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The ketogenic diet influences the levels of excitatory and inhibitory amino acids in the CSF in children with refractory epilepsy

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Abstract

The ketogenic diet (KD) is an established treatment for medically refractory pediatric epilepsy. Its anticonvulsant mechanism is still unclear. We examined the influence of the KD on the CSF levels of excitatory and inhibitory amino acids in 26 children (mean age 6.1 years) with refractory epilepsy. Seventeen amino acids were determined before and at a mean of 4 months after the start of the KD. Seizures were quantified. Highly significant changes were found in eight amino acids: increases in GABA, taurine, serine, and glycine and decreases in asparagine, alanine, tyrosine and phenylalanine. However, aspartate, glutamate, arginine, threonine, citrulline, leucine, isoleucine and valine/methionine remained unchanged. A significant correlation with seizure response was found for threonine ($P = 0.016$). The GABA levels were higher in responders (>50% seizure reduction) than in nonresponders during the diet ($P = 0.041$). In the very good responders (>90% seizure reduction), the GABA levels were significantly higher at baseline as well as during the diet. Age differences were found with significantly larger decreases in glutamate and increases in GABA in connection with the diet in younger children. Our results indicate that the KD significantly alters the levels of several CSF amino acids that may be involved in its mechanism of action and the increase in GABA is of particular interest.

Keywords: Amino acids; GABA; Ketogenic diet; Children; Cerebrospinal fluid; CSF

1. Introduction

The ketogenic diet (KD) is a high-fat, low-protein and very low-carbohydrate diet that has been used in the treatment of pediatric epilepsy since the 1920s (Wilder, 1921). The total caloric needs of the particular child and the caloric contents of the meals are calculated by a dietician. Currently, the KD is used primarily to treat pharmacologically refractory childhood epilepsy (Freeman et al., 1998; Vining, 1999).

The efficacy of the diet in the treatment of pediatric epilepsy is well established. Studies have shown

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that one-half to two-thirds of the participating children achieve a >50% seizure reduction (Vining, 1999). Despite its long use and satisfying efficacy, the mechanism of action by which the KD suppress seizures remains unknown. Several hypotheses have been proposed. The high-fat and low-carbohydrate intake induces nonglycolytic pathways with subsequent ketosis. Animal studies have shown that ketosis is necessary for the anticonvulsant effect of the KD (Appleton and DeVivo, 1974; Nakazawa et al., 1983). However, further studies have suggested that the ketone beta-hydroxybuturic acid was not directly involved in the anticonvulsant effect (Bough et al., 2000), indicating that ketosis may not be a sufficient prerequisite. Changes in the brain energy reserve, alterations of the brain acid–base balance and effects of changes in the lipid profile have also been proposed as modes of action (Stafstrom, 1999).

Alterations of the amino acid neurotransmitters, including GABA, have been suggested as a mechanism of action. In a study of adult rats fed a ketogenic diet, no changes were found in the total brain GABA levels (Al-Mudallal et al., 1996). In animal studies, ketones induced increases in GABA and decreases in aspartate levels (Erecinska et al., 1996; Daikhin and Yudkoff, 1998), but in mice fed a KD, reduced aspartate but unchanged GABA was found (Yudkoff et al., 2001). These authors hypothesize that ketosis induces changes in the brain's handling of amino acids with reduced transamination of glutamate to aspartate and hence increased GABA. In a pilot study using magnetic resonance spectroscopy (MRS), two out of three investigated children showed increased GABA levels (Wang et al., 2003). However, studies in humans evaluating the levels of amino acid neurotransmitters in relation to the KD have not been conducted.

The aim of this study was to compare the levels of excitatory and inhibitory amino acids in the CSF before and after institution of the KD in a cohort of children with medically refractory epilepsy.

2. Material and methods

2.1. Ethics

The study was approved by the Ethics Committee of the Karolinska Hospital and the informed consent of the parents and, when possible, of the patients, was obtained.

2.2. Patients

The present study was conducted at the Neuropediatric Department, Karolinska Hospital, during 1998–2002. It was part of a larger prospective open trial on the efficacy and safety of the KD in children with epilepsy. The patients were enrolled consecutively as they attended the Epilepsy Outpatient Clinic and the decision to start the KD was made.

The inclusion criteria were an age of 1–18 years, pharmacologically refractory epilepsy with a prior trial of at least three AEDs with appropriate doses and plasma levels, epilepsy surgery having been considered, no medical contraindications for a trial with the KD, the family and patient are considered to be able to cooperate in a trial with the KD, and approval for performing two lumbar punctures (LPs). Thirty-five children satisfied the criteria. No patient was lost to follow-up. However, nine children were excluded because the second LP could not be performed due to the fact that the diet was discontinued or the parents did not agree to the LP (seven and two children, respectively). Thus, 26 children were included in the final cohort.

Fifteen boys and 11 girls participated in the study. Their mean age was 6.1 years (±3.0 S.D.; median, 5.5; range, 1.3–15.8); for demographic data, see Table 1. The onset of epilepsy occurred at a mean age of 0.8 years ((±0.8 S.D.; range, 0.0–3.0). The type of epilepsy and the types of seizures as well as epileptic syndromes were classified according to the International League Against Epilepsy (ILAE) classification, 1981 and 1989. Generalized epilepsy was found in the vast majority, 22 children, whereas 4 had partial epilepsy. The most common seizure types were myoclonic and tonic. At the time of the study, the mean number of seizure types was 2.5 (±0.8 S.D.). As can be seen from the table, an epileptic syndrome or etiology could be identified in 22 children. All but one child were mentally retarded and the majority had other associated neurological disorders, such as autism spectrum disorder and/or motor handicaps. Prior to entering the study, the patients had been on long-term therapy with a mean of 7.0 AEDs (range, 4–10). At the time of the study, they were on treatment with a mean of 2.1 AEDs (range, 0–4).