

INTRACTABLE SEIZURE DISORDERS: EFFICACY OF THE CLASSIC KETOGENIC DIET

P.Karimzadeh MD¹,
S. Tabarestani MD²,
F. Mahvelati MD³,
S.H. Tonekaboni MD¹,
M. Ghofrani MD⁴

1. Pediatric Neurologist, Associate Professor of Pediatric Neurology Department, Pediatric Neurology Research Center, Shahid Beheshti Medical University (SBMU)
2. Pediatric Neurologist
3. Pediatric Neurologist, Assistant Professor of Pediatric Neurology Department, Pediatric Neurology Research Center, Shahid Beheshti Medical University (SBMU)
4. Professor of Pediatric Neurology, Pediatric Neurology Research Center, Shahid Beheshti Medical University

Corresponding Author:
P.Karimzadeh MD
Tel: +98 21 22909559
Fax: +98 21 22909559
Email: Pkarimzadeh@sbm.ac.ir

Abstract

Objective

The ketogenic diet is a high-fat, low carbohydrate, adequate protein diet, developed in the 1920s for the management of intractable seizure disorders in children. To evaluate efficacy and tolerability of the classic ketogenic diet, we analyzed records of the children started on the diet from 1999 to 2006 at the Mofid children's hospital.

Materials & Methods

The subjects were 87 children, mean age 55 months. Before initiation of the diet, 55% of the patients had seizures, at least 1-4 times per day, 36% - 5 or more per day and 9% - 2 to 4 times per week. Mean number of Anti Epileptic Drugs (AEDs) tried for them was 8 and 67% were receiving three or more drugs.

Results

The ketogenic diet showed drastic improvement, with at least 50% reduction in seizure frequency in 87% of our patients, 39% of whom showed complete seizure control in the third month. After one year, in 80% of the patients who returned, improvement continued, with 26% of them being seizure free; besides, 23% had one AED decreased, 36% had two or three AEDs decreased, and 25% (one child) had all AEDs discontinued. Of the 30 improved cases, 20%, at the end of the first year, had improved behavior as well, and 23% of them had become more alert. The median diet duration of the improved group was 15 months.

Conclusion

The improvement in our patients, low side effects, and the duration of diet by families reveal that the ketogenic diet can still be a very useful alternative therapy in certain epileptic children.

Key words: seizures, epilepsy, diet, ketogenic

Introduction

Seizure disorders in childhood are a frequently occurring neurologic problem (1). The prevalence of single and recurrent nonfebrile seizure in children aged under 10 years, ranges from 5.2 to 8.1 per 1000.(2) Antiepileptic drugs (AEDs) are primary treatment modalities and, in most children, provide good seizure control. However, more than 25% of children with seizure disorders either have intractable seizures or suffer from significant adverse effects secondary to medication. Standard AEDs produce side effects in 50% or more of patients and are associated with a number of chronic toxicity syndromes; besides, only a limited number of children benefit from

surgical therapy (2).

The classic 4:1 ketogenic diet was devised in 1920 for treatment of refractory seizures in children when limited AEDs were available. With such a diet, most of the calories are provided as fat as heavy cream and butter; no sugar is allowed, and vitamins and minerals are supplemented. The diet is very rigid and requires strict nutritional supervision. Despite continuing interest in the diet long-term acceptability, effectiveness should be determined (2,3,4).

In this study, we analyzed the records of 87 patients who had been prescribed and had started the diet at Mofid children's hospital (1999 to 2006), to evaluate the efficacy and acceptability of the classic ketogenic diet .

Materials & Methods

The files of 87 children started on the diet at Mofid children hospital, between April 1999 and March 2006, were reviewed by telephone, follow-up with parents, nutrition and neurologic clinics notes, used to supplement hospital records. We were unable to obtain adequate information on 11 patients. Mean follow-up time was (range 1-24 months) 9.4 ± 9.8 SD. Only children who had been refractory to most other forms of therapy or those who had had severe adverse reactions to AEDs, were offered the diet after the family conditions were evaluated and found to be appropriate, regarding competency and cooperation.

