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Ketogenic Diet for Refractory Epilepsy in Children-An Institutional Experience

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Abstract

Introduction: Ketogenic diet consists in a adequate protein diet (1 qram/kg), low in carbohydrates and rich in lipids, which induces a prolonged state of ketosis that modifies the cerebral energetic metabolism. This study aims to characterize the children with refractory epilepsy treated with ketogenic diet, enrolled in a Child Development Center in Portugal. It intends to evaluate the efficacy and tolerability of the diet and to identify in which epilepsy syndromes and etiologies the diet is effective.

Methods: Retrospective analysis of the cases of refractory epilepsy treated with ketogenic diet.

Results: Sixteen children were included, eleven boys. The mean age of seizures onset was 13.9 months (0-72 months) and of ketogenic diet onset was 4.4 years (5 months-16 years). At the end of the first month, 62.5% had a seizure reduction of more than 50%. The efficacy reached 43,8% at the end of third month and 31.3% at the end of the sixth month. In 31.3% there was a reduction of the number of anti-epileptic drugs and 56.3% had an improvement in the behavior/cognition. The diet was more effective in infantile spasms, Lennox-Gastaut and Dravet syndromes and genetic and structural epilepsies, particularly in malformations of the cortical development. The mean time to a clinical response was 1.4 months. The diet had a good tolerability, with side effects only in 31.2%, none with clinical severity.

Conclusion: In this study, ketogenic diet has proven to be safe and effective and should be considered in children with severe and refractory epilepsies.

Keywords: Ketogenic diet; Child; Epilepsy; Treatment outcome; Side effects

Introduction

Ketogenic diet consists in a high fat, adequate-protein (1 gram/kg) and low-carbohydrate diet with precisely calculated proportions so that 75 to 90% of calories are from lipid source [1,2]. The beginning of its use as anti-epileptic therapy dates back to the 1920 s. With the rapid development of new anticonvulsant agents for epilepsy, ketogenic diet has fallen into disuse between 1940 s and 1980 s, having resurged in the 1990 s [2].

Currently there are four different types of ketogenic diet: classic ketogenic diet, medium chain triglycerides (MCT) diet, Modified Atkins Diet and Low Glycaemic Index Diet Treatment (LGIT) [2-6].

The classic ketogenic is a 4:1 or 3:1 ratio of fat to combined protein and carbohydrate, and is individually tailored to typically provide 75% to 80% of the recommended daily allowance of calories. The fat includes long chais triglycerides (LCT) and partial medium chain triglycerides (MCT) [2].

In MCT diet, the major fat source comes from medium chain triglycerides, which are more efficiently absorbed, resulting in a greater production of ketone bodies. As a result, less total fat is needed in the diet and more protein and carbohydrates can be allowed. (30-60% of MCT; 11-45% of TCL; 25-29% of proteins and carbohydrates) [3].

The Modified Atkins diet is a less restrictive option, which induces ketosis from a high proportion of lipid and a carbohydrate restriction (10 to 20 g/day) without protein or caloric restriction [4,5]. LGIT is a recent and even less restrictive diet, based on achieving stable blood glucose levels for seizure control. Therefore, this diet liberalizes the amount of carbohydrate in 40 to 60 g per day, allowing only those that cause minor variations in glycaemia [6].

These different types of diet appear to have similar efficacy results, with literature referencesbeing more limited for Modified Atkins diet and LGIT [4,7-10].

The mechanism by which the ketogenic diet suppresses seizures remains unclear and is likely multifactorial. The hallmark feature is the induction of a starvation state, forcing the body to use ketone bodies as primary energy source, which have anticonvulsant properties.

Multiple theories have been postulated, considering the optimization of brain energy metabolism, changes in neurotransmitter concentrations, changes in cell membrane properties and the direct effect of ketone bodies, as possible mechanisms for seizurescontrol [1].

Ketogenic diet has proven to be effective in the control of seizures frequency and reduction of anticonvulsant therapy, as well as in cognitive and behavioral improvement [3,7,11-16].

Based upon the available evidence, an international consensus has been published, in 2009, recommending the use of ketogenic diet in children with epilepsy refractory to at least two antiepileptic drugs [17]. The expert consensus group identified specific epilepsy syndromes and clinical conditions in which Ketogenic diet seems to be particularly effective, such as glucose transporter protein carrier 1 (GLUT-1) deficiency, pyruvate dehydrogenase deficiency, Doose, Dravet, Lennox-

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Gastaut and Rett syndromes, tuberous sclerosis and infantile spasms [17].

