



Case Report

Implementation of ketogenic diet in children with drug-resistant epilepsy in a medium resources setting: Egyptian experience☆

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ABSTRACT

Background: Even with the extensive use of ketogenic dietary therapies (KD), there still exist many areas of the world that do not provide these treatments. Implementing the ketogenic diet in different countries forms a real challenge in order to match the cultural and economic differences.

Aim: To assess the feasibility of implementing a ketogenic diet plan in a limited resource setting with identification of the compliance, tolerability and side effects in the target population and to assess the efficacy of the ketogenic diet in children with intractable epilepsy.

Method of the study: The medical records of 28 patients with intractable epilepsy, treated at The Children's Hospital – Cairo University from December 2012 to March 2014 with ketogenic dietary therapy were reviewed. The non-fasting protocol was followed without hospital admission. All children were started on a standardized classic ketogenic diet with a ratio ranging from 2.5–4:1 (grams of fat to combined carbohydrate and protein). Patients were followed at 1, 3 and 6 months after diet initiation.

Results: The median age was 60 months (range, 30–110). After 1 month from diet initiation, 16 patients (57%) remained on the diet. One of them (6.3%) had more than 90% reduction in seizure frequency, an additional 6 patients (37.5%) had a 50–90% reduction in seizure frequency. In total, seven out of the 16 patients continuing the diet for 1 month (43.8%) had more than 50% improvement in seizure control from the base line. Despite having 50–90% seizure control, three children discontinued the diet after one month.

Three months after diet initiation, 6 patients (22%) remained on diet, 4 of them (66.7%) had more than 50% reduction in seizure frequency.

At 6 months, only 3 patients remained on diet, 2 of them (66.6%) had 50–90% reduction in seizure frequency, while one patient (33.3%) showed better than 90% decrease in seizure.

Conclusion: The current study shows that the ketogenic diet could be implemented in medium resources countries and should be included in the management of children with intractable epilepsy.

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1. Introduction

Using diet as a therapy is becoming a rising trend in the modern researches. Many authors are investigating the efficacy of different dietary modalities in treating various health issues. One of the most well-known dietary therapies is the ketogenic diet (KD) which has been used as a therapeutic option for drug-resistant epilepsy for more than 90 years now [1]. Many recent studies are searching for more indications of the KD, including cancer, Alzheimer, and obesity [2].

Many clinical studies have recognized KD as significantly effective and consequently, it became available in many centers all over the world [3].

Even with the extensive use of ketogenic dietary therapies, there still exist many areas of the world that do not provide these treatments. There are many reasons for the lack of dietary therapy in these parts of the world. However, the financial costs of a large ketogenic diet team, the required pre-initiation and follow up investigations, supplements for patients, even the expenses of the high-fat food (e.g., dairy and meats) are considered to be the main obstacles [4].

The meticulous information as provided in the Consensus Statement of the International Ketogenic Diet Study Group may appear discouraging for health caregivers willing to establish a new ketogenic diet center in a country with inadequate financial resources [5,6].

☆ Declaration of interests: none.

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At the 2010 Global Symposium on the Dietary Treatments for Epilepsy and other disorders held in Edinburgh, the problem of adopting the ketogenic diet in different countries was addressed in order to match the cultural and economic differences [1].

As Egypt, among many other countries, falls in the lower middle class according to The World's Bank classification of the world economies [7]; a decision was made to initiate ketogenic diet center matching the social, economic, and cultural trends pertinent to the Egyptian patients' population.

The primary aim of this study was to assess the feasibility of implementing a ketogenic diet plan in a limited resource setting. Secondary aims were to assess the efficacy of the ketogenic diet in treating epilepsy in children resistant to regular antiepileptic drugs and to identify the compliance, tolerability, and side effect of the diet on the targeted population.

2. Patients and methods

After IRB approval with waived informed consent, we reviewed the medical records of 40 patients who were treated with the ketogenic diet plan at Cairo University Children Hospital from December 1st, 2012 till March 31st, 2014.

Complete record data were available for 28 patients only and were included in the current analysis.

2.1. Pre-diet evaluation included

- Proper history taking including types of seizures, baseline seizures frequency, duration of disease, numbers, and response to AED, and progression of the disease were collected from the parents for 2 weeks before initiating the diet.
- The following laboratory tests were available for all patients prior to diet initiation: CBC, Fasting blood sugar, baseline chemistries (serum electrolytes, liver, and kidney function tests), lipid profile (fasting serum cholesterol and triglycerides), and urine analysis.
- EEG and MRI were obtained for all patients.

