Epilepsy Research 116 (2015) 53–58

Contents lists available at www.sciencedirect.com

Epilepsy Research

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

The ketogenic diet in infants – Advantages of early use

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ARTICLE INFO

Article history:
Received 25 March 2015
Received in revised form 8 June 2015
Accepted 23 June 2015
Available online 9 July 2015

Keywords:
Ketogenic diet
Epilepsy
Infants
Liquid formula
Infantile spasms

ABSTRACT

Objective: To evaluate the efficacy and safety of the ketogenic diet (KD) in infants (<1.5 years of age) compared with older children.
Methods: Patients with complete follow-up data of ≥3 months after initiation of the KD were analyzed retrospectively. Infants <1.5 years at initiation of the KD (Group A) were compared with children >1.5 years (Group B).
Results: 127 children were screened, 115 (Group A: 58/Group B: 57) were included. There were no significant differences between groups with respect to responder rates (63.8% vs. 57.9% at 3 months), but more infants became seizure free (34.5% vs. 19% at 3 months; 32.7% vs. 17.5% at 6 and 12 months). This result remained stable also after termination of the KD (30.6% vs. 3.9% at last follow-up) ($p = 0.000$). Looking at infants <9 months of age separately ($n = 42$), this result was even stronger with significantly more infants being seizure free at 6 and at 12 months ($p = 0.005$, $p = 0.014$, respectively). In addition, a significantly higher number of infants remained seizure free in the long-term ($p = 0.001$).

No group differences between infants and children with respect to safety were observed. Overall 52/115 patients (45.21%) reported side effects, but withdrawal of the KD was only necessary in one infant. Acceptance of the KD was better in infants compared with children at 3 months (0 vs. 14, $p = 0.000$), but became difficult when solid food was introduced (16 vs. 14; n.s.).
Significance: According to our results, the KD is highly effective and well tolerated in infants with epilepsy. Seizure freedom is more often achieved and maintained in infants. Acceptance of the diet is better before the introduction of solid food. Therefore, we recommend the early use of the KD during the course of epilepsy.

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1. Introduction

The ketogenic diet (KD) is a high-fat, low-carbohydrate, and adequate-protein diet well-established as treatment option for drug resistant childhood epilepsies (Freeman et al., 2007).

Using the KD early after less than three antiepileptic drug (AED) trials has been found to be a positive predictor for efficacy (Dressler et al., 2010; Freeman et al., 2009; Kossoff et al., 2008b).

In the past, neonates and infants were infrequently treated with the KD, as they were considered to show difficulties in maintaining ketosis on the hand and meeting protein and energy requirements on the other (Nordli et al., 2001).

However, neonates and infants have shown metabolic advantages compared with adults with respect to the utilization of ketone bodies. After birth, the newborn is provided with energy by its own glycogen stores, as well as by lactate (Hellmann et al., 1982; Medina, 1985). When suckling sets in, plasma ketone bodies increase rapidly (Nehlig et al., 1991). The ability to metabolize ketone bodies is six-fold higher in this period compared to adults (Cremer et al., 1976; Hawkins et al., 1971).

Moreover, it has been demonstrated that ketone bodies play a crucial role in myelination, as they are transformed into sterols and fatty acids in the brain (Edmond, 1974; Edmond et al., 1985) during the 3rd trimester of pregnancy and throughout the first year of life, when proliferation and myelination are most active (Davison and Dobbing, 1966). In addition, nutrition in infants causes high

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http://dx.doi.org/10.1016/j.eplepsyres.2015.06.015
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amounts of plasma ketone levels (Kraus et al., 1974), especially when breast-fed (Lucas et al., 1981).

In a recently published expert consensus statement introduction of the KD in infants was recommended only after failure of two AEDs (Kossoff et al., 2009). However, efficacy was significantly higher in fluid-fed infants (with ≥90% seizure reduction observed in 59% compared with only 27%) than in solid-fed children (Kossoff et al., 2008b), data on complete seizure freedom have not been reported.

During infancy, only seizure freedom safeguards psychomotor development and it has recently been demonstrated that even in critically ill children a higher seizure burden predicts further neurological decline, independent of the primary disease or etiology (Payne et al., 2014).

For this reason not only seizure reduction ≥50%, but early seizure freedom is the primary objective of seizure control.

Consequently, the principal aim of this retrospective single center study was to evaluate the efficacy of the early use of the KD in infants below 1.5 years of age compared to older children. Special emphasis was set on seizure freedom. Second aim was to assess safety and compliance issues.