The main adverse effects of Ketogenic diet usually occur early in the implementation phase and include hypoglycemia, anorexia, nausea, vomiting and weight loss. In a later phase, the diet may lead to gastrointestinal symptoms (12-50%) as constipation, vomiting, diarrhea and abdominal pain, metabolic disorders such as hypercholesterolemia (14-59%), hyperuricemia (2.26%), hypocalcaemia (2%) and hypomagnesemia (5%), nephrolithiasis (7%), decreased growth rate, and cardiac complications as QT prolongation and dilated cardiomyopathy [15,18-20].

Portuguese experience with ketogenic diet has been poorly studied. This study aims to characterize the children with refractory epilepsy treated with ketogenic diet, enrolled in a Child Development Center in Portugal. It intends to evaluate the efficacy and tolerability of the diet and to identify in which epilepsy syndromes and etiologies the diet is particularly effective.

Methods

All clinical cases of children with refractory epilepsy submitted to ketogenic diet in Child Development Center Torrado da Silva, between 1992 and 2012, were retrospectively reviewed. The institution protocol uses diet with a 3:1 ratio of MCT to carbohydrate and protein, since it is a less restrictive and equally effective diet, more accepted and tolerated by children as it is more palatable [3-4,7-10]. Therefore all children enrolled used MCT diet and followed the institution protocol based on the international consensus recommendations [17].

According to the protocol, all children and their families had an interview with the dietician prior to the initiation of ketogenic diet, in order to clarify the implementation and side effects of the diet, as well as the family's expectations. All children underwent a nutritional assessment and baseline laboratory workup with evaluation of: complete blood count with platelets, electrolytes including calcium, magnesium and phosphate, serum iron and ferritin, serum liver and kidney tests (albumin, aspartate and alanine transaminases, blood urea nitrogen and creatinine), metabolic screening, fasting lipid profile, fasting blood glucose level, urinalysis and determination of anticonvulsant drug levels.

The ketogenic diet was initiated as outpatient or inpatient, without initial fasting and fluid restriction. All children received calcium and multivitamin supplements. All had regular followup with clinical evaluations at the end of the first month of diet and every three months in the first year of therapy.

Population was characterized based on age, sex, age of seizures onset, age of the institution of the diet, epilepsy etiology and electroclinical syndrome defined according to the 2010 International League Against Epilpepsy classification [21].

Diet efficacy was evaluated according to: 1-reduction of seizures frequency; 2-reduction in the number of anticonvulsants; 3-effect on cognition, behavior and socialization.

To evaluate the reduction of seizures frequency, Huttenlocher criteria were applied, [22] stratifying reduction in five levels: complete seizure reduction, reduction of more than 90%; reduction of 50 to 90%; reduction of less than 50%; and no seizure reduction. A responder was defined as having a reduction of more than 50% of seizure frequency.

Cognitive, behavioral and socialization effects were assessed subjectively by parents or observed in consultation. In order to objectify this effect, we used a pediatric quality of life scale, validated for the Portuguese pediatric population–Portuguese PedsQLTM. The scale was applied only to children submitted to ketogenic diet during the three previous years, in order to minimize the bias of a retrospective questionnaire.

Diet tolerability was evaluated based on: diet duration; reasons for discontinuation; and side effects.

Data were analyzed using Microsoft Office Excel 2007 for Windows®.

Results

Eighteen children were submitted to ketogenic diet in this Portuguese Child Development Center, in the last twenty years. Two of them fulfilled less than fifteen days of diet, developing intolerance symptoms, for which they were excluded from this study.

The final sample comprises 16 children, five females and eleven males. The age of onset of epilepsy ranged from 1 day to 72 months (mean 13.9 months). The mean age of ketogenic diet introduction was 4.4 years with a minimum of 5 months and a maximum of 16 years. Fourteen children started diet as inpatients and two as outpatients. The epilepsy etiologies and electroclinical syndromes of the children enrolled in the study population are represented in Table 1.

Ten children (62.5%) had seizure reduction of more than 50%, three of which (18.8%) had a reduction of more than 90%, and seven (43.8%) had a reduction between 50 and 90%. None of them became seizure-free. This efficacy in the reduction of seizures frequency decreased over time. The percentage of responders decreased to 43.8% after three months and to 31.3% after 6 months of ketogenic diet as show in Figure 1.