2.2. The ketogenic diet plan

- Specific diet plans were individually designed for each patient according to his age, weight and protein requirements.
- Each patient was given a specific menu with different options for 3 meals and one snack, this menu was tailored to meet the patient's preference regarding food type, frequency, and texture.
- Caloric requirements for each patient were calculated according to WHO (World health organization) recommendations [8] according to his/her age, sex, and lifestyle. Taking into consideration his pre-diet caloric intake obtained from the parents by 3-day food record.
- Protein requirements were calculated to meet the minimum daily needs (1 g/kg/day).
- All children were started on a standardized classic ketogenic diet with a ratio of 3:1 (grams of fat:combined carbohydrate and protein), with a gradual increase in the fat content over 3 days.
- No fluid restriction was implemented.

2.3. Diet initiation

- The original ketogenic diet protocol created by Wilder [9], and elaborated by the Johns Hopkins Hospital [5], was modified by starting the diet without initial fasting and the diet was initiated in the outpatient setting.
- Parents were instructed to detect the acetone in urine using the dipsticks several times a week.
- Multivitamins were prescribed to meet the patients' requirements.

- The parents were encouraged to follow the diet for a minimum of 4 weeks so that the diet could be fine-tuned to achieve optimal tolerance and seizures control to allow potential improvement to occur.
- While on diet, patients were re-evaluated by the treating physicians after 1, 3 and 6 months from the date of diet initiation.
- During the follow-up visits, pediatric neurologist assessed seizure frequency, and pediatric clinical nutritionist checked food tolerability and side effects.
- The percentage reduction in seizure frequency from the baseline, and the length of time remaining on treatment were both used to assess the diet efficacy.
- Diet responders were defined as those who had a $\geq 50\%$ decrease in seizure frequency from baseline collected from parent seizure calendars for 2 weeks before diet initiation. Patients who achieved $< 50\%$ reduction in seizure frequency were defined as non-responders.

2.4. Statistical methodology

Demographics, clinical features, and dietary intervention measures were described using descriptive statistics. Median and interquartile range (IQR) were used for continuous variables, frequencies and percentages were used for categorical and ordinal variables. All statistical procedures have been done using SPSS v 22.0 for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc windows (MedCalc Software bvba 13, Ostend, Belgium).

3. Results

3.1. Patients and disease characteristics

The median age of the treated children at the time of diet initiation was 60 months (range, 30–110).

Mother's education level was used as a surrogate for the socioeconomic status. Out of the 28 mothers, only 6 (21%) were college graduates, while the rest were either high school graduates 10 (36%) or just received primary education 11 (39%). One of the mothers didn't receive any form of education.

Patients with variable diagnoses were included in the study. Nine patients (39.2%) were diagnosed with epileptic encephalopathy (3 diagnosed as Lennox–Gastaut syndrome, 2 as Dravet syndrome and 4 were unclassified).

In four patients (14.3%), the epilepsy was a post-encephalitic event, while in 6 patients (21.4%) the etiology was perinatal hypoxic–ischemic injury. Three patients (10.7%) had Rasmussen's encephalitis, and 6 patients (10.7%) had idiopathic epilepsy.

According to the etiology of epilepsy, patients were either symptomatic (78%) or idiopathic (22%).

Out of the 28 enrolled children, 11 patients (39%) had multiple types of seizures. Generalized tonic–clonic, myoclonic, focal seizures were the most common with 4 patients each group. Ten patients (35.7%) had > 10 seizures/day. Detailed clinical characteristics are displayed in Table 1.

The children had previously received a mean of six different AEDs and were on a mean of 3.5 AEDs when the diet was initiated.

Table 1
Seizure types and frequency for enrolled patients.

		Seizure frequency per day			Total
		<5	5–10	>10	
Type of seizures	Multiple	4	4	3	11
	Psychomotor	0	1	2	3
	atonic	1	0	0	1
	Generalized tonic clonic	1	2	1	4
	Myoclonic	1	2	1	4
	Focal	0	1	3	4
	Tonic	1	0	0	1
Total		8	10	10	28

3.2. Dietary intervention

3.2.1. Menu preparation

Prior to diet initiation, an individualized dietary plan was crafted for each patient according to his caloric needs, and based on a ratio of fat to carbohydrate and protein at 3:1. Multivitamins were prescribed to all patients.

Example of a one-day menu designed for a 3 years old boy, weighing 14 kg. (1150 kcal/day and 20 g protein) is shown in Table 2.

A non-fasting initiation protocol was used for all children without hospital admission.

3.2.2. Duration on diet

Patients remained on diet for a median of 4 weeks (range, 2–24). Ten patients (40%) discontinued the diet after 2 weeks. At one month from diet initiation, 16 patients (57%) were on diet. At three months, 26 patients were still adherent to their dietary plan (21.4%). Six months after initiating the diet, only 3 of the initial 28 (11%) remained on the diet.