2. Methods

2.1. Patients and follow-up

Clinical charts of all children treated with the KD at the Medical University Vienna, Department of Pediatrics from March 1999 to April 2014 were reviewed. Included were all children with complete clinical data (i.e. detailed documentation of seizure frequencies, enteral feeding protocols and side effects) and observation periods of at least 3 months after initiation of the KD. Data for children remaining on the KD included follow-up visits at 3, 6, 12 months and >12 months (last follow-up) after initiation of the KD. Long-term adherence to the KD ("retention") and seizure relapse rates both during and after termination (end of treatment) of the KD were evaluated.

2.2. Outcome parameters

For the assessment of efficacy data from parental seizure diaries were collected at each visit, and EEG was recorded when indicated for epilepsy syndrome and disease course.

Seizure frequency three months before KD initiation was defined as "baseline". Treatment response was defined as the absolute reduction in seizure frequency of ≥50% at follow-up, compared to baseline.

Safety was evaluated using standardized routine medical examination, parental interviews for efficacy, parental side effect questionnaires, and laboratory assessments including blood analysis (complete blood count, electrolytes, serum liver and kidney profile, fastin lipid profile, serum acylcarnitne, beta-hydroxybutyrate) and urine analysis as well as abdominal ultrasound two times per year according to the international guidelines (Kossoff et al., 2009).

At each visit, a nutritional assessment was performed by a registered dietician.

For compliance percentages of drop-outs were calculated and parental food protocols including eating volumes and acceptance of recipes were collected and evaluated.

2.3. Implementation of the diet

At our center, the KD is introduced and maintained according to the Johns Hopkins protocol (Kossoff et al., 2009) without fasting and fluid restriction. The KD is introduced as second line treatment as proposed in literature (Pellock et al., 2010), however introduced earlier when parents preferred to consider the diet earlier. The ketogenic ratio in infants during the first year of life is usually 3:1 or 2.5:1 (target plasma ketone levels <5 mmol/l) and the amount of protein is calculated as required for age according to the dietary reference intakes for Germany, Austria and Switzerland (Deutsche Gesellschaft für Ernährung (DGE) et al., 2015), in older children the ketogenic ratio used is 4:1.

An interdisciplinary "keto-team" (pediatric epileptologist, dietician, pediatric epilepsy nurse) introduces the KD on an inpatient basis and performs all follow-up visits according to patients' needs. Details have been published recently (Dressler et al., 2010).

2.4. Data and statistical analysis

Finally, the influence of clinical variables on outcome – i.e. etiology, epilepsy syndrome, duration of epilepsy and number of AED trials prior to the initiation of the KD – was investigated.

For data analysis, patients were divided into two groups according to age:

Group A included all infants <1.5 years of age (starting the diet on a ketogenic formula).

Group B included all children >1.5 years of age (starting the diet on solid food).

An additional subgroup analysis for efficacy was performed looking at the group of infants below 9 months of age.

Statistical analysis was performed using the IBM Statistical Package for Social Science (SPSS Statistics Version 21). Descriptive statistics (mean, minimum, maximum, standard deviation, and median – when appropriate) were used. Student's *t*-test was applied for parametric data, Pearson's chi-square and Fisher exact test for all non-parametric data, respectively. The significance level was set at $p \leq 0.05$.

3. Results

3.1. Patients' characteristics

From March 1999 to April 2014, 127 children were treated with the KD at our center. Three children in whom the observation period was less than three months at study initiation were excluded. Nine further children were excluded as they dropped out during the first days after initiation of the KD due to food refusal and/or incompliance of caregivers.

Follow-up data from 115 children (56 males) were finally analyzed: The KD was started at the classic 4:1 ratio in 36 children (31.3%), at a 3:1 ratio in 53 (46.1%), at a 3.5:1 ratio in 6 (5.2%), at a 2.5:1 ratio in 17 (14.8%), and at a 2:1 ratio in 3 (2.6%).

The mean age at initiation of the KD was 2.86 years ± 3.1 (min. 0.0–max. 16.8). 58/115 (50%) of the children were <1.5 years at initiation of the KD (Group A). 57/115 children were >1.5 years at initiation of the KD (Group B).

The mean duration of epilepsy prior to the initiation of the KD (treatment lag) was 1.84 years ± 2.34 (min. 0.00–max. 13.34), and the number of AEDs used before initiation of the KD was mean 4.02 ± 2.85 (min. 0–max. 13). For Group differences see Fig. 1 and Table 4.

3.2. Efficacy (Fig. 1 and Table 1A/1B)

At three months follow-up (Table 1A), 61% were responders, 27% were seizure free. There was no significant difference between infants and older children with respect to responder rates (63.8% vs. 57.9%), but more infants (Group A) became seizure free (34.5% vs. 19.2%) ($p = 0.067$).

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