Five children (31.3%) were able to reduce the number of

EPILEPSY ETIOLOGY		
Structural/Metabolic		11
Malformation of cortical development		7
Difuse	5	
Focal	2	
Acquired perinatal insults		4
Hipoxic-ischemic encephalopathy	1	
Thalamic hemorrhage	1	
Cerebrovascular accident	2	
Genetic		2
GLUT 1 deficiency	1	
Presumed genetic	1	
Unknown etiology		3
ELECTROCLINICAL SYNDROME		
Incancy		6
West syndrome		2
Infantile spasms		3
Dravet syndrome		1
Childhood		3
Epileptic encephalopathy with continuous spike-and-wave during sleep		1
Lennox Gastaut syndrome		2
Other non syndromic epilepsies		7
Mesial temporal lobe epilepsy		1
Focal epilepsy		4
Mioclonic epilepsy		1
Multifocal epilepsy		1

Table 1: Epilepsy etiologies and electroclinical syndromes of children enrolled in the study.

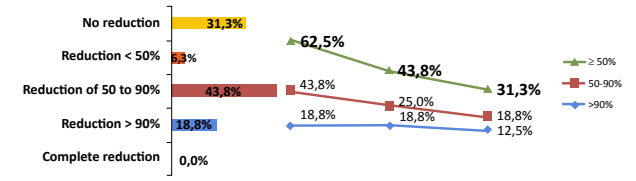

Figure 1: Ketogenic diet efficacy in the reduction of seizure frequency, evaluated in the first, third and sixth month of therapy. As we can see in the figure, 62.5% of children had a reduction of more than 50% of seizures after the first month of diet. The percentage of responders decreased to 43.8% after three months and to 31.3% after 6 months of ketogenic diet.

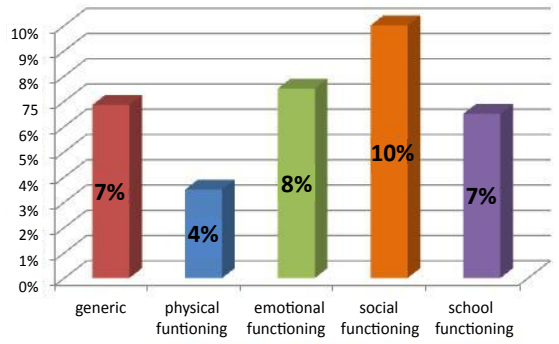

Figure 2: Evaluation of the improvement in the quality of life of children submitted to Ketogenic diet, using PedsQLTM. The questionnaire was fulfilled by parents of children older than 2 years, submitted to the diet in the last three years (n=5). The medium overall rate of improvement in childrens' quality of life was 7%, being social and emotial functioning the areas with a better improvement.

anticonvulsants, eight children (50%) maintained the number of anticonvulsants and three (18.8%) had to increased the number of anticonvulsant drugs. Nine children (56.3%) showed cognitive and behavioral improvement. None revealed deterioration in cognition and behavior.

All children evaluated with PedsQLTM scale showed an improvement in the quality of life with ketogenic diet, with social and emotional functioning being the areas with most significant improvements as shown in Figure 2.

Efficacy response varied according to the etiology of epilepsy and the electroclinical syndrome. Although the numbers of cases were small, children with GLUT 1 deficiency, malformations of cortical development, infantile spasms, Lennox Gastaut syndrome and Dravet syndrome had the best efficacy results (Table 2).

The diet was effective in all the children less than 1 year of age and in 62.5% of children aged between 1 and 5 years. Above five years old, the ketogenic diet was effective in only 33% of cases.

No adverse side effects were reported in 11 patients (68.8%). Minor side effects were reported in 5 patients (31.2%), but none led to the interruption of the diet. Constipation was the most frequent side effect, reported in 3 children (18.8%). Two patients (12.5%) developed dyslipidemia, one (6.3%) reported nephrolithiasis and in one other (6.3%) there was a significant weight loss with ketogenic diet. None had growth delay after the therapy.

The mean time for a clinical response to the diet was 1-4 months (minimum 1 week, maximum 5 months).

The total duration of the diet ranged from 1 to 24 months with a mean of 10 months. Five children (31.3%) maintained the diet for 12 to 24 months and 5 (31.3%) discontinued the diet in the first 3 months. Currently, 2 children (12.5%) still maintain the diet.

The most frequent reason for abandoning the diet was secondary therapeutic failure with relapse of initial seizure control, reported in 6 patients (37.5%). Four (25%) abandoned the diet for primary treatment failure, two (12.5%) for intolerance to diet, one (6.3%) due to medical decision after seizure control and other (6.3%) in order to perform epilepsy surgery.

Discussion

In this study, we report a 43,8% efficacy in the reduction of seizures at 3 months of ketogenic diet. This result is comparable to results reported in other studies, in which the diet efficacy ranges from 38% to 63% [3,7,14,15,20].

The gradual loss of efficacy over months is also reported in other published studies [7,16,23]. This may reflect either a gradual addiction to ketosis or a decrease in therapeutic adherence over time, due to the high demands imposed by the diet and the primary therapeutic failure observed in some cases.

As reported in literature [20,24,25], we also found a high rate of cognitive and behavioral improvement with the diet. This fact is particularly important and prized by parents. In an article published in 2006 [24], 90% of parents reported high expectations of improvement in the child's behavior and cognition with ketogenic diet. The article concluded that the achievement of these expectations was strongly correlated with a longer duration and adherence to the diet.

	Seizure reduction ≥ 50%	Seizure reduction > 90%
EPILEPSY ETIOLOGY		
Structural/metabolic		
Malformation of cortical development	6/7	1/7
Difuse	4/5	1/5
Focal	2/2	0/2
Acquired perinatal insults	1/4	0/4
Hipoxic-ischemic encephalopathy	1/1	0/1
Thalamic hemorrhage	0/1	0/1
Cerebrovascular accident	0/2	0/1
Genetic		
GLUT 1 deficiency	1/1	1/1
Presumed genetic	1/1	1/1
Unknown etiology	1/3	0/3
ELECTROCLINICAL SYNDROME		
Infancy		
West syndrome	0/2	0/2
Infantile spasms	3/3	1/3
Dravet syndrome	1/1	1/1
Childhood		
Epileptic encephalopathy with continuous spike-and-wave during sleep	0/1	0/1
Lennox Gastaut syndrome	2/2	0/2
Other non syndromic epilepsies		
Mesial temporal lobe epilepsy	0/1	0/1
Focal epilepsy	2/4	0/4
Mioclonic epilepsy	1/1	1/1
Multifocal epilepsy	1/1	0/1

Table 2: Ketogenic diet efficacy according to epilepsy etiology and electroclinical syndromes.

In our study ketogenic diet was shown to be particularly effective in GLUT-1 deficiency, in malformations of cortical development, infantile spasms, Lennox Gastaut syndrome and Dravet syndrome. While ketogenic diet is recognizably effective in Glut 1 deficiency, infantile spasms, Lennox Gastaut and Dravet syndromes [17], data are not so certain for malformations of cortical development. Nevertheless, some recently published studies [26,27] have also reported surprisingly good responses of ketogenic diet in children with malformations of cortical development.

In a retrospective study enrolling 22 children, ketogenic diet had excellent responses in refractory focal epilepsies with recent worsening [28]. These data suggest that ketogenic diet may be useful as supportive therapy in the subgroup of children awaiting epilepsy surgery.

In our study, the diet was more effective in younger children, especially under 5 years old. Although in the majority of studies no relationship was found between child's age and diet efficacy, there are a few studies showing higher efficacy rates in children up to 10 years old [29]. This may be due to a greater capacity of younger children to use ketone bodies as energy substrate, but also to the fact that younger children are totally dependent on the preparation and administration of meals by their caregivers [29] Ketogenic diet showed good tolerability in our study. There were no serious adverse effects reported and most children did not report any side effect at all. This study showed that Ketogenic diet was safe and effective in treating children with severe epilepsy refractory to other therapies. Based on our results, we can point an ideal patient profile for ketogenic diet treatment, which is a child under 5 years old, with one of the following clinical entities or epileptic syndromes: GLUT 1 deficiency, malformations of cortical development, infantile spasms, Lennox Gastaut or Dravet syndromes. However, this study has some limitations, such as the small sample size and the fact that it is a retrospective study. Therefore, a national multicenter study should be encouraged in order to properly assess the Portuguese experience with the ketogenic diet.

It is important to remember that the efficacy and adherence to the diet require a multidisciplinary approach. Regular and multidisciplinary monitoring of these children and their families are crucial, in order to adjust the diet, evaluate its efficacy and tolerability, and identify and correct the adverse effects precociously.

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