3.2.3. Causes of discontinuation

Ten patients (35.7%) discontinued the dietary intervention because they found it too restrictive and/or intolerable. Six patients (21.4%) discontinued the diet because of dietary ineffectiveness. Other causes behind diet discontinuation and the timing of discontinuation are illustrated in Table 3.

3.2.4. Adverse effects and tolerability

One or more minor adverse events were reported in 15 (54%) patients. Those included constipation in 5 patients (17.8%), fatigue in 2 patients (7.1%), hypoglycemia in 2 patients (7.1) and vomiting in 3 patients (10.7%). Eight patients (28.5%) suffered from 2 or more of the previously mentioned side effects. None of the noted adverse events was significant enough to require dietary modification.

3.3. Seizure control outcomes

At 1 month from diet initiation, 16 patients (57%) remained on the diet. One of them (6.3%) had more than a 90% reduction in seizure frequency; an additional 6 patients (37.5%) had a 50–90% decrease in seizure frequency.

In total, 7 out of the 16 patients continuing the diet for 1 month (43.8%) had a $\geq 50\%$ improvement in seizure control from the baseline. Despite having 50–90% seizure control, three children discontinued the diet after one month.

Three months after diet initiation, 6 patients (22%) remained on diet, 4 of them (66.7%) had a $\geq 50\%$ reduction in seizure frequency.

Table 2

Example of the KD menu with the 3:1 ratio of fat and not-fat (For a three-years-old child).

Food Items	Carbohydrates	Protein	Fat	Calories
Breakfast:				
• One egg	0.1 g	6 g	5.4 g	70
• Butter 35 g	0.1 g	0.2 g	28.7 g	259
• Green Pepper 50 g	2 g	0.6	0.1 g	12
• Green Onion 25 g	2.3 g	–	–	12
Lunch:				
• Minced beef 30 g	–	6 g	5.3 g	72
• Eggplant 70 g	3.6 g	1 g	–	21
• Tomato 50 g	1.5 g	0.5 g	–	10
• Oil 30 g	–	–	30 g	270
Dinner:				
• Cauliflower 100 g	4 g	2.3 g	–	28
• Cheddar Cheese 10 g	0.1 g	2.6 g	3.2 g	40
• Oil 30 g	–	–	30 g	270
Snack:				
• Strawberry 50 g	3.8 g	0.3 g	0.1 g	16
• Cream 40 g	1.1 g	0.8 g	14.8 g	138
Total	18.6 g	20.3 g	117.6 g	1118

Table 3

Causes of diet discontinuation.

Reasons for discontinuation	Discontinued <1 month (n = 12[43%])	Discontinued 1–3 months (n = 10[35%])	Discontinued >3 months (n = 3[11%])
Too restrictive	11	4	1
Ineffective	2	6	2
Social reasons	1	2	1
Side effect	1	1	0

At 6 months, only 3 patients were still on diet, 2 of them (66.6%) achieved 50–90% seizure reduction, while one patient (33.3%) achieved >90% reduction in seizure frequency. Table 4 shows the outcomes of the ketogenic diet at different time points.

4. Discussion

In the current report, we describe the creation of a Ketogenic diet menu originating from the Egyptian kitchen in an attempt to make it accessible to the different socioeconomic levels in this country.

Furthermore, the results of our study demonstrated that the ketogenic diet appears to be an effective and well-tolerated treatment for children with drug-resistant seizures.

No ketogenic diet based formula was used to minimize the expenses. An age limit was made for offering the diet to patients (2–15 years) with no major comorbidities. This comes in concordance with recommendations of the International League Against Epilepsy (ILAE) task force4.

Due to children's inability and parents' refusal of fasting, we modified the original Johns Hopkins' protocol9 to a non-fasting one without hospitalization. This method of diet introduction was supported by the study conducted by Vaisleib et al., which recommended that it is possible to successfully initiate the ketogenic diet on an outpatient basis without fasting, fluid or caloric restriction [10].

Moreover, in another study comparing the fasting versus the non-fasting protocol, Kim et al. [11] concluded that the initial fasting and fluid restriction are not essential for the KD and that the omission of those two steps renders the protocol more tolerable. These recommendations are in parallel to that of the International Ketogenic Diet Study Group, in which 73% of the panel believed an outpatient initiation could be used [5].

Compliance with KD was variably reported. Some studies limited compliance reporting to those patients who showed clinical progress and did not consider those with no improvement who stopped the diet to be non-compliant.

In most of the published series, compliance rates at three and six months ranged from 62%–91% and 38%–78% respectively [12–18].

In our current analysis, we reported a compliance rate of 22% at three months and 11% at six months. Despite having 50–90% seizure control, three children discontinued the diet after one month. In fact, the most common source of protein for low-income families in Egypt is basically derived from legumes especially black beans, which is known for its high carbohydrate content. Thus, eliminating such type of food from our patients' food menu rendered the diet “too restrictive or “difficult to follow” and this was the main reason for early diet discontinuation.

