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Effects of ketogenic diet on epileptiform activity in children with therapy resistant epilepsy

Tove Hallböök[a,*], **Sven Köhler**[b], **Ingmar Rosén**[b], **Johan Lundgren**[a]

[a] *Department of Clinical Sciences, Division of Paediatrics, University Hospital, SE-221 85 Lund, Sweden*
[b] *Department of Clinical Sciences, Division of Clinical Neurophysiology, University Hospital, Lund, Sweden*

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Summary
Purpose: The purpose was to quantify changes of epileptiform activity during ketogenic diet (KD) treatment in children with therapy resistant epilepsy, and evaluate how these changes are related to activity stage and to clinical effects on seizure frequency, seizure severity, attentional behaviour, quality of life (QOL), and beta-hydroxybutyrate (βOHb).
Methods: Eighteen children were investigated with 24 h ambulatory EEG monitoring 1 week prior to KD initiation and, after 3 months of KD treatment. Epileptiform activity was evaluated by automated spike detection. This data was compared with data presented in a previous study published in *Epilepsia* 2006, on sleep structure and different activity stages, clinical data on seizure frequency, seizure severity, QOL and attentional behaviour on the same children [Hallbook, T., Lundgren, J., Rosén, I., 2007. Ketogenic diet improves sleep quality in children with therapy resistant epilepsy. Epilepsia 48, 59—65].
Results: After 3 months of KD treatment the number of interictal epileptiform discharges (IEDs) was significantly reduced ($p < 0.001$). When considering the four activity stages separately, the reduction was significant during non-rapid eye movement sleep stage 2, slow wave sleep (SWS) and rapid eye movement (REM) sleep ($p = 0.001$, 0.001, 0.002), and not significantly so during awake ($p = 0.07$). Beta-hydroxybutyrate was significantly increased ($p < 0.001$). There was a significant correlation between the reduction in IEDs and clinical seizures (Spearman $r = 0.6$, $p = 0.005$) and between improvement in attentional behaviour and the increase in βOHb (Spearman $r = 0.5$, $p = 0.03$). There was no significant correlation between changes in attentional behaviour and IEDs or clinical seizures.
Conclusion: This study shows that KD reduces the number of IEDs, especially during sleep. It shows a correlation between reduction in epileptiform activity and clinical seizures. There were no correlations between reduction in epileptiform activity and clinical seizures and improvement in QOL or attention. The increase in βOHb correlated with improvement in attention.

Introduction

Ketogenic diet (KD) is a high-fat, low-carbohydrate and low-protein diet. It has been used for childhood therapy resistant

* Corresponding author.
E-mail address: tove.hallbook@skane.se (T. Hallböök).

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epilepsy since the 1920s. KD was developed to mimic the ketotic state of starvation (Geyelin, 1921; Wilder, 1921). A standard approach to KD treatment includes a 2-year diet period with a 6—12 months wean (Freeman et al., 1994). Fasting and fall in blood glucose reduces plasma insulin production and stimulates lipolysis and production of fatty acids. Fasting is also up-regulating the MCT-1, monocarboxylic transport system of ketone bodies to the brain. Ketone bodies can pass directly into the neuronal mitochondria. Once in the mitochondria, beta-hydroxybutyrate (βOHb) is converted to acetoacetate and acetoacetate-CoA for ATP production in the tricarboxylic acid cycle. Although no class I and II studies have been published concerning efficacy and safety, several studies present more than 50% reduction in seizure frequency in at least 50% of children with therapy resistant epilepsy (Anonymous, 1989; Freeman et al., 1998; Henderson, 2006; Keene, 2006; Lefevre and Aronson, 2000). The reported improvement in attention seems to be unrelated to the level of attained seizure control (Murphy and Burnham, 2006; Pulsifer et al., 2001). A number of previous studies have used animal models to examine the anticonvulsant effects of the KD (Bough et al., 2003, 2006; Hori et al., 1997; Likhodii and Burnham, 2003; Likhodii et al., 2003; Nylen et al., 2006; Thavendiranathan et al., 2003). As far as we know, no previous studies evaluating effects of KD on interictal epileptiform activity have been conducted.

The purpose of this study was to quantify interictal epileptiform activity following KD in children with therapy resistant epilepsy and to correlate possible alterations with different activity stages and changes in clinic effects on seizure frequency, seizure severity, QOL, and attention. Clinic effects on seizure frequency, seizure severity, QOL, and attention was also correlated with changes in βOHb.

