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Ketogenic diet effects on neurobehavioral development of children with intractable epilepsy: A prospective study

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ABSTRACT

Objective: This study aimed to determine the impact of a ketogenic diet (KD) on neurobehavioral development when used to treat children with intractable epilepsy, confirming the efficacy of the KD, as well as the correlation between early electroencephalography (EEG) changes in the early stage with treatment efficacy.
Methods: We enrolled 42 children who were starting treatment for intractable epilepsy with the classic KD protocol. The total development quotient as well as the development quotients for adaptability, gross motor movements, fine motor movements, language, and individual–social interaction on the Gesell developmental scales were assessed before and after 3, 6, 12, and 18 months of KD treatment. The efficacy assessment was based on changes in seizure frequency after KD as recorded by the parents. We conducted 24-h video-EEG before and after 1 month of KD treatment.
Results: Developmental quotients of five energy regions in the Gesell developmental scales assessment were used to compare adaptability ($P1 = 0.000$), gross motor movements ($P2 = 0.010$), and fine motor movements ($P3 = 0.000$); the results showed significant differences. After KD treatment at different time points, 69.0%, 54.8%, 40.5%, and 33.3% patients, respectively, achieved a ≥50% reduction in seizure frequency. The reduction of epileptiform discharges in the awake state after 1 month of KD treatment correlated with the efficacy after 3 months of KD treatment.
Conclusions: Ketogenic diet treatment tends to be associated with improved neurobehavioral development, and more significant improvement can be obtained with prolonged treatment. The KD is safe and effective in treating children with intractable epilepsy. Early EEG changes correlate with clinical efficacy, to a certain degree.

1. Introduction

Intractable/refractory epilepsy refers to seizures that remain uncontrolled despite treatment with two or more first-line antiepileptic drugs (AEDs), administered serially as monotherapies or in combination, with the dose reaching the maximum tolerated dose for an appropriate treatment course [1]. Despite the advances in vagus nerve stimulation and other operations and the development and clinical use of new AEDs, 20%–30% of children eventually develop intractable epilepsy [2].

A ketogenic diet (KD) is a high-fat, adequate-protein, and low-carbohydrate diet administered under medical supervision, which tends to maintain chronic ketosis in the body as well as provide adequate protein and calories for growth and development [3]. The KD has become an important treatment for children with intractable epilepsy, and its effectiveness has been demonstrated in numerous studies [4–8]. A broad scope of cognitive deficits and behavioral abnormalities is associated with intractable epilepsy. However, few studies have investigated the effects of add-on therapy with KD on the neurobehavioral development. This study aimed to determine the impact of ketogenic diet (KD) on neurobehavioral development in treating children with intractable epilepsy, confirming the efficacy of KD, as well as the correlation between early electroencephalography (EEG) changes in the early stage with treatment efficacy.

2. Patients and methods

2.1. Sample

This study involved a total of 42 children with intractable epilepsy who visited the Rehabilitation Center of Cerebral Palsy Children in the Third Affiliated Hospital of Zhengzhou University between May 2012 and June 2013 and were treated with a KD (ketogenic products provided by Guangzhou Ketone Co. Ltd.). The inclusion criteria were as follows: (1) patients who were ineligible for surgical treatment and

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met the diagnostic criteria for intractable epilepsy [1]; (2) patients who were aged ≥6 months and ≤6 years; (3) patients whose average seizure frequency was >4 times per month; (4) patients without a history of treatment with a KD within the past 3 months; (5) children who were treated with a KD for at least 3 months; and (6) children whose family consented to treatment with a KD and provided written informed consent. The exclusion criteria were as follows: (1) those who were in the active stages of fever or infective diseases; (2) those with severe vomiting or severe digestive, cardiovascular, respiratory, hepatic, urinary, or metabolic diseases; and (3) those who could not receive the KD or had contraindications to treatment with a KD. This study was approved by the ethics committee of the Third Affiliated Hospital of Zhengzhou University (approval number: 2012-001).

