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Efficacy and safety of the ketogenic diet in Chinese children

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ABSTRACT

Objective: To evaluate the efficacy and safety of the ketogenic diet (KD) treatment of refractory childhood epilepsy in China and determine which children are more likely to respond.
Methods: Between 2004 and 2011, we prospectively enrolled 317 children with refractory epilepsy for the KD treatment in Shenzhen Children's Hospital and followed up for at least a year. Outcome was measured by seizure frequencies before and after the diet, change in anticonvulsant use and adverse effects. We also evaluated influences of different variables (starting age, duration of epilepsy and underlying conditions) on the outcome.
Results: Intent-to-treat analysis showed that after 3, 6 and 12 months, 62.8%, 42.0% and 24.3% remained on the diet, 35.0%, 26.2% and 18.6% showed >50% seizure reduction, including 20.8%, 13.6% and 10.7% seizure free, respectively. Starting age may influence efficacy. The ≥10 age group showed worse response than the <10 age group, though the difference was statistically significant ($p = 0.039$) at 3 month only. Other variables such as duration of epilepsy at the start of the diet, seizure types and aetiologies showed no significant influence on efficacy. Frequently reported complications included GI disturbance, food refusal and hypoproteinaemia.
Conclusions: The KD is a safe and efficacious therapy for intractable childhood epilepsy in Chinese children. The influence of age on efficacy is worth further investigation.

1. Introduction

Despite recent development of anticonvulsants, 20–30% of childhood epilepsies are medically refractory.[1] The resurgence of the ketogenic diet (KD), a high-fat, adequate-protein and low-carbohydrate diet, has offered new hope to children with difficult-to-control epilepsy. This field has generated much research interest in the last twenty years, and the recent development was summarised in Kessler et al.[2] Currently, the KD has been carried out in many different countries. Despite the perceived difficulty of acceptance because of starch-based Asian diet, the KD has been introduced in China as well. However, the only existing study[3] on the efficacy of the KD in China was an early-stage preliminary evaluation conducted on a small patient group in Shenzhen Children's Hospital.

Shenzhen Children's Hospital is the first institution in China to implement a KD programme and the one with the most KD patients to our knowledge. We believe this is a valuable therapy to offer to children in China and therefore implemented its use in 2004. This report analyses 7 years' clinical data to assess the efficacy and safety of the KD for Chinese children, and whether response to the KD differs according to starting age, duration of epilepsy, and disease classification.

2. Methods

2.1. Patient selection

Between October 2004 and August 2011, 317 consecutive patients started the KD in Shenzhen Children's Hospital. They were children with intractable epilepsy, who had tried at least 3 anticonvulsants but still had more than 4 seizures per week. Children with known metabolic disorders, or severe systemic illnesses were excluded. We noted that there was a wide variation in the geographical and economic backgrounds of the children.

2.2. The KD initiation

All children were encouraged to initiate the KD as inpatients for at least one week. Among the 317 children, 304 were admitted as

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inpatients and closely monitored for any acute adverse effects for the first week. During the inpatient period, parents were educated on the rationale of the diet and ways to prepare the KD at home. The remaining 13 children started the KD as outpatients. All children were treated with the Johns Hopkins Hospital protocol[4] with an initial fasting stage of about 24 h, and a diet lipid-to-non-lipid ratio of 4:1. Every child was provided an average energy intake of 60–80 kcal/kg per day, with 1–1.5 g/kg of protein supplemented with potassium citrate, multi-vitamins and essential minerals.

The first 30 children, starting between October 2004 and June 2007, had self-prepared meals planned according to the Ketogenic Diet Meal Planner (designed by Liao using Chinese recipes). The next 28, starting between September 2007 and September 2008, used predominantly KetoCal (Nutricia) ketogenic formula as part of their diet. To increase the palatability and variety of the diet, Qitong ketogenic liquid milk (Zeneca), Qitong ketogenic cookies (Zeneca) and packaged ketogenic set-meals (Zeneca) were developed by Liao, and added in as supplements to the Ketogenic Diet Meal Planner since October 2008. All three Zeneca products have a lipid-to-non-lipid ratio of 4:1, with 60% of the total lipid long-chain triglyceride (LCT) and 40% medium-chain triglyceride (MCT).

All children were recommended to use the KD products such as KetoCal (Nutricia), Qitong ketogenic liquid milk (Zeneca), Qitong ketogenic cookies (Zeneca) and packaged ketogenic set-meals (Zeneca) during the diet initiation stage, so as to achieve a stable blood ketone level before switching to more flexible self-prepared food. The anticonvulsants were maintained unchanged for the first 3 months of the diet and adjusted according to children's conditions afterwards.