Methods

Subjects

Eighteen children (nine boys and nine girls) aged 2—15 years (median 7.5 years) with the diagnosis of therapy resistant epilepsy with developmental impairment, and absence of non-epileptic seizures or specific sleep disorders were started on KD.

Ketogenic diet

All children were admitted to the hospital and started gradually on the diet following a 12-h out-patient fast. The children were started on the classical KD. Fifteen received a 4:1 and, three a 3.5:1 ratio implying 4 g or 3.5 g of fat to 1 g of combined protein and carbohydrates. Sixteen children were kept stable and two changed from ratio 4:1 to 3.5:1 during the 3 months because of nausea and problems with tolerance. The children also received the recommended daily intake of vitamins and minerals and were supplemented with calcium, magnesium, phosphorous, potassium and carnitine. The children were closely monitored to exclude intake of extra carbohydrates. In two children the diet was introduced via a gastrostomy tube, using Ketocal and a soy milk-based standard ketogenic formula.

EEG monitoring and spike detection

Eighteen children were investigated with 24 h EEG monitoring 1 week prior to KD initiation and, after 3 months of KD treatment. The recordings were ambulatory with the children in their natural surroundings. Meals, naps, other activities, time of sleep and seizure events were registered in a diary. Via the Embla A10 Flaga-Medcare digital data recorder, using sampling rate 200 Hz with 16 bits resolution, data were recorded on a PC memory flash card. EEG was recorded with a standard ambulatory montage, with 11 scalp electrodes and a referential electrode (F3, F4, C3, C4, T3, T4, P3, P4, O1, O2, Cz, Ref.) according to the 10—20 International System. The digitalized data were converted to Nervus Tauragreining EEG format (Valor format). The epileptiform activity was counted in comparable assessment periods according to time of day and activity stage. The assessment periods were the same for all children except in three children where the periods were selected, never more then 30 min, earlier or later than stipulated because of movement artefacts. Seizure events or disturbances in the recordings due to movement artefacts or technical problems were not selected. In one child (#11) selected channels with continuous artefacts were excluded. Because of fragmented and scattered daytime sleep the periods of sleep during daytime were not selected. The spike counting was based on automatic spike detection, Persyst® EEG Suite Spike Detector system version 01-26-2006. In an earlier article, a single blind pilot study was performed comparing visual spike detection and the Persyst® EEG Suite Automatic Spike Detector system (Hallbook et al., 2005). The automatic spike detection was performed in its most sensitive setting. All events were visually evaluated and edited for false detections. The investigation was blinded for the patient's clinical data and order of investigation, baseline or treatment (Hallbook et al., 2005; Wilson et al., 1999).

Monitoring

Data on sleep structure and different activity stages from polysomnographic recordings, clinical data on QOL, seizure frequency, seizure severity scored with the National Hospital Seizure Severity Scale (NHS3), and attentional behaviour assessed with Ponsford and Kinsella's visual analogue rating scale on these children, are analyzed in a previous study published in *Epilepsia* 2006 (Hallbook et al., 2007). Fasting (morning) βOHb (μmol/l) was measured in whole blood 1 week prior to KD initiation and after 3 months of KD. Capillary βOHb (μmol/l) via a semi-quantitative analysis for instant results was also performed daily during initiation of KD. These results are not presented. Follow-up assessments were performed after 3 months of KD.

Statistical evaluation

Wilcoxon signed rank test was used for comparison of IEDs. Wilcoxon signed rank test was also used for comparison of the clinical data on seizure frequency, seizure severity, QOL, attention and βOHb before KD initiation and 3 months later. Spearman rank correlation coefficient (r) was used to calculate the correlation between IEDs and clinical effects. The level of significance was set at $p < 0.05$.

The present study was conducted at the Paediatric Department, University Hospital, Lund, during 1999—2003. The study was accepted by the Ethics Committee of the Faculty of Medicine, Lund University. Written informed consent from the parents and, when possible, from the patients was obtained.

Results

The type of epilepsy and the types of seizures were classified according to the International League Against Epilepsy classification 1981, 1989 (Anonymous, 1989, 1981). Three children had GTCS, five tonic—clonic with two generalized seizures, five had tonic generalized, three atonic drop, four tonic drop, three atypical absences and three myoclonic