On the first day following admission to hospital, EEG was performed and laboratory studies (CBC, plt count, chemistry panel) were carried out. The child fasted in the hospital for 24-72h, until 4+ ketonuria was produced. All carbohydrate-containing medications were discontinued. The diet was started at the classic 4:1 ratio (ratio of grams of fat to protein plus carbohydrate). Calories were calculated on the basis of age and weight to provide appropriate calories and protein intake for growth. Younger children were started at the lower ratio (3:1) to allow more protein. Fluids were restricted to 75% of maintenance level, considering the fact that urine specific gravity was not more than 1030 and weight loss was not over 1%. Total carbohydrate intake per day was not more than 30 gr and not less than 10 gr. Patients were observed in the hospital for the signs and symptoms of hypoglycemia and severe ketonemia, with blood glucose

and urine ketone being checked twice a day. When the urine ketones reached 4+ or 3+, depending on the child's age, the diet was initiated. The child received one meal at one third of total calories, and following toleration, was advanced to two third of the total calories for three meals and then consumed his or her first full meal (2,5). Prior to discharge, mothers had been educated, supplements were added and AEDs were reduced. After discharge, patients received follow up at neurologic and nutrition clinics in the first, the third and the sixth month and the first, the second and the third year. Assessment of seizure control was based on the reports of parents. We used X² statistic test and Fisher exact test for data analysis.

Results

. Patients

Of the patients, 56% were male and 28% were microcephalic; 85% of them had neurologic handicaps, mental, physical or both, while 16% were in normal neurologic range; 3 of them were suspected of having a neurodegenerative process, and 16 patients had static specific diagnoses like asphyxia, TORCH, Stroke and Sequel of meningitis or encephalitis. There were one Turner syndrome and one Tuberos sclerosis among our patients. Mean age at diet initiation was 55 months ($55 \text{ months} \pm 24 \text{ SD}$), range of 17-108 months.

Mean age of seizure onset was 14 months ($14 \text{ months} \pm 17 \text{ SD}$) range neonatal period to 78 months. The percentage of different types of seizures in our patients were as follows: 29% myoclonic, 25% mixed type, 24% partial (including simple or complex), 8% generalized tonic clonic, 10% generalized tonic and 3% atonic (table 1). In 41 patients with EEG data, 24% had EEG features consistent with Lennox-Gestaut syndrome (LKS), 12% had hypsarrhythmia, 7% had focal epileptic activity and others had generalized epileptic activity consisting of spikes, sharp waves, spike waves or High Voltage Slow Waves (HVSWS).

The mean number of AEDs tried before the diet was 8, and at diet initiation, 67% of children were receiving three or more drugs. The frequency of seizures in 55% of the patients was at least 1-4 times/per day, in 36% was 5 or more times/ per day and 9% of them had seizures at least 2-4 times/ per week. Mean follow-up time was

9.4 months.

2. Results post diet

Seventy-one percent of patients who returned at the end of the first month showed a decrease in seizure frequency of at least 50%; 20% become virtually seizure free, but unfortunately there was no improvement in 29% of them. At the end of the third month, acceptable decrease in seizure frequency (at least 50%) had occurred in 87% of children, of which 39% had complete seizure control. At the end of sixth month, in 63% of them, reduced seizure frequency was set to continue and all of former

seizure free patients, also remained seizure free.

After one year, of 80% of patients followed up, improvement had continued and 26% of them were seizure free; moreover, 44% of the improved group from the first month, remained on the diet with acceptable seizure control (Figure 1).

Cessation of diet occurred in 5%, because of inability or unacceptability; the side effects that necessitated cessation however were observed in three cases, two with severe infection and one with AEDs toxicity.

Table1. Effectiveness of ketogenic diet on 76 children with refractory seizures in Mofid children’s hospital

Seizure control	First month 1 st	Third month 3 rd	Sixth month 6 th	First year 1 st yr	Over one year	Number of patients*
Seizure free	16	13	13	8	7	76
80% reduction	19	22	18	12	8	58
50% reduction	19	14	8	4	1	47
No response	22	7	8	6	0	30
No follow-up	11	2	3	9	14	16

*At the initiation of the diet

Table 2. Seizure control in the sixth month according to seizure type

Generalized tonic-clonic	Generalized tonic*	Atonic	Partial	Mixed type	Myoclonic+	Seizure type
						Therapeutic results
1 (17%)	3 (38%)	—	5 (28%)	3 (16%)	1 (4.5%)	Seizure free
3 (50%)	—	—	5 (28%)	6 (32%)	7 (32%)	80% reduction
—	1 (13%)	2 (100%)	4 (22%)	5 (26%)	3 (14%)	50% reduction
2 (33%)	2 (25%)	—	4 (22%)	5 (26%)	10 (45%)	No response
6	8	2	18	19	22	number

