert SBP and DBP values in the system of the machine for the calibration). Two sliders (tracking gates) were positioned on a 2D ultrasound image of the common carotid artery, at the front and back walls of the adventitia of the vessel. All acquisitions were synchronized with the electrocardiographic (ECG) signal. The main indices of arterial stiffness b-index, arterial compliance (AC), AIx, local PWV, and Young elastic modulus (Ep) were automatically calculated, as a mean of five beats, according to established formulas. Regarding the AIx (Augmentation Index), it must be noted that the arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. Waves are reflected from the periphery, mainly at branch points or sites of impedance mismatch. In elastic vessels, reflected wave tends to arrive back at the aortic root during diastole. In presence of stiff arteries, the reflected wave arrives back at the central arteries earlier, adding to the forward wave and augmenting the systolic pressure. This phenomenon can be quantified through the Augmentation Index (AIx) defined as the difference between the second and first systolic peaks expressed as a percentage of the pulse pressure.[9]

Arterial compliance (AC) is defined as the change in arterial blood volume for a given change in arterial blood pressure (BP). By simultaneously measuring the diameter of a blood vessel and the