2.2. Methods

2.2.1. KD protocols

After admission, all children underwent routine blood evaluations, liver-, kidney-, and heart-function tests, blood lipid level determination, urinary system color ultrasonography, 24-h video-electroencephalography (VEEG), electrocardiography, Gesell developmental scales assessments, and other related examinations. The types and doses of the original AEDs taken within 3 months before the KD treatment were maintained. All children eligible to receive KD treatment required hospitalization. Classic KD treatment protocols were used, that is, fasting in the beginning and a 4:1 ratio of fat to combined proteins and carbohydrates. After admission, the KD management group (consisting of physicians, nutritionists, and nurses) educated the children's families (on topics such as the use of a blood ketone meter, blood glucose meter, and electronic balance, the recording of seizure manifestations and frequency, and treatment precautions). Every day, the nurses supervised the families to continue the oral administration of the correct dose of the original AEDs on schedule, and the nutritionists supervised the diet of the children. Children were fasted for 24 h to 48 h, during which blood ketone and blood glucose levels were detected once every 6 h. Patients with blood glucose levels lower than 2.1 mmol/L were given orange juice and underwent continuous blood glucose level monitoring. Fasting was stopped when the blood ketone level reached 3 mmol/L, or the fasting had lasted for 48 h. After the beginning of KD treatment, blood ketone and blood glucose levels were detected once every 8 h, and the caloric requirement was calculated according to height, weight, and other standards in each child by the nutritionists. The planned total amount of calories in the KD was 80% of the amount required for healthy children of the same age, evenly divided into 3 daily portions. Children were given 1/3 of the total amount on the first day of KD treatment, 2/3 on the second day, and the total amount on the third day. If adverse reactions occurred or other special individual conditions were present during the adding-on process, the add-on speed was adjusted. The hospital observation period ranged from 7 to 10 days, during which adverse reactions, seizure frequency, seizure severity, duration, etc. were recorded in detail. During KD treatment, children were given supplements of the appropriate amounts of potassium citrate and various types of vitamins and minerals according to their specific circumstances.

2.2.2. VEEG

We performed 24-h VEEG in an environment of quiet, soft lighting, and suitable temperature, including awake, drowsy, and sleeping states. Electrodes were placed according to the International 10–20 system, in which the electrode in the earlobe was considered as the reference electrode, with 19 leads. A bipolar lead was applied as the record electrode. When the recording was started, the children who could cooperate under physician supervision with hyperventilation by blowing paper, flash stimulation of 1–20 Hz, and regular tracings with open and closed eyes. For those children who were unable to cooperate background rhythms were obtained by the physician covering the patients' eyes when necessary.

2.2.3. Follow-up

After discharge, data on the children's seizures and diet (seizure time, manifestation, frequency, duration, KD conditions, and adverse reactions) were recorded by their families. The urine ketone level was detected daily, and blood ketone and blood glucose levels were detected once a week. The nutritionists performed a weekly telephone follow-up of the parameters specified above and adjusted the diet. Children were required to attend outpatient visits and undergo repeat tests for liver and kidney functions, blood glucose levels, and urinary system color ultrasonography at 1, 2, 3, 6, 12, and 18 months of KD treatment. They underwent 24-h VEEG before the treatment and after 1 month of the treatment. The Gesell developmental scales scores were repeated after 3, 6, 12, and 18 months of KD treatment. The results of the 24-h VEEG and Gesell developmental scales assessments before and after the treatment were analyzed by physicians with 10 and 13 years of experience in electroencephalographic and Gesell developmental scales assessments, respectively.

2.3. Efficacy assessment

Assessment of neurobehavioral development was also performed. The total development quotient as well as the development quotients for adaptability, gross motor movements, fine motor movements, language, and individual–social interaction on the Gesell developmental scales were determined before and after 3, 6, 12, and 18 months of KD treatment. Improvements were observed in each quotient after KD treatment. The total development quotient (DQ) was divided into 6 grades: normal (DQ > 85), boundary situation (76 ≤ DQ ≤ 85), mild growth retardation (55 ≤ DQ ≤ 75), moderate growth retardation (40 ≤ DQ ≤ 54), severe growth retardation (25 ≤ DQ ≤ 39), and extremely severe growth retardation (DQ < 25). An improvement of ≥1 grade in the total development quotient was considered to indicate improvement in neurobehavioral development.

Reduction in clinical seizure frequency was assessed by determining the Engel grade [9] at 3, 6, 12, and 18 months of KD treatment: grade I (no seizures): complete control of seizures; grade II (significant effect): ≥75% reduction in seizure frequency; grade III (effectiveness): ≥50% reduction in seizure frequency; and grade IV (ineffectiveness): <50% reduction in seizure frequency. The total efficiency was defined as the number of patients with favorable results (no seizures + significant effectiveness + effectiveness) divided by the total number of patients and multiplied by 100%.

We also analyzed the correlation of changes in the epileptiform discharges index corresponding to the awake and sleeping states on 24-h VEEG before and after 1 month of KD with clinical efficacy after 3 months of KD treatment. The epileptiform discharge indexes at 1 h after the children woke up and 1 h after they went to sleep were calculated (the total time of epileptiform wave discharge(s) / total observation time × 100%). The onset of sleep was defined as the disappearance of occipital brain waves or falling asleep and closing the eyes. Epileptiform discharges within 30 min of each clinical seizure were excluded to avoid changes due to the seizure. The EEG was performed before and after KD treatment, at the same time of day as much as possible to reduce the effects of circadian rhythms and AED concentrations on epileptiform activity. Effective KD treatment was defined as a ≥50% reduction in clinical seizure frequency after 3, 6, 12, or 18 months of KD treatment; a reduction of <50% indicated ineffective treatment.

2.4. Statistical analysis

Statistical analyses were performed using SPSS 17.0 software. Count data were expressed as the number of cases (%), and measurement data