*Two patients discontinued the diet

+One patient did not return

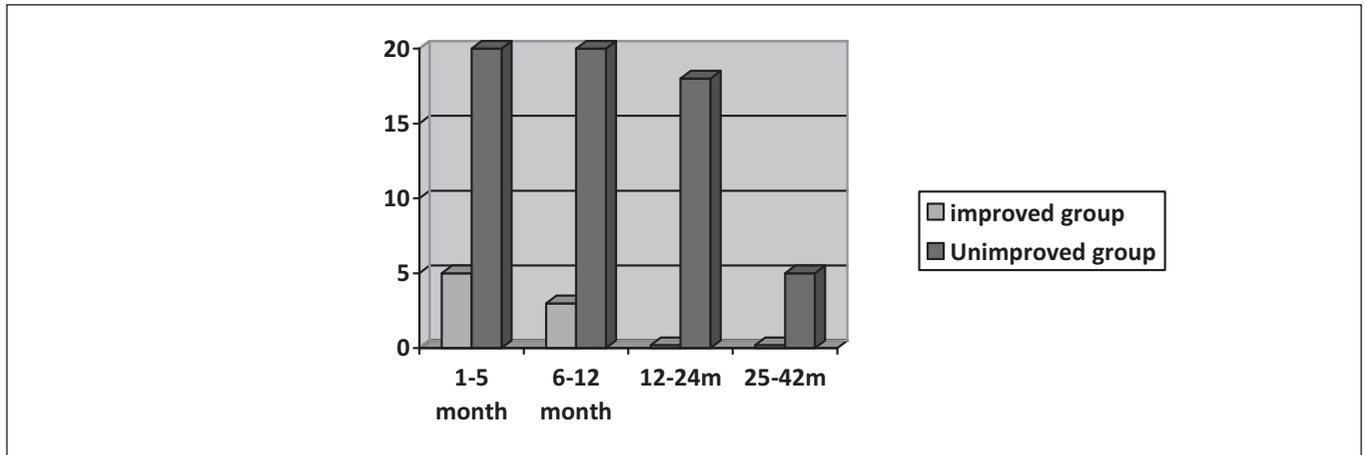


Fig. 1: Diet duration status of patients; those remaining on the diet, those who improved, compared to those who did not; 15 did not return after the first year.

At the end of the sixth month, of the 39 improved patients, 23% was using one less AED, while 2.5% (one child) had all AEDs discontinued; 20% of 30 improved children, at the end of first year, had improved behavior as well, and 23% of them became more alert, based on the basis of their mothers' reports.

From our data, there is no relationship between success with the diet and age ($p=1$), type of seizure ($P=0.3384$, $df=3$, $X^2=3.36$ and neurologic development ($P=0.066$, $X^2=3.38$, $df=1$) even though, the diet induced better response in normally developed children ($P=0.0380$, $X^2=4.30$, $df=1$). This indicates that most of neurologically normal patients were in the improved group with 80% reduction in seizure frequency in comparison with improved group with 50% reduction in seizure frequency..

The median diet time of the improved group, at the end of sixth month, was 15 months (15 months \pm 10.6 SD) and that of the unimproved group was 2.27 months (2.27 \pm 1.5 SD), with significant statistical difference ($P<0.001$) (figure1).

The diet was effective in 6 of 10 patients with clinical and EEG features of LKS (60%), while it showed improvement just in 2 of 5 cases with infantile spasm with hypsarrhythmia.

Side effects

Side effects are reported here categorized in two groups, the early and the late side effects groups; in the first week, transient hypoglycemia occurred in 8 children

(10%) who got better by drinking sweet fluids; moreover, mild transient epistaxis occurred in one boy, nausea and vomiting in 7 patients (9%) and cessation of diet was necessary in one case.

During the first month, frequent vomiting and hematemesis in one child led to cessation of the diet.

In the late side effects group, levels of cholesterol and triglycerides increased in 2, and there was loss of appetite in 2 others. One child developed renal stones after the second year of the diet; one showed indications of cardiomyopathy in the 15th month, and one had gastritis in the first year (based on endoscopy results).

One child had AED toxicity at the sixth month of the diet (toxic blood levels of phenobarbital and phenytoin, followed by admission due to unconsciousness and frequent seizures, and eventually discontinuation of the diet.

Discussion

The Ketogenic diet has been used in children with intractable seizures for over 90 years. Epilepsy in children can mostly be controlled with one medication; those whose seizures cannot be controlled with the first, properly used, medication, have a less than 20 percent chance of their seizures being controlled with the second medication. Children with seizures that are difficult to control with two medications have only a 25 to 40 percent chance of their seizures being controlled with other medications; this latter group of children, whose seizures were not controlled by three or more

medications, have been termed, by some, as intractable or difficult to control(4).