In addition to the previously mentioned reasons, one more cause of diet discontinuation was that it was easier for most of the parents to

Table 4

Seizure reduction in patients maintained on ketogenic diet at 1, 3, and 6 months duration of treatment compared to baseline.

Seizures reduction (%)	1 month N (%)	3 months N (%)	6 months N (%)
No reduction	4 (25%)	0	0
<50% reduction	5 (31.2%)	2 (33.3%)	0
50–90% reduction	6 (37.5%)	3 (50%)	2 (66.7%)
>90% reduction	1 (6.3%)	1 (16.7%)	1 (33.3%)

keep their children on more than 3 or 4 medications rather than changing their whole lifestyle. Besides, anti-seizure medications could be provided through charity foundations or through health insurance coverage, making medications of lower cost than the ketogenic diet food menu.

Freeman et al. [17] emphasized that the most common reason for discontinuing the diet was neither the tolerance of the diet nor the difficulty in diet preparation, but rather that the diet was not satisfactorily effective. If seizures are significantly reduced (>50%), the probability of remaining on the diet at 12 months is 80%. If seizure reduction is <50%, we see a falling percent in the number of patients remaining on the diet throughout time.

In a systematic review of the Use of the Ketogenic Diet in Childhood Epilepsy, Keene concluded that the estimated rate for achieving complete seizure control was 15.6% (95% CI 10.4–20.8%) with 33% (95% CI 24.3–41.8%) reporting more than 50% reduction in seizures [19]. The results of this analysis propose that approximately half of the children with drug-resistant epilepsy will have clinical improvement after treatment with the ketogenic diet.

In the current study, 16 of the initial 28 patients (57%) remained on the diet at one month. One of them (6.3%) had more than a 90% reduction in seizure frequency; an additional 6 patients (37.5%) had a 50–90% reduction in seizure frequency. Thus, 7 out of the 16 continuing the diet for 1 month (43.8%) had ≥50% improvement in seizure control from the baseline. Three months after starting the diet, 4 patients (66.7%) had a ≥50% reduction in seizures frequency.

In a randomized controlled study by Neal et al., they reported that 28 children (38%) in the diet group had more than 50% seizure reduction compared with four (6%) controls ($p < 0.0001$), and five children (7%) in the diet group had greater than 90% seizure reduction compared with no patients in the control group ($p = 0.0582$) [20].

The lower seizure control rates reported in our study could be justified by that most of our patients started the diet late in the disease course after developing resistance to most of the AEDs. There might also have been selection bias in some of the other studies, with the diet offered to children with a type of epilepsy that was recognized to be more responsive to the dietary therapy.

No children under the age of 2 years were included in the current analysis as our institutional policy was not to offer this type of diet to this age group due to the unavailability of the ketogenic diet based formula. This might have affected the results as children in this age group are known to respond more satisfactorily than older children do [21].

Some of the limitations of our study were the small sample size and the short follow-up duration (6 months).

One more limitation in our study and in most of the other published reports is to assess the long-term effectiveness of KD. Seizure control is dependent on strict compliance with the dietary plan and there is no way to guarantee a 100% adherence to the KD plan at home. Consequently, deviation from the prescribed food menu could result in breakthrough seizures which would be mistakenly reported as ineffectiveness. Furthermore, assessment of efficacy depends on the parental statement which is subjective and may be conflicting even among members of the same family.

Establishing ketogenic diet center in a developing country like Egypt was never an easy mission, alongside the previously mentioned limitations; there are other obstacles specific to our community, such as lack of health insurance coverage to most of the affected population. This means that the cost of the investigations and supplements would add burden to the families besides the costly food. Moreover, most of the medications and the shelf food have no nutritional labels, which create a real challenge in counting the calories and the carbohydrate contents in each food item. Also, we can't ignore that the Ketogenic diet is expensive and was not easily affordable to all families included in the study.

In a trial to match the restricted financial resources, we adopted certain policies to cut down the cost of the dietary therapy. First, the non-fasting protocol was implemented at diet initiation to avoid the need for hospital admission. Second, the ketogenic diet based formula was not used and local vitamins and supplements were used. Third, some families couldn't afford and/or use the digital scale, so the scale was replaced with standardized measuring tools (e.g. tablespoons, cups). The recipes were designed using those tools, not in grams.

Future directions in research in KD in low-medium income countries should focus on assessing other types of ketogenic diet, especially the low glycemic index diet, which would result in expanding the food menu and render it more suitable to the cultural trends in the diet.

5. Conclusion

The current study shows that the ketogenic diet could be implemented in low to medium resources countries and should be included in the management of children who have drug-resistant epilepsy.

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