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Long-term outcome and tolerability of ketogenic diet treatment for refractory epilepsies in children – A tertiary centre Malaysian experience

[1]Teik-Beng Khoo *MBBS MMed (Paeds),* [2]Siti Mariam binti Tukimin *BSc Hons (Dietetics),* [2]Sharifah Mariam binti Syed Zainal Abidin *BSc Hons (Dietetics),* [2]Jaan-Jiar Lai *BSc Hons (Dietetics),* [2]Noor Adzha binti Yusoof *BSc Hons (Dietetics)*

[1]Paediatric Neurology Unit, Department of Paediatrics, Institute of Paediatrics, [2]Department of Dietetics and Food Services, Hospital Kuala Lumpur, Malaysia

Abstract

Objective: To evaluate the long-term efficacy, retention rate and tolerability of ketogenic diet treatment (KD) for children with medically refractory epilepsies from a single tertiary centre in Malaysia. *Methods:* Children who were treated with ketogenic diet since 2006 and had at least 2 years follow up after initiation of the KD were evaluated retrospectively using intention-to-treat principle. Response is defined at seizure reduction of > 50%. Efficacy was assessed as percentage of patients who had seizure reduction by >50%, >90% and seizure freedom and retention rate was the proportion of patients who remained on ketogenic diet. *Result:* A total of thirty children were included. The median duration of treatment was 8 months (range: 7 days to 6 years). Retention rates at 3, 6, 12 and 24 months were 80%, 70%, 50% and 40% and responder rates were 70%, 63%, 47% and 37% respectively. The common adverse effects were constipation (43%), hunger (23%), excessive weight gain or loss (20%), vomiting (10%), hyperuricaemia(30%), hypocalcaemia (20%) and renal calculi (13%). The common reasons for stopping were because the diet was too restrictive (33%), infrequent seizure or seizure freedom (23%), not effective (17%) but none was due to the adverse effects.
Conclusion: Ketogenic diet treatment is effective and well-tolerated by Malaysian children in general.

INTRODUCTION

The ketogenic diet (KD) is a high fat, adequate protein, restricted carbohydrate diet used successfully to treat epilepsy since first described in the 1920s.[1] The modified Atkins diet (MAD) is a less restrictive alternative ketogenic diet where the daily carbohydrate intake was restricted to 10-20 g but free amount of protein and calories is allowed.[2] They have also been used successfully in emergency treatment of refractory status epilepticus.[3] Levy *et al.*[4] in their Cochrane database systemic review on ketogenic diet and other dietary treatment for epilepsy concluded that in children, the ketogenic diet results in short to medium term benefits in seizure control, the effects of which are comparable to modern antiepileptic drugs. For those with medically intractable epilepsy or those in whom surgery is unsuitable, a ketogenic diet could improve seizure control, but the tolerability is poor.

Ketogenic diet treatment for children with medically refractory epilepsies was started in Malaysia at Institute of Paediatrics, Hospital Kuala Lumpur in 2006 and modified Atkins diet was later introduced in 2009. Its use was further extended to acute intensive care setting for children with refractory status epilepticus due to febrile illness related epilepsy syndrome (FIRES) since 2007.

The current study aims to evaluate the efficacy, retention rate and tolerability of ketogenic diet treatment for children with refractory epilepsies treated at our hospital since 2006.

METHODS

Our paediatric neurology unit at the Institute of Paediatrics, Hospital Kuala Lumpur is a tertiary referral center that caters for children with epilepsy living around Kuala Lumpur, the capital city of Malaysia as well as the more refractory cases from other states in Malaysia.

This is a retrospective case review where all patients aged between 0 to 18 years old with

Address correspondence to: Dr. Teik-Beng Khoo, Paediatric Neurology Unit, Institute of Paediatrics, Hospital Kuala Lumpur, Jalan Pahang, 50586, Kuala Lumpur, Malaysia. Tel: 6-012-553 6432, E-mail: khootb@gmail.com

medically refractory epilepsy that were treated with ketogenic diet since 2006 and had at least 2 years follow up after initiation of the KD were evaluated using intention-to-treat principle. The patients' characteristics including their demographic data, seizure types and frequencies, epilepsy syndromes, aetiologies, number of prior antiepileptic drugs was analysed. We define 'response' as seizures frequency reduction by > 50% compared to baseline, 'responder rate' as percentage of patients with seizure frequency reduction by >50% at the end of a specified period of time, 'retention rate' as percentage of patients continuing to take KD at the end of a specified period of time (i.e. 3, 6, 12 and 24 months). Efficacy is also expressed in percentage reduction in seizure frequency, such as by>50%, >90% and seizure freedom.

RESULTS

A total of 30 cases that were treated consecutively from December 2006 until June 2012 were included. Their demographics, clinical characteristics and epilepsy syndromes are shown in Table 1. All of them had frequent daily seizures except two

Table 1: Patient characteristics and treatment

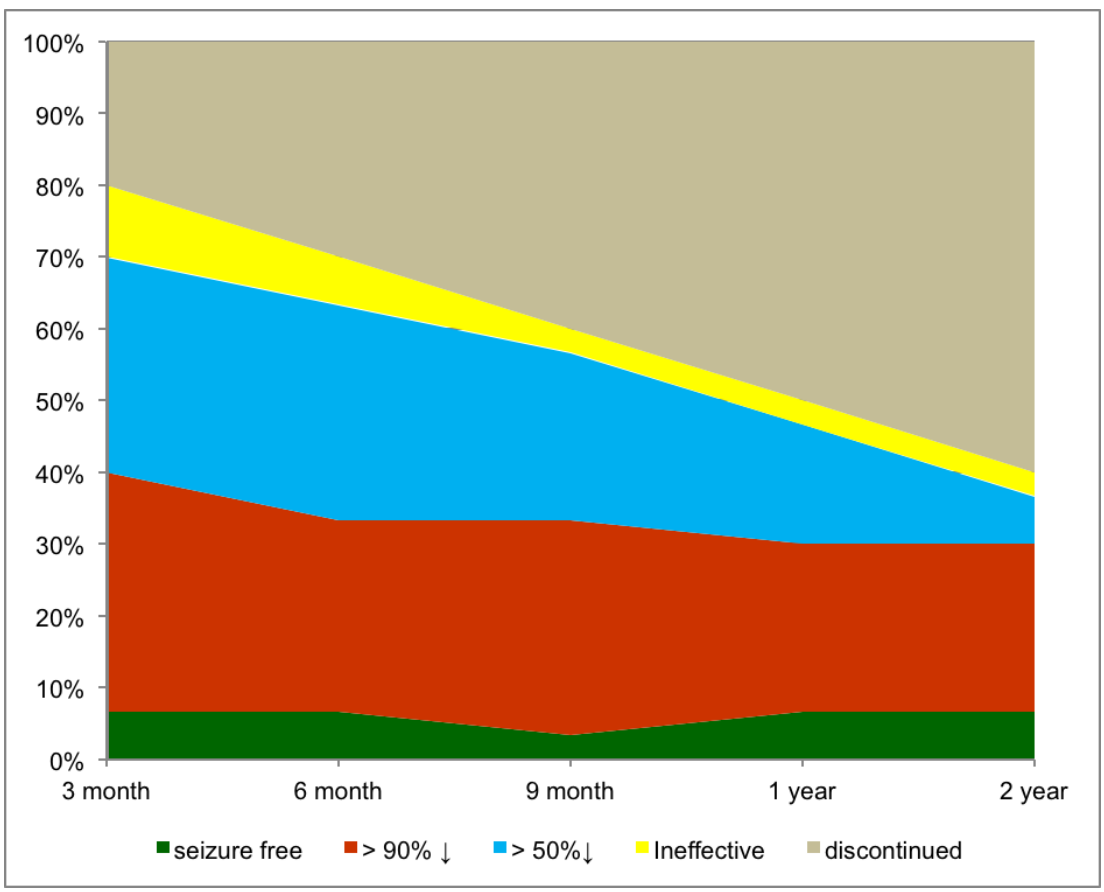
Characteristics	
Gender	
Male: Female	18 : 12
Seizure types*	
Generalized	
Tonic clonic	6
Atypical absences	4
Myoclonic absences	1
Myoclonic	11
Clonic	3
Tonic	4
Atonic	7
Focal	19
Epileptic spasm	5
Epilepsy syndromes and other epilepsies	
Medically refractory epilepsies	
Early myoclonic encephalopathy	5
West syndrome	1
Dravet syndrome	2
Epilepsy with myoclonic-atonic seizures	1
Lennox-Gastaut syndrome	4
Rasmussen syndrome	1
Epilepsies due to structural / metabolic cause	6
Epilepsies of unknown cause	4
Refractory status epilepticus due to FIRES	6
Number of AEDs tried prior to KD	
Mean (range)	7.4 (4 to 14)
Age at seizure onset, mean (range)	2.8 years (7days – 11 years)
Age at initiation of KD, mean (range)	6.8 years (8 mo – 17 years)
Type of KD at initiation	
Classical KD	
4:1 ratio	12
3:1 ratio	11
2:1 ratio	3
Modified Atkins diet	4
Duration of KD, median (range)	8 months (7 days – 6 years)

* Some patients had more than one seizure type. FIRES: Febrile illness related epilepsy syndrome; AEDs: Antiepileptic drugs, KD: Ketogenic diet treatment;

patients with Dravet syndrome who had clusters of weekly seizures. Twenty-four of them were medically refractory epilepsies who had tried from 4 to 14 antiepileptic drugs. Six had refractory status epilepticus due to febrile illness related epilepsy syndrome. The mean age at KD initiation was 6.8 years old (range: 8 months to 17 years) and the median duration of treatment was 8 months (range: 7 days to 6 years). Twenty-six of them were started on classical KD and the remaining six on MAD. The responder rates of our cohort of patients were 70%, 63%, 57%, 47% and 37%; and retention rates were 80%, 70%, 60%, 50% and 40% at 3, 6, 9, 12 and 24 months respectively as shown in Figure 1.

KD was initiated at paediatric intensive care unit for the six patients who had refractory status epilepticus, five of them had FIRES and one had anti-NMDAR antibody positive autoimmune encephalitis. The patient with autoimmune encephalitis became seizure free and was weaned off the KD after 1.5 months. The rest had seizure reduction by>90% at 3 months and the KD was continued for varying duration as shown in Table 2.

Adverse effects were reported in 25 out of 30 (83.3%) patients of our cohort during the course of their treatment as shown in Table 3. However most of them were mild. Constipation occurred in 43 % and was managed with oral laxative or glycerine enema. Other gastrointestinal adverse effects were transient. Renal calculi or nephrocalcinosis were noted in four patients (13%) of our cohort in as early as second month after initiation of the KD but could be as late



	3 months	6 months	9 months	1 year	2 years
Responder rate	70%	63.3%	56.7%	46.7%	36.7%
Retention rate	80%	70%	60%	50%	40%

Figure1. Figure showing the responder and retention rates

Table 2: Ketogenic diet treatment for refractory status epilepticus

No.	Age / Gender	Diagnosis	Seizure (at 3 months)	Duration of KD	Outcome at end of KD
1	10 m /M	FIRES	>90%↓	10 m	Seizure free
2	11 y /M	Anti-NMDAR +ve encephalitis	Seizure free	1.5 m	Seizure free
3	5 y /F	FIRES	>90%↓	6 y (still on)	Infrequent seizure
4	3 y /M	FIRES	>90%↓	2 y	Infrequent seizure
5	9 y /M	FIRES	>90%↓	1 y 9 m	Weekly seizure
6	6 y /F	FIRES	>90%↓	6 m (loss of efficacy)	Daily seizure

FIRES: Febrile illness related epilepsy syndrome; KD: Ketogenic diet treatment; m:month ; y:year; M:male; F:female; NMDAR: N-methyl-D-aspartate receptor

as 4 years on follow up. Only one of them was co-medicated with topiramate. All of them were asymptomatic and resolved by urinary alkalisation with Ural sachet for an average of six months. Common biochemical abnormalities noted were hyperuricaemia (30%), hypocalcemia (20%), hypokalemia (7%) and hypertriglyceridemia (7%). All of them were transient and were easily corrected through supplementation and changes made to the patient's diet.

The reasons for stopping the KD are shown in Table 4. One third of the patients stopped the diet because it was too restrictive. It was stopped in 5 because it was ineffective and 2 due to loss of efficacy. Three patients stopped the KD after they achieved seizure freedom and 4 with infrequent seizures were weaned off the KD after two years. Four patients were still on the KD. None of them stopped the KD because of adverse effects.

DISCUSSION

The efficacy of KD on children with refractory epilepsies in this study is comparable to that of a recent meta-analysis[5] that included 38 retrospective and prospective studies with KD as treatment option for epilepsy. The retention rate of KD in this study is favourably compared to the use of KD and MAD for children in China and Denmark respectively.[6,7] We noticed that our patients were more likely to continue taking the restrictive diet over time if they had >90% seizure reduction or seizure freedom compared to those who only had >50% seizure reduction.

Table 3: Adverse effects

	n	%		n	%
Clinical			**Biochemical**		
Constipation	13	43	Hyperuricaemia	9	30
Hunger	7	23	Hypocalcaemia	6	20
Excessive weight loss	4	13	Hypokalaemia	2	7
Vomiting	3	10	Hypertriglyceridemia	2	7
Excessive weight gain	2	7	Hypercholesterolemia	1	3
Lethargy	2	7	Hyponatremia	1	3
Anorexia	1	3	Hypomagnesaemia	1	3
Growth retardation	1	3	**Ultrasound**		
Hair changes	1	3	Renal calculi / nephrocalcinosis	4	13

Table 4: Reasons for stopping ketogenic diet

	n	%
1. Too restrictive	10	33
2. Not effective	5	17
3. Loss of efficacy	2	7
4. Family not coping	1	3
5. Epilepsy surgery	1	3
6. Seizure freedom	3	10
7. Infrequent seizures and KD > 2 years	4	13
8. Still on ketogenic diet (> 2 years)	4	13
Total	30	

KD: Ketogenic diet treatment

Similar to the experience from other worldwide centers[8], the main challenges of ketogenic diet treatment among Malaysian children were compliance to the strict diet and some tolerability issues. Some of these were overcome in recent years by having a Malaysian ketogenic diet recipe book and adaptation of local food and menu.

The adverse effect profile is comparable to what were reported by other series[9,10,11] except a high rate of renal calculi or nephrocalcinosis in this study. This is likely contributed by our active ultrasound surveillance of all our patients and our tropical weather. In view of this relatively high incidence of renal calculi or nephrocalcinosis among Malaysian children, prophylactic urinary alkalinisation, liberal fluid intake and renal ultrasonography surveillance might be advisable.

As this is a retrospective study involving a single centre, there could be important limitation such as selection bias of the cases offered the KD. Other important long term adverse effects of KD[8,12,13] on bone density and micronutrient deficiency such as secondary carnitine and selenium deficiency could not be excluded among our patients as they were not determined during the study period.

In Conclusion, KD treatment is effective and generally well-tolerated for Malaysian children with refractory epilepsies.

DISCLOSURE

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