The results of our study are similar to those of a previous report of a 10-year prospective follow up from this hospital in 1987(6), and also other studies of Kinsman(1992), Vining(1996), Schwartz(1989), Livingston(1972) and Swink(1997) (2,3,7,8,9). Of note, those studies mentioning either type of seizures (3,6,8,9) or sex, age and EEG findings (9) have not shown any relationship between the earlier mentioned and response to the diet documented results in agreement with ours.

According to low number of infantile spasms, i.e. only 4, we cannot comment precisely on the efficacy of the diet about it ; nevertheless, response of 23 infantile spasm patients, at Johns Hopkins institution with a 4 year-follow up, reported the diet to be a safe well-tolerated and effective alternative to other therapies; a lower efficacy however was observed when EEG showed hypsarrythmia(10).

In LKS, better response was seen in myoclonic seizures than other types; even in one unimproved patient with just 30% reduction in seizure frequency, the maximum reduction was observed in drop attacks. In comparison, other researches reported remarkable reduction in myoclonic, atonic and atypical absence type (11); moreover, even after 36 hours fasting in the Freeman study has induced more than 50% reduction was seen in myoclonic and atonic attacks (12).

The knowledge and experience of dieticians are fundamental to this diet; our nutritionist planned the diet keeping in mind regional dietary habits and encouraging the desired attitude and acceptance in child and family.

Consistent with results of other researches, our study reveals good association between continuation of the diet and therapeutic response (3,6); however ability to remain on/adhere to the diet, affects seizure control.

There are many limitations in this study including lack of information about some patients especially after the first year, retrospective evaluation and reliance on parental reports.

The mechanism by which this regimen controls convulsions is still unknown; it is independent of respiratory or metabolic acidosis and the accumulation of ketone bodies, and the anticonvulsant effects are not a result of the direct effect of ketone bodies on voltage and

ligand-gated ion channels. Switch in cerebral metabolism involving the use of B-hydroxybutyrate instead of glucose as a energy substrate may reduce neuronal excitability (1,13). There are several hypotheses regarding this; alteration in either the metabolism of brain aminoacids or extracellular milieu (13,14) and enhancement on activation of mitochondrial uncoupling protein which exert neuroprotective effects (15). The large number of children who now are free (or nearly free) of medications, are free (or nearly free) of seizures and are currently off the diet should encourage search for the mechanisms by which the diet not only suppresses seizures but perhaps also alters the underlying epileptogenicity of the brain. (4) Renal stones developed in one patient (1.5%), reported to be up to 10% in other studies (4); however with more prolonged diet (mean 7.8 years), this figure reached up to 25% (16). Risk factors for renal stones include lower age at the initiation of the diet (our patient was 2 years old) and hypercalciuria (17). Although occasionally patients need lithotripsy or surgical removal of the stones, this was no reason for cessation of diet in children whose seizures had improved (4). Cardiac complications of the ketogenic diet in the absence of selenium deficiency have not been reported, while prolonged QT interval (QTC), cardiac chamber enlargement and cardiomyopathy have been found. There was a significant correlation between prolonged QTC and both low serum bicarbonate and high beta-hydroxybutyrate (18).

One patient with severe cardiomyopathy in 15th month of diet, normalized when the diet was discontinued.

Lack of double blind studies is an issue preventing wider acceptance by the medical profession. Double blind studies help elimination, placebo effect, spontaneous remission and researchers expectations of prejudice about their observations (19).

Another limitation of the diet is strictness; furthermore, Atkins diet type has been supposed by other specialists since there is no need to admit the child and it is easier to administer and will not require a more rigorous diet. If the child does not respond, they initiate the traditional ketogenic diet . It is of interest to note that the Atkins diet also can reduce seizure frequency in focal and multifocal epilepsy (16).

Another alternative is the low-glycemic-index diet with more liberal total carbohydrate intake but restricted to

foods that produce relatively little increase in blood glucose (glycemic index <50); Ten of 20 patients treated with this regimen experienced over 90% reduction in seizure frequency (20).

One study aiming to establish a dose-response relation for the efficacy of ketogenic diet, showed that the conventional 4:1 diet does not confer the greatest level of seizure protection. They concluded that a 6:1 diet which shows no evidence of neurotoxicity, is maximally efficacious in rats (21). In the future, it may be possible to offer a range of ketogenic diets consisting different ratios of carbohydrate and fat depending on characteristic features of patients or their seizure disorders.