2.3. Follow-up

Children were followed up at 1, 3, 6 and 12 months after the KD initiation. They were either brought back to outpatient clinics or contacted by phone calls. Seizure frequencies, adverse effects and compliance with the diet were recorded. Height, weight, blood tests, renal ultrasound (optional) and EEG (optional) were done either in Shenzhen Children's Hospital or at local hospitals based on the Recommendations of the International Ketogenic Diet Study Group.[5] However, 18 children were lost to follow-up; their outcomes were assessed by the records at the time of their last contact and they were regarded as having stopped the diet after the last contact.

The main measure of efficacy was the decrease in seizure frequency as assessed through parental report and seizure diaries. The average seizure number in one month before a timepoint was compared to the baseline seizure number (i.e. average seizure number in the month before the start of the diet), and expressed as a percentage of reduction. The seizure control was categorised into the following categories: (1) no change or increase in seizure frequency, (2) <50% seizure reduction, (3) 50–90% seizure reduction, (4) >90% seizure reduction, and (5) seizure free.

Table 1
Retention rate and seizure outcomes at 3, 6 and 12 months after initiation of the KD.

	3 month		6 months		12 months	
	Number	Percentage	Number	Percentage	Number	Percentage
Seizure free	66	20.8%	43	13.6%	34	10.7%
Reduction 90–99%	9	2.8%	11	3.5%	10	3.2%
Reduction 50–90%	36	11.4%	29	9.1%	15	4.7%
Reduction <50%	25	7.9%	18	5.7%	6	1.9%
No change	63	19.9%	32	10.1%	12	3.8%
Retention	199	62.8%	133	42.0%	77	24.3%

2.4. Statistical analysis

To evaluate the effect of age, duration of epilepsy, epilepsy aetiology and seizure syndromes on the efficacy of treatment, we divided the cohort according to these variables and separately analysed the efficacy of the diet for each group. Classifications of epilepsy aetiology and seizure syndromes were based on the 2001 ILAE report.[6] We note that some terms, especially those used to classify aetiologies, have since changed in the 2010 ILAE report.[7]

Statistical evaluation was performed using two-tailed Fisher Exact Tests. A p-value less than 0.05 was regarded as statistically significant.

3. Results

3.1. Patient characteristics

Out of the 317 children, 206 were male and 111 were female. The starting age of the KD ranged from 2 months to 17 years 8 months, with a mean of 39.6 months (standard deviation 37.1 months). The duration of the KD ranged from 1 day to 48 months, with a mean of 5.7 months (standard deviation 7.0 months).

3.2. Treatment efficacy

At 3 months after the initiation of the KD, 199 (62.8%) of the 317 children remained on the diet: 111 (35.0%) showed >50% seizure reduction, and 66 (20.8%) were seizure free using an intent-to-treat analysis (Table 1). At 6 months, 133 (42.0%) children remained on the diet: 83 (26.2%) showed >50% seizure reduction, and 43 (13.6%) were seizure free. At 12 months, 77 (24.3%) children

Table 2
Comparison of efficacy of the KD by different ages or duration of epilepsy at the start of the diet.

	Age starting the KD			Duration of epilepsy[a]		
	<10 years	≥10 years	p-Value	<5 years	≥5 years	p-Value
3 months						
Responder[b]	109	2	0.0390	92	10	0.4584
Non-responder	190	16		173	27	
6 months						
Responder	81	2	0.1725	69	8	0.6886
Non-responder	218	16		196	29	
12 months						
Responder	57	2	0.5427	52	3	0.1115
Non-responder	242	16		213	34	

[a] 15 cases with no duration of epilepsy data are excluded from analysis.
[b] Here and afterwards, responders refer to patients with at least 50% reduction in seizure frequency, the rest are non-responders.

Table 3
Efficacy data at 12 months after the KD initiation according to different ages and duration of epilepsy at the start of the KD.

