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Efficacy of the ketogenic diet on ACTH- or corticosteroid-resistant infantile spasm: a multicentre prospective control study

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ABSTRACT

Objective. To determine the efficacy of ketogenic diet (KD) therapy on adrenocorticotropic hormone- (ACTH) or corticosteroid-resistant infantile spasm (IS), and identify relevant associated factors.

Methods. A prospective controlled study was undertaken at 10 tertiary children's medical centres in mainland China. Participants were non-randomly assigned to KD therapy or control (adjustment of antiepileptic drugs). The primary outcome was the reduction in spasms and remission of hypsarrhythmia at the 16th week, divided into Grade I (spasm-free for at least one week with hypsarrhythmia remission), Grade II (≥50% spasm reduction and/or hypsarrhythmia remission) and Grade III (<50% spasm reduction with hypsarrhythmia).

Results. In total, 227 patients were recruited and assigned to the KD (135 patients) and control (92 patients) groups. The efficacy in the KD group was superior to that in the control group (Grade I: 13.4% vs. 10.9%; Grade II: 40.7% vs. 20.7%, p=0.025). Patients with a ketogenic ratio <3:1 had a higher rate of Grade I than those with ketogenic ratio ≥3:1 (66.7% vs. 33.3%, p=0.037). No significant correlation was found between the efficacy of KD and level of serum ketosis, aetiology of IS, or age.

Significance. The efficacy of KD therapy was superior to adjustment of oral antiepileptic drugs in children with ACTH- or corticosteroid-resistant infantile spasms.

Key words: ketogenic diet; infantile spasms; efficacy; genomics

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The ketogenic diet (KD) is a high-fat, low-carbohydrate diet with an appropriate amount of protein, which is widely used for children with refractory epilepsy [1]. Infantile spasm (IS) is one of the most common epileptic encephalopathies in infancy characterized by epileptic spasms, hypsarrhythmia, and developmental retardation or regression [2]. The first-line treatments recommended for IS include adrenocorticotropic hormone (ACTH), vigabatrin (VGB), and high-dose oral corticosteroids [3], and the responder rates are 42%-87% [4-8], 35%-65% [9, 10], and 63%-75% [11-13], respectively. Although the KD has been widely used for the treatment of IS, the evidence on the effectiveness of the KD in prospective and controlled studies is limited to date [14-16]. To determine the efficacy of the KD on ACTH- or corticosteroid-resistant IS, we conducted a prospective controlled study in 10 tertiary children's medical centres in mainland China.

Methods

Study design

This multicentre prospective control study to evaluate the efficacy of KD therapy on ACTH- or corticosteroid-resistant IS, and identify relevant associated factors, was undertaken at 10 tertiary children's medical centres in mainland China, including the Peking University First Hospital, Children's Hospital Affiliated to Zhengzhou University, Xiangya Hospital of Central South University, Children's Hospital of Fudan University, Children's Hospital of Chongqing, Qilu Hospital of Shandong University, Wuhan Children's Hospital, Beijing Children's Hospital, Fujian Medical University Union Hospital, and Jiangxi Provincial Children's Hospital. The study was approved by the Clinical Research Ethics Committee of all the 10 tertiary children's medical centres. The study has been registered in the Chinese Clinical Trial Registry (ChiCTR-IPN-17014209).

Participants

The participants were recruited from 10 tertiary children's medical centres in mainland China. Written informed consent was obtained from all parents of the enrolled patients before entering the study.
Eligible patients met the following inclusion criteria:
- age of 3–36 months;
- epileptic spasms and hypsarrhythmia on EEG;
- poor response to ACTH or corticosteroids (intravenous ACTH or oral corticosteroids ≥1.5 mg/kg/d for at least 14 days and terminated hormonal treatment for more than 14 days);
- frequent epileptic spasms, with at least four clusters per week; and (5) no previous treatment with the KD.

Exclusion criteria included:
- a metabolic profile showing contraindications of the KD;
- brain MRI indicative of epilepsy surgery as a curative option;
- and possible KD intolerance manifesting as severe vomiting, poor feeding, and malnutrition with other diets.

Procedures

All the enrolled patients were non-randomly assigned to the KD or control group according to parental decision. Patients in the KD group were started on the KD (Guangzhou Kinton Foods for Special Medical Purpose Co., Ltd.) without fasting. The initial ratio was 2:1, and the KD ratio was adjusted according to seizure outcome and ketone level, with a maximum of 4:1. If seizures were controlled, the ketogenic ratio was not increased, otherwise the ketogenic ratio was appropriately adjusted in order to maintain the level of serum ketone at between 3 to 5 mmol/L. This principle was applied to all medical centres. During the KD treatment, baseline antiepileptic drugs (AEDs) were not increased. In the control group, oral AEDs were continued and adjusted according to seizure outcome. New AEDs could be started, and the children remained on their previous diet (not ketogenic) in the control group. The observation period for the two groups was 16 weeks.
EEG (at least for four hours including awake and sleep phase) was examined within two weeks before enrolment and 16 weeks after treatment. EEGs were evaluated by two EEG experts from each centre, blinded to the study, and were scored according to the extent of amplitude and epileptiform discharges [17]. Hypsarrhythmia was defined based on a score of 4 or 5. In the KD group, the Gesell development scale was used during the first week after enrolment and repeated at the 16th week. Trio whole-exome sequencing (WES) was performed in the two groups (Cipher Gene, LLC). Routine testing for blood and urine, liver and renal function, electrolytes, and lipid profile was regularly performed in the KD group. The parents in the two groups were instructed to keep diaries of seizures and were followed regularly (*figure 1*).