Our study showed good effectiveness, appropriate acceptance, low side effects and improvement in behavioral and cognitive scales in our patients. Since so many questions need to be answered about the diet, its adverse effects should be always considered in comparison to the impacts of frequent seizures and side effects of AEDs.

References

1. Sankar R, Koh S and Menkes J H. Paroxysmal disorders. In: Menkes J and Sarnat BH (eds), child neurology, 7th ed, Philadelphia: Lippincott Williams & Wilkins; 2006. P.905-906.
2. Wheless J W and Ashwal S. The ketogenic diet. In: Swaiman KF and Ashwal S (eds), pediatric neurology principles and practice, 3th ed, Philadelphia: Mosby; 1999. P.719-726.
3. Kinsman S Land vining EP Vining EP, Quaskey SA, Mellits D, Freeman JM. Efficacy of the ketogenic diet for intractable seizure disorders: Review of 58 cases. *Epilepsia* 1999, 33(6): 1132-1.
4. Hemingway C , freeman J M, DJ Pillas, PL Pyzik. the ketogenic diet: A 3-to 6-year follow-up of 150 children enrolled prospectively. *Pediatrics* 2001;168 (4): 898-905.
5. Livingston S. Dietary treatment for epilepsy. In: Livingston (ed), Living with epileptic seizures, Michigan: Springfield, Charles, Thomas; 1963. P.143-150
6. Mostagimi P, Ashrafzadeh F, Ghofrani M. Efficacy of the ketogenic diet on intractable epilepsy in children and report of 215 cases. *J of medial council of Islamic republic of IRAN* 2001; 18(4): 288-294.
7. Vining EP. Clinical efficacy of the ketogenic diet. *Epilepsy Res* 1999;37(3):181-190.
8. Maydell BU, Wylliet , Akhtar N, Kotagal P, Powaski K, Cook K, et al. Efficacy of the ketogenic diet in focal versus generalized seizures. *Pediatr Neurol* 2001;25(3):208-212.
9. Vining P, freeman JM, Ballaban KG, Camfield C, Camfield PR, Holmes GL, et al. A multicenter study of the efficacy of the ketogenic diet. *Arch Neurol* 1998;55(11):1433-1437.
10. Kossoff EH, Pyzik PL, McGrogan JR, Vining EPG, Freeman JM. Efficacy of the ketogenic diet for Infantile Spasms. *Pediatrics* 2002;109(5): 780-783.
11. Wheless JVU, Constantinou J E. Lennox-Gastaut syndrome. *Pediatr Neurol* 1997; 17(3): 203-211.
12. Freeman J M , vining E P. Seizures decreased rapidly after fasting: preliminary studies of the ketogenic diet. *Arch Pediatr Adolesc* 1999;153(9): 946-949.
13. Schwaetzkroin P A. Mechanisms underlying the anti-epileptic efficacy of the ketogenic diet. *Epilepsy RES* 1999;37(3): 171-180.
14. Yudkoff M, Daikhin Y, Nissim I, Lazarow A, Nissim I. ketogenic diet, amino acid metabolism and seizure control. *J of neuroscience research* 2001; 66(5): 931-940.
15. Sullivan PG, Rippey NA, Dorenbos K, Concepcion RC, Agarwal AK, Rho JM. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. *Annals of Neurology* 2004;55(4):570-580.
16. Wilner A N. Long-term effects of the ketogenic diet. *Neurology* 2006; 66(2): 41.
17. Furth SL, Casey JC, Pyzik PL, Neu AM, Docimo SG, Vining EP, et al. Risk factors for urolithiasis in children on the ketogenic diet. *Pediatric nephrology* 2000;15(1-2): 125-128.
18. Best TH, Franz DN, Gilbert DL, Nelson DP, Epstein MR. Cardiac complications in pediatric patients on the ketogenic diet. *Neurology* 2000;54(12): 2328-233.
19. Kang HC, Chung DE, Kim DW, Kim HD. Early-and-onset complications of the ketogenic diet for intractable epilepsy. *Epilepsia* 2004;45(9): 1116-1123.
20. Heidi H, Pfeifer RD, E.A. Thiele. Low-glycemic -index treatment: A liberalized ketogenic diet for treatment of intractable epilepsy. *Neurology* 2005;65:1810-1812.
21. Bongh KJ, Yoa SG, Eagles DA. Higher ketogenic diet ratios confer protection from seizures without neurotoxicity. *Epilepsy Res* 2000 Jan; 38(1):15-25.