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Original Article

Can we predict efficacy of the ketogenic diet in children with refractory epilepsy?

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ABSTRACT

Background: The ketogenic diet (KD) can be effective in reducing seizures in children. Predictors of success have not been identified yet.

Aims: To evaluate efficacy of KD treatment and to search for child- or diet-related factors that can predict its efficacy at 12 months follow-up. In addition we wish to determine the usefulness of a 3-month KD trial period.

Methods: Single center retrospective study in a university paediatric hospital of children with refractory epilepsy in which the KD had been initiated. Patient and diet characteristics as well as seizure reduction data were obtained from medical records and parental review. Efficacy of the KD was defined as $\geq$ 50% seizure reduction. Variables were evaluated in their relation to a successful treatment at three and 12 months after diet initiation.

Results: During a 9.5-year period, the KD was initiated in 59 children with refractory epilepsy. Twenty-four children were still on the KD after 12 months, and 21 experienced $\geq$50% seizure reduction. Success of the KD at three months was significantly related to a successful response to KD treatment at 12 months ($p < 0.001$).

Conclusions: The KD can be an effective treatment in reducing seizures in children with refractory epilepsy. No significant relationships between variables and efficacy at 12 months were revealed. Children with a successful response at 3 months were significantly more likely to achieve success at 12 months of KD treatment.

1. Introduction

Worldwide, many children with epilepsy still suffer from seizures despite optimal treatment with anti-epileptic drugs (AEDs). The ketogenic diet (KD) is a high-fat, low-carbohydrate, adequate protein diet developed in the 1920s for the treatment of refractory epilepsy in children.[1] The exact mechanisms of the diets antiepileptic effects remain unclear,

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but it is thought to mimic the biochemical response to starvation providing ketones as an alternative fuel for the brain.[1] The three main types of diet are the classical diet, which includes mainly long-chain triglycerides (LCT), the medium chain triglyceride (MCT) diet and the modified Atkins diet.[2,3] These diets are comparable in efficacy and tolerability.[3] Various studies showed an efficacy rate in the range of 27–62% at three months after diet initiation, with success being defined as ≥ 50% seizure reduction.[4] Reported efficacy rates at 12 months range between 9 and 83%.[5]

The KD became less popular as a treatment option due to development of AEDs.[6] However, in a substantial amount of children (20–30%) epilepsy remains refractory.[7] These children are still in need of other treatment options. Therefore the KD has gained renewed interest in the past two decades.[6]

In patients with glucose transporter type1 (GLUT-1) and pyruvate dehydrogenase complex (PDC) deficiencies KD is first choice of treatment.[8,9] Treatment with the KD is compliance demanding and requires a high degree of medical and dietetic monitoring because of its side effects and restrictiveness. Therefore predictors of success are needed. To date, no predictors have been identified that can reliably indicate treatment success 12 months after KD initiation. Predictors of success will help to identify those children most likely to benefit from the diet. In a previous study a three-month period has been determined as a reliable period to evaluate the effect of the KD and to decide whether to continue or stop the treatment.[6]

In our study, we evaluated the results of children in which the KD has been initiated at the Sophia Children's Hospital and searched for child and diet related factors predicting a successful treatment, defined as ≥ 50% seizure reduction after 12 months of treatment. In addition we studied the reliability of a three-month period as a useful predictor for long-term success of the treatment.

2. Materials and methods

2.1. Patients

Since 2001, the Sophia Children's Hospital provides the KD as a treatment option for children with refractory seizures. Refractory epilepsy is defined by inadequate control of seizures despite optimal treatment with a minimum of 2 AEDs.[10] In 2008 a multidisciplinary outpatient clinic was introduced to monitor the patients in a structured and intensive manner.

Patient and diet characteristics as well as data on seizure reduction were retrospectively obtained using medical records. Each patient's seizure status was reviewed at baseline and 3, 6, 9 and 12 months after diet initiation.

2.2. Outcome

Seizure reduction was classified into 4 categories: 100% seizure reduction, 90–100% seizure reduction, 50–90% seizure reduction and <50% seizure reduction. Success was defined as ≥ 50% seizure reduction.

2.3. Variables

Variables evaluated with respect to their possible predictive value for a successful treatment outcome at 12 months were: gender, age at epilepsy onset, age at diet initiation, time elapsed between epilepsy onset and diet initiation, success of the KD at 3 months follow-up and number of AEDs used before diet initiation.

To classify the epilepsy, we used the International League against Epilepsy (ILAE) Proposal for Revised Terminology of Organization of Seizures and Epilepsies 2010[11]: seizure type (generalised, focal, unknown), aetiology (genetic, structural-metabolic, unknown) and electroclinical syndromes (electroclinical syndrome, nonsyndromic epilepsy). We also divided the types of epilepsy in one or multiple seizure types. Multiple seizure types could be either several generalised or focal seizure types or a combination of generalised and focal seizures or infantile spasms.

2.4. Statistical analysis

Findings were analysed using SPSS Statistics 20.0. The Pearson Chi-square test, the Fisher's exact test and the Fisher-Freeman-Halton test were used when appropriate. A p-value below 0.05 was considered significant.

3. Results

3.1. Demographic and clinical characteristics

From May 2000 to July 2009, the KD had been initiated in 59 patients (38 male, 21 female) with refractory epilepsy at the Sophia's Children's Hospital. End date of follow-up was November 30, 2010.

Average age at seizure onset was 1.8 years (range: 1 day–15.4 years). Mean time elapsed between epilepsy onset and initiation of the KD was 2.6 years (range: 11 days–9.4 years). Mean age at diet initiation was 4.3 years (range: 1 month–15.6 years). Average duration of KD treatment was 10.5 months (range: 6 days–4.7 years). Children had received an average of 6.2 AEDs prior to treatment with the KD (range: 2–10 AEDs).

In our study population, 26 children were treated with the classical KD, 20 children were treated with the MCT version of the KD and 13 children started the combination diet of LCT/MCT. The version of the KD used was tailor-made: based on age, food choice and eating habits.

In 36 children the predominant seizure type was generalised, in five children it was focal and in 18 children seizures were categorized as 'unknown'. Nineteen children had only one seizure type and 40 children had multiple seizure types. Eleven children had a genetic cause of their epilepsy, in 20 children the epilepsy was caused by a structural or metabolic condition or disease and in 28 children the nature of the underlying cause was unknown (Table 1). In 20 children an electroclinical syndrome was found before diet initiation; 13 children had West syndrome, 6 children had Lennox Gastaut syndrome, and one child had Landau Kleffner syndrome (Table 2).