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Ketogenic diet in patients with epileptic encephalopathy with electrical status epilepticus during slow sleep

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Summary Epileptic encephalopathy with electrical status epilepticus during slow sleep (ESES) belongs to the group of epileptic encephalopathies that often prove refractory to AED treatment. The ketogenic diet (KD) has been used as an alternative to antiepileptic drugs (AEDs) for patients with refractory epileptic encephalopathies.
Purpose: In this retrospective study we assess the efficacy and tolerability of the KD in patients with ESES syndrome.
Methods: Between March 1, 1990 and April 1, 2013, 65 patients who met diagnostic criteria of ESES syndrome were seen at our department. Twelve of them were placed on the KD and followed for a minimum of 18 months.
Results: The children had previously received a mean of 5.5 different AEDs and were on a mean of 3 AEDs when the diet was started. Eighteen months after initiating the diet, seven of the initial patients (58%) remained on the diet; one patient (8.3%) had become seizure free, one (8.3%) had a 75—99% decrease in seizures, two (16.6%) had a 50—74% decrease in seizures, and the remaining three children (24.9%) had a <50% decrease in seizures. In the patient who had become seizure free and in the one who had a 75—99% seizure decrease AEDs were reduced.
Conclusion: The KD is a well-tolerated treatment option for patients with ESES syndrome, not only for structural cases but also for those with an unknown etiology. The diet should be considered in the management of this syndrome.

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Introduction

The KD is currently considered a safe and effective optional therapy not only for children but also for adults with intractable epilepsy (Freeman et al., 1998, 2009; Cross and Neal, 2008; Kossoff et al., 2008; Caraballo and Vining, 2013). Although a number of new antiepileptic drugs (AEDs) have been introduced, interest in the diet has been increasing.

A wide range of hypotheses has been proposed to explain the efficacy of the KD (Stafstrom and Rho, 2004; Hartman, 2008; Bough and Rho, 2007; Bough, 2008). One hypothesis is that ketone bodies have anticonvulsant activity similar to antiepileptic drugs. In an experimental animal study, ketone bodies increased the inhibition mechanisms in the hippocampal dentate gyrus (Stafstrom and Rho, 2004; Hartman, 2008). Acetone may also exert an anticonvulsant effect. A brain ketone may be elevated by the KD (Stafstrom and Rho, 2004; Hartman, 2008; Kossoff et al., 2008). Alternative mechanisms for the action of the KD are the direct action of aceto acetate or β-hydroxy-butyrate, and changes in the source or utilization of energy within the brain, an increase in brain gamma-aminobutyric acid, and the potential effects of changes in water and electrolytes have also been indicated as antiepileptic mediators (Stafstrom and Rho, 2004; Hartman, 2008).

A recent randomized controlled trial supports the use of the KD in children with treatment-intractable epilepsy (Neal et al., 2008). After three months, 28 patients (38%) of the diet group had a greater than 50% seizure reduction compared with four (6%) controls, and five children (7%) in the diet group had a greater than 90% seizure reduction compared with no controls (Neal et al., 2008). A randomized trial of classical and medium-chain triglyceride KDs in the treatment of childhood epilepsy has shown that both diets are comparable in efficay and tolerability. The authors concluded that these two ways of formulating the diet have their place in the treatment of childhood epilepsy (Neal et al., 2009).

It has been suggested that the diet might be beneficial for seizure control in specific epileptic syndromes including epileptic encephalopathies (Eun et al., 2006; Laux et al., 2004; Kossoff et al., 2002; Caraballo et al., 2005, 2006, 2011, 2015; Caraballo, 2011; Veggiotti et al., 2011; Nangia et al., 2012; Lemmon et al., 2012). The KD is effective in all types of epileptic seizures (Freeman et al., 1998; Kossoff et al., 2008; Caraballo and Vining, 2013). In the literature, very little experience with the KD in ESES has been reported (Bergqvist et al., 1999; Nikanorova et al., 2009).

Recent reports of series of patients after one year on the diet show an overall efficacy ranging from 15 to 50% of patients having a >50% reduction in seizures (Kossoff et al., 2008; Freeman et al., 2009; Caraballo et al., 2013).

Epileptic encephalopathy with electrical status epilepticus during slow sleep (ESES) is now classified among the epileptic encephalopathies (Engel, 2001; Berg et al., 2010) that are generally refractory to AEDs. ESES syndrome is characterized by (Tassinari et al., 2002; Caraballo et al., 2013): (1) Onset with focal or apparently generalized seizures and focal EEG discharges; (2) Further appearance of atypical absences, and myoclonic, atonic (with or without epileptic falls), and/or generalized seizures; (3) Cognitive impairment and/or behavioral disturbances related to the ESES period; (4) ESES occurring in more than 85% of non-REM sleep; however, a lower percentage — between 85% and 30% — may also be included (Tassinari et al., 2002; Caraballo et al., 2013). Cases with ESES syndrome of a genetic or probably genetic, structural, and unknown etiology have been described.

The challenge of the management of ESES syndrome lies in its resistance to classic AEDs, steroid dependence, and the fact that little is known about the effectiveness of the KD in ESES. Nevertheless, a few reports suggest to include the diet as an alternative treatment option (Bergqvist et al., 1999; Nikanorova et al., 2009).

In this retrospective study, we evaluate the efficacy and tolerability of the KD in patients who met the diagnostic criteria of epileptic encephalopathy with ESES.

Materials and methods

Between March 1, 1990 and August 31, 2013, 65 patients who met the diagnostic criteria of epileptic encephalopathy with ESES were seen at our center. Twelve of these 65 patients were placed on the KD using the Hopkins protocol and followed for a minimum period of 18 months. The KD has been proposed to the parents as a treatment option because of drug resistance. Five patients with refractory seizures were not offered the KD as they came from families with a low socioeconomic level who were considered not to be prepared to follow the diet.

Frequency of the seizures was registered using daily seizure calendars kept by the parents. Electroencephalograms during wakefulness and sleep were performed at least three months before starting, while on, and after discontinuing the KD. All patients underwent intermittent photic stimulation (IPS). Baseline blood tests and lipid profiles were also obtained. Serum bicarbonate levels were measured in all patients.

Efficacy criteria did not only include seizure reduction, but also sleep-EEG and neuropsychological outcome.

Children started fasting in the hospital for 36—48 h and were then gradually initiated on the classic KD (Johns Hopkins protocol). Children were begun on a 4:1 ratio (fat: protein plus carbohydrate) and stayed in hospital for another four days for close monitoring. During this period parents were taught about the diet. They were asked to keep the child on the diet for at least two months to regulate the diet for optimal tolerance and seizure control. The ratio of the diet was progressively modified as needed to maintain 80 to 160 mg/dl urinary ketosis and to avoid weight loss. Adverse events and reasons for diet discontinuation were recorded, as were changes in medication.

Results

Sixty-five children with a diagnosis of epileptic encephalopathy with ESES were followed for 2 to 21 years. Of these children, 12 (eight boys and four girls) were placed on the KD as add-on to the use of one to three AEDs. Ages at initiation of the KD were between 7 and 11 years (mean 8.5 years).