	0–2 years (n = 147)	2–5 years (n = 102)	5–10 years (n = 50)	≥10 years (n = 18)
Outcome with regard to starting age				
Seizure-free	17 (11.6%)	11 (10.8%)	5 (10.0%)	1 (5.6%)
Reduction 90–99%	3 (2.0%)	4 (3.9%)	3 (6.0%)	0 (0.0%)
Reduction 50–90%	7 (4.8%)	5 (4.9%)	2 (4.0%)	1 (5.6%)
Reduction <50%	2 (1.4%)	1 (1.0%)	2 (4.0%)	1 (5.6%)
No change	4 (2.7%)	4 (3.9%)	3 (6.0%)	1 (5.6%)
Retention	33 (22.4%)	25 (24.5%)	15 (30.0%)	4 (22.2%)
	0–1 years (n = 113)	1–2 years (n = 73)	2–5 years (n = 79)	≥5 years (n = 37)
Outcome with regard to duration of epilepsy				
Seizure-free	14 (12.4%)	10 (13.7%)	7 (8.9%)	1 (2.7%)
Reduction 90–99%	1 (0.9%)	1 (1.4%)	6 (7.6%)	1 (2.7%)
Reduction 50–90%	6 (5.3%)	5 (6.8%)	2 (2.5%)	1 (2.7%)
Reduction <50%	1 (0.9%)	1 (1.4%)	0 (0.0%)	3 (8.1%)
No change	2 (1.8%)	3 (4.1%)	4 (5.1%)	3 (8.1%)
Retention	24 (21.2%)	20 (27.4%)	19 (24.1%)	9 (24.3%)

remained on the diet: 59 (18.6%) showed >50% seizure reduction, and 34 (10.7%) were seizure free.

Out of the 77 children who remained on the diet at 12 months, 27 achieved reduction of the number of anticonvulsants used, including 15 who discontinued all drugs. Twenty-seven of these 77 children had a positive effect on development and behaviour, as reported by the parents, including 6 children for whom seizure control was not optimal i.e. <50% seizure reduction.

3.2.1. Effect of starting age and duration of epilepsy on diet efficacy

We also compared the seizure outcomes at 3 months on the KD according to age at the start of the diet, and found that children more than 10 years old showed statistically worse ($p < 0.05$) response to the KD than the rest of the children (Table 2). However, this distinction became less significant at 6 months and 12 months into the diet. Duration of epilepsy at the start of the diet was not a statistically significant factor influencing children's response to the diet (Table 2). The detailed 12-month efficacy statistics for children of different starting ages and duration of epilepsy are presented in Table 3.

3.2.2. Effect of aetiology and seizure types on diet efficacy

For children with idiopathic epilepsy, 41.7% remained on the diet at 12 months and 33.3% showed >50% seizure reduction, compared to 24.2% and 18.0% respectively for children with cryptogenic aetiology, and 22.9% and 18.1% for children with symptomatic aetiology. Although a higher percentage of children with idiopathic epilepsy had good seizure control, it was not statistically different from the rest ($p = 0.2465$), possibly due to the small number of children in this group. Children with infantile spasms (IS), Lennox–Gastaut Syndrome (LGS) and tuberous sclerosis (TS) behaved similarly to the whole group in terms of retention rate and seizure outcomes, and there was no statistically significant difference according to seizure types ($p = 0.2497$ for IS, $p = 1$ for LGS, $p = 1$ for TS, see Table 4). None of the DS children remained on the diet at 12 months. However, due to small sample size in this population, the difference was inconclusive ($p = 0.3557$).

3.2.3. Vertical comparison of diet efficacy in Shenzhen Children's Hospital

According to diet composition, the 317 patients can be divided into three groups: the first 30 patients treated between 2004 and 2007 using meals prepared with the KD Meal Planner, next 28 patients treated between 2007 and 2008 using KetoCal, and the remaining 259 patients using Qitong KD products. Patient retention and efficacy are summarised in Table 5.

3.3. Tolerability and adverse effects of the KD

Common adverse effects experienced by children included food refusal, gastrointestinal disturbance and hypoproteinaemia (Fig. 1). Gastrointestinal disturbance, including vomiting, diarrhoea and constipation, typically occurred within the first week of diet initiation. On the other hand, hypoproteinaemia mostly appeared two weeks after the start of the KD.

Thirty-nine (12.3%) children experienced hypoproteinaemia. Except one 12-year-old case, all hypoproteinaemia cases were found in children below 5 years. Food refusal was often reported by parents to precede hypoproteinaemia. There was no statistical association between children's starting weight-for-age percentile (calculated according to Li et al.[8]) and their likelihood of experiencing hypoproteinaemia. For children with hypoproteinaemia, lipid-to-non-lipid ratio of the diet was lowered to increase protein intake, and severe cases were successfully controlled with intravenous infusion of albumin. There were still 9 children who discontinued the diet due to hypoproteinaemia.

Seven children had renal stones, among which 4 discontinued the diet due to this complication. Three children had thrombocytopenia, and 2 out of 3 withdrew from the diet, platelet count returned to normal after 2 weeks in the third child.

Table 4
Retention rate and seizure outcomes at 12 months after the KD initiation according to different aetiologies and seizure types.

	Overall	Idiopathic	Cryptogenic	Symptomatic	IS	LGS	DS	TS
Cases	317	12	161	144	157	39	7	7
Seizure-free	34 (10.7%)	1 (8.3%)	19 (11.8%)	14 (9.7%)	18 (11.5%)	4 (10.3%)	–	1 (14.3%)
Reduction 90–99%	10 (3.2%)	2 (16.7%)	4 (2.5%)	4 (2.8%)	2 (1.3%)	2 (5.1%)	–	0 (0%)
Reduction 50–90%	15 (4.7%)	1 (8.3%)	6 (3.7%)	8 (5.6%)	5 (3.2%)	1 (2.6%)	–	0 (0%)
Reduction <50%	6 (1.9%)	1 (8.3%)	4 (2.5%)	1 (0.7%)	2 (1.3%)	2 (5.1%)	–	0 (0%)
No change	12 (3.8%)	0 (0%)	6 (3.7%)	6 (4.2%)	7 (4.5%)	2 (5.1%)	–	0 (0%)
Retention	77 (24.3%)	5 (41.7%)	39 (24.2%)	33 (22.9%)	34 (21.7%)	11 (28.2%)	0 (0%)	1 (14.3%)

Table 5
Patient retention and efficacy data for patients using Ketogenic Diet Meal Planner, KetoCal and Qitong products.

	3 months retention		12 months retention		3 months responders		12 months responders	
	Count	Percentage	Count	Percentage	Count	Percentage	Count	Percentage
Meal planner group	19	63.3%	4	13.3%	7	23.3%	4	13.3%
KetoCal group	12	42.9%	6	21.4%	6	21.4%	6	21.4%
Qitong group	168	64.9%	67	25.9%	98	37.8%	49	18.9%

During the follow-up, 10 children died, among which 3 had withdrawn from the KD for more than 6 months before death, 2 died of status epilepticus, 2 died of pneumonia, 1 fell from height, and for the remaining 2 cases, parents were unwilling to disclose the cause of death.

3.4. Reasons for withdrawal

A total of 158 children reported their reasons of withdrawal. More than one reason might be cited. Among these, the main reason for diet discontinuation was limited efficacy (46.2%). Other top reasons included food refusal (39.2%) adverse effects (22.8%), parents' difficulty to continue (7.0%), incurrent illness (6.3%). In addition, 7 children (4.4%) stopped within 12 months, although they were seizure-free, due to parents' concern of the cost or fear of long-term side effects. These children all had stopped anticonvulsant use when they discontinued the diet and remained seizure-free in the most recent follow-up.

4. Discussion

This study is the first study evaluating the use of the KD in Chinese children with refractory epilepsy. At 12 months after the KD initiation, 18.6% of the children achieved >50% seizure reduction, and 10.7% were seizure free. Other studies had a range of 20–50% for patients with >50% seizure reduction, and a range of 4.8–25% for seizure free cases.[4,9–11]. Our results were comparable but towards the lower end of the range. This was possibly caused by the low retention rate. Out of the 317 children, 118 stopped the KD before 3 months, among which 31 stopped before 2 weeks, despite recommendation to the parents that the KD should be maintained for at least 3 months in order to confirm its efficacy.

Families withdrew from the diet for various reasons. Limited efficacy was the most common, reason similar to other reports.[9,12] However, a significant proportion of our children discontinued the diet due to intolerance. As the Chinese diet is heavily starch-based, it was expected that Chinese children would find it difficult to accept such a high-lipid diet. In addition, parents also reported difficulties in diet preparation such as incorporating the KD into Chinese recipes and relative inaccessibility to high-lipid, low-carbohydrate food like butter and cream. A lot of effort has been put in to improve the tolerability of the diet. This includes the development of Chinese recipe-based Ketogenic Diet Meal Planner, Qitong ketogenic liquid milk (Zeneca), Qitong ketogenic cookies (Zeneca) and packaged ketogenic set-meals (Zeneca). As seen in Table 5, 3 and 12-month retention/response rate generally improved since switching to Qitong. However, significant problems with tolerance of the diet still exist. Other factors such as geographical inconvenience and economic difficulties also contributed to the low retention rate; many children lived several thousand kilometres away from our KD centre and the financial situation of different families varies. The recent establishment of additional centres throughout China may improve the ability to provide the diet effectively and increase the retention rate.

Similar to results from previous reports,[13–19] our study showed that the KD is beneficial in seizure control for IS, LGS and TS. As in Freeman et al.,[4] Kang et al.,[10] and DiMario et al.,[20] no statistically significant differences in efficacies were found among groups of different epilepsy syndromes or aetiologies. However, contrary to Caraballo et al.,[21] children with DS did not show favourable response, though the difference was inconclusive and likely caused by small group size. The small idiopathic group had a 12-month responder percentage of 33.3% compared to the 18.0% in the remaining children. Though statistically insignificant, the better response among this small group suggests further study into this population.

Starting age also had an effect on efficacy, with children older than 10 years having a worse response to the KD than younger children, although the difference was significant at 3 months only. It has been observed in other studies that the KD may be more effective in younger children [4,11], and several explanations have been suggested. One possibility is that older children are less tolerant of the diet. However, in our study, children above 10 years old had 3-month, 6-month and 12-month retention rates of 61.1%,

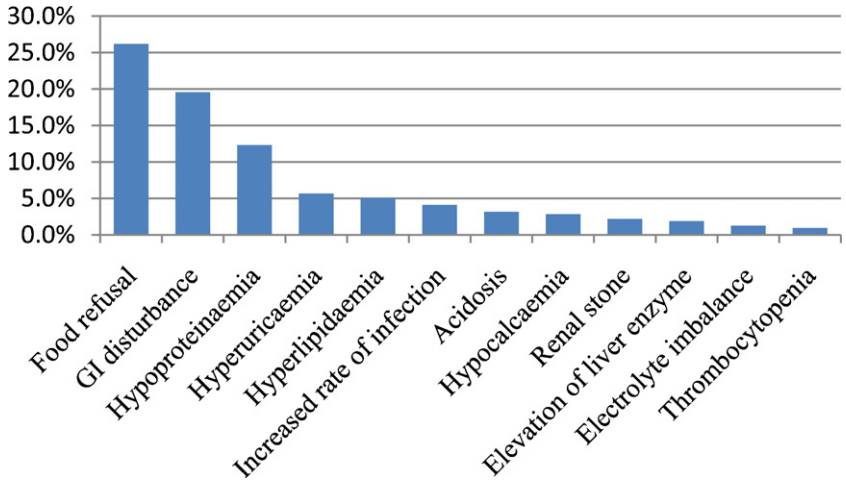

Fig. 1. Adverse effects of the KD, ranked by occurring frequencies ($n = 317$).

33.3% and 22.2% respectively, which were comparable to the 62.9%, 42.5% and 24.4% for children below 10. The second possible explanation is that older children have had epilepsy for a longer period of time and there are studies showing that diet was most effective in those who had experienced seizures for the shortest period of time.[22] Hence we tested the influence of the duration of epilepsy on the efficacy of the diet. No statistically significant result was found, but the *p*-value of 0.112 in the 12-month response (Table 2) suggests a link worth further investigation. The third possible explanation is that younger children are better at extracting ketones from the blood into the brain.[23] We were unable to verify this claim using our clinical data.

Compared to other studies,[24–26] a relatively high percentage of our children experienced hypoproteinaemia. Parents' reported association between food refusal and hypoproteinaemia and the fact that lowering lipid-to-non-lipid ratio alleviated the problem suggested that hypoproteinaemia might be caused by food refusal and insufficient protein intake. Hypoproteinaemia was predominantly observed among children below 5 years. However, the lack of association between hypoproteinaemia and starting weight percentile makes it difficult for us to further screen for susceptible patients among younger children. Aiming to reduce hypoproteinaemia, we recently started a trial of using 2:1 lipid-to-non-lipid ratio.

Our reported rates of other adverse effects were comparable to those of previous reports.[4,25,27] Seven children died during the diet. It is difficult to judge whether the KD had contributed to the deaths, and care should be taken in monitoring children on the KD closely.

In conclusion, as the first institution to have implemented the KD programme in China, we observed that the KD is a safe and efficacious treatment option for refractory epilepsy in Chinese children. The KD is shown to be effective in children with infantile spasm, Lennox–Gastaut syndrome and tuberous sclerosis, and the treatment efficacy is better among children below 10 years. However, as the Chinese diet has significantly less fat and more carbohydrate than Western ones, difficulties with diet maintenance and food refusal were experienced. Future work is needed to improve tolerability.

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