

KETOGENIC DIET FOR THE TREATMENT OF REFRACTORY EPILEPSY

A 10 year experience in children

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ABSTRACT - Ketogenic diet (KD) is a high fat and low carbohydrate diet, which controls refractory epilepsy. We analyzed the KD effects on 54 children of the Children's Institute of the University of São Paulo. Efficacy, tolerability, and adverse effects were studied. Response to KD was effective (E) if seizure control was >75%, good (G) when 50-75%. When possible, we correlated the results with the epileptic syndrome and patient's age. By the second month on diet, 57.4% of the patients had E response and 31.4% G results. At the 6th month, 63.8% had E response and 25.5% G. At the 12th month, 71.8% had E and 25.6% G. At the 24th month, 62.1% had E and 37.9% G. Antiepileptic drugs have been reduced, and generalized epilepsy was the most sensitive. Age-related differences were not observed. Adverse effects were rarely observed. In conclusion, KD proved to be an effective treatment for refractory epilepsy.

KEY WORDS: ketogenic diet, refractory epilepsy, children.

Avaliação da dieta cetogênica no tratamento da epilepsia refratária em crianças: 10 anos de experiência

RESUMO - A dieta cetogênica (DC) tem alto teor de gordura e baixo de carboidratos e proteínas, sendo usada no tratamento da epilepsia refratária. Analisamos os efeitos da DC em 54 crianças do Instituto da Criança da Universidade de São Paulo. Eficácia, tolerabilidade e efeitos adversos foram estudados. A DC foi considerada eficaz (E) quando houve redução de crises >75% e boa (B) quando a redução foi entre 50-75%. Correlacionamos, quando possível, esses resultados com a síndrome epiléptica e com a idade dos pacientes. Observamos resultados (E) em 57,4%, 63,8%, 71,8% e 62,1% dos pacientes no 2º, 6º, 12º e 24º meses, respectivamente e (B) em 31,4%, 25,5%, 25,6% e 37,9%, respectivamente. Houve redução significativa das drogas antiepilépticas. A DC foi mais eficaz nas epilepsias generalizadas e não houve diferenças quanto a idade. Efeitos adversos foram raros. Em conclusão, a DC é um tratamento antiepiléptico eficaz em casos refratários.

PALAVRAS-CHAVE: dieta cetogênica, epilepsia refratária, criança.

Ketogenic diet (KD) is a high fat, low carbohydrate and adequate-protein diet, developed in the 1920's as an attempt to control refractory epilepsy, in an era when available antiepileptic drugs (AED), as well as their efficacy, were limited. There was a renewed interest in the 70s about KD, following a period of disuse during the 40's and 50's¹.

Several hypotheses have tried to explain the mechanism of action of KD. Some of these theories are: metabolic acidosis, extra and intra cellular dehydration, direct action of acetoacetate and β -hydroxy-

butyrate, and a shift of energy supply sources to the brain². A recent study has shown that, despite advances in neuropharmacology and the development of a new generation of AED, KD remains as an important alternative therapy for epilepsy, especially in children³.

This study analyzed the long term follow-up of a large series of children with refractory epilepsy who were consecutively enrolled, in the past 10 years, in the KD program of the Children's Institute of the University of São Paulo aiming to evaluate: (i) efficacy

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(seizure control and AED dose reduction); (ii) tolerability; and (iii) adverse effects.

METHOD

The study comprised a chart and protocol revision of 70 consecutive children enrolled in a standard KD protocol that had been previously completed, from 1992 to 2001 by one or two of the authors (AF, JAP, MJMD).

This study, numbered as 290/02, has been approved by Hospital das Clinicas Ethical Committee (CAPPesq).

Patient selection – Patients were referred from tertiary centers with a diagnosis of refractory epilepsy and presented at least 2 seizures per week. Refractoriness was defined as the use of 2 adequate AED in maximum or tolerated doses. Patients with evidence of metabolic disorder were excluded.

Ketogenic diet protocol – Prior to diet introduction, metabolic and hematological profiles were obtained. This investigation included: full blood count, glucosis, calcium, magnesium, electrolytes, urinary and plasmatic amino acids, urinary and plasmatic organic acids, creatinine, urea, anion gap, blood gases, blood lactate, ammonia and pyruvate, liver function tests, urine reducing substances, ketones, acid and alkaline phosphatase, cholesterol, triglycerides, and EEG.

The KD program was carried out according to the Johns Hopkins protocol¹. Patients were admitted as inpatients for five days. In a first step, they underwent a period of fasting in order to achieve ketosis. Once under this condition, a 4:1 classic KD protocol was introduced. Following hospital release, patients returned for reevaluations after 1, 2, and 4 weeks. Later on, they were reevaluated on the 2nd, 6th, 12th, and 24th months of KD. Nutritional analysis and vitamin supplementation (multivitamins, calcium, folic acid, iron supplements, and in cases receiving VPA, carnitine) were done during follow-up, in all patients.

Outcome measurements – (i) Efficacy was measured by seizure frequency decrease and AED reduction. Seizure frequency was evaluated according to parents' calendar. These data were compared to previously obtained baselines, meaning seizure frequency per month prior to KD introduction. Response to KD was measured after 2, 6, 12, and 24 months. An optimal control was considered if patients achieved 75% of seizure frequency reduction and considered effective if seizure control was higher than 50%, compared to prior baselines. Wilcoxon test was used for sta-

tistical analysis of AED reduction. (ii) Tolerability of diet acceptance by patient was evaluated as presence of nausea, vomits or both. The child was considered intolerant to diet when these symptoms occurred after the fasting period. (iii) Adverse effects and reasons for diet discontinuation were registered through personal interviews. The results were entered into a database and statistically analyzed.

RESULTS

Patients' demographics – The studied group was made by 37 boys (52.8%) and 33 girls (47.2%). Patient ages, at time of diet initiation, ranged from 13 months to 12 years and 1 month (mean 6.3y; median 5.1y). Diet duration ranged from 2 months to 5 years (mean 1.1y; median 1y)

Epilepsy was classified according to International League Against Epilepsy (ILAE) and it is outlined on Table 1.

Diet efficacy – From the 70 patients who initiated treatment, 16 (22.8%) patients were excluded because they did not complete a minimum period of 2 months on diet. The KD efficacy was measured in the 54 patients who remained on treatment.

Seizure control – Results, evaluated with 2, 6, 12, and 24 months, are shown on Table 2. From the 49 children who remained on KD for 6 months, 44 (89.3%) presented more than 50% decrease in seizure frequency. Moreover, none of them presented *status epilepticus* episodes during their treatment.

Table 1. Patients demographics (n=54).

Epilepsy etiology	
Idiopathic	–
Cryptogenic	23
Symptomatic	31
Predominant seizure type	
Generalized	44
Partial	10
N. of seizures types	
1	13
>2	41

Table 2. Seizure control in 54 patients.

Seizure status	Diet duration			
	2mo (n=54)	6mo (n=49)	12mo (n=39)	24mo (n=29)
>75%	30 (57.4%)	31 (63.8%)	28 (71.8%)	18 (62.1%)
50-75%	17 (31.4%)	13 (25.5%)	10 (25.6%)	11 (37.9%)
<50%	7 (11.1%)	5 (10.6%)	1 (2.5%)	–

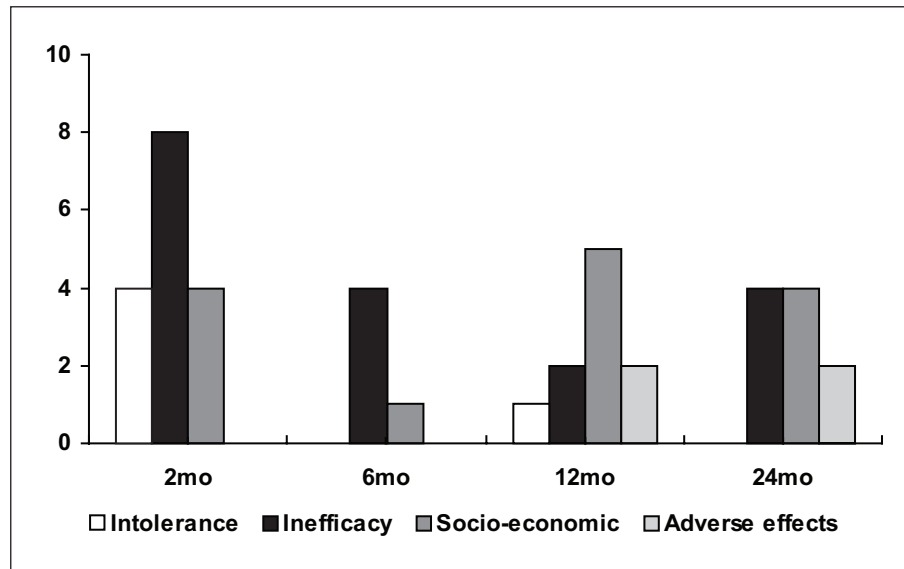


Figure. Reasons for interruption.

The efficacy for generalized epilepsy was significantly higher ($p < 0.001$) compared to partial, in all time of KD. However no difference was observed regarding etiology (symptomatic [51.6%], cryptogenic [48.4%] $p = 0.03$) or age.

According to parents, all patients experienced cognitive improvement in life quality and cognitive skills, independent of seizure control.

AED – At the time when patients had initiated KD, 51/54 (94.4%) patients were taking 2 or more AED and 3/54 (5.5%) were on monotherapy. In eight of 54 (14.8 %) patients, complete AED withdrawal was possible, and in the remaining, reduction of AED (dose and/or number) was accomplished. The statistical analysis demonstrated a significant ($p < 0.001$) reduction in AED prior and after diet.

Tolerability – During the program, five of 54 (9.2%) refused the diet by its palatable characteristics, and two (3.7%) presented nausea and vomiting. The other reasons for diet discontinuation are presented in the Figure.

Adverse effects – During the fasting period three of 54 (5.5%) presented transitory nausea and vomits and four (7.4%) had nonsymptomatic hypoglycemia. However only two of these patients received orange juice and none needed IV glucose. Only four patients presented major illnesses leading to diet interruption during the program, such as nephrolithiasis in two patients of 54, nephritis and sepsis in one patient each.

DISCUSSION

Intractable or refractory epilepsy is defined as unsatisfactory control of epileptic seizures, despite adequate treatment with conventional AED. It is associated with high mortality rates, low productivity, and cognitive loss⁴. There are a number of reports proving the efficacy of KD that ranges from 30 to 60% in different studies⁵⁻¹⁰. Our results corroborate previous data, indicating that KD presents higher rates of efficacy than observed with use of several new generations AED¹¹.

At the moment, there are no conclusive studies about which type of epileptic seizure responds more favorably to KD, although others reported its effectiveness with focal and generalized epilepsy¹². In our series, the heterogeneity presented by the group did not allow a proper comparison among syndromes. Prasad and Stafstrom¹³ noticed that, in their patients, KD was more effective for myoclonic control and atonic seizures and in the Lennox-Gastaut syndrome, whereas success in partial was variable, and was poor in temporal lobe seizures and myoclonic absences.

Prasad and Stafstrom¹³ reported an improved efficacy of KD in younger children and postulated that this response could be related to a higher plasmatic concentration of β -hydroxybutyrate and acetoacetate. In disagreement to these authors, we did not observe this age-related efficacy, which seems to be a controversial issue as also demonstrated by others^{9,10,14}.

A few important complications have been described in patients on classical or modified KD, sev-

eral of them during the fasting period, such as: hypoglycemia, vomiting, diarrhea, and refusal of food reintroduction. These adverse effects were observed in this series but in none of the patients, KD interruption was considered mandatory. During follow-up severe adverse effects, leading to suspension of KD, occurred in four children: nephrolithiasis, nephritis, and sepsis. Renal problems are often reported^{15,16}, whereas immunosuppression by diet may be an incidental finding^{17,18}. The patient with nephritis underwent clinical treatment and, after six months, KD was reintroduced with satisfactory result and no further adverse effects.

Ballaban-Gil et al.¹⁹ described severe adverse effects in five patients on KD, where in two of them, adverse effects were related to concomitant use of VPA. This association usually potentializes idiosyncratic and dose-dependent adverse effects of VPA. Therefore, in patients that must remain on VPA during KD, dietary supplementation with carnitine is recommended as a preventive measure. In our children receiving carnitine supplementation, during KD associated to VPA, no adverse effects were observed. Association of KD with topiramate (TPM) increases the risk of nephrolithiasis, but this is not an absolute contra-indication for using TPM. In these patients, it is important to remove TPM as soon as possible. The two patients who developed nephrolithiasis were not in use of TPM.

In conclusion, KD has proven to be an effective clinical treatment for children with difficult-to-control seizures, often allowing medication reduction or discontinuation. Moreover, it may be more effective and better tolerated than many of the new AED. Adverse effects occurred, but only in few patients they were a condition for diet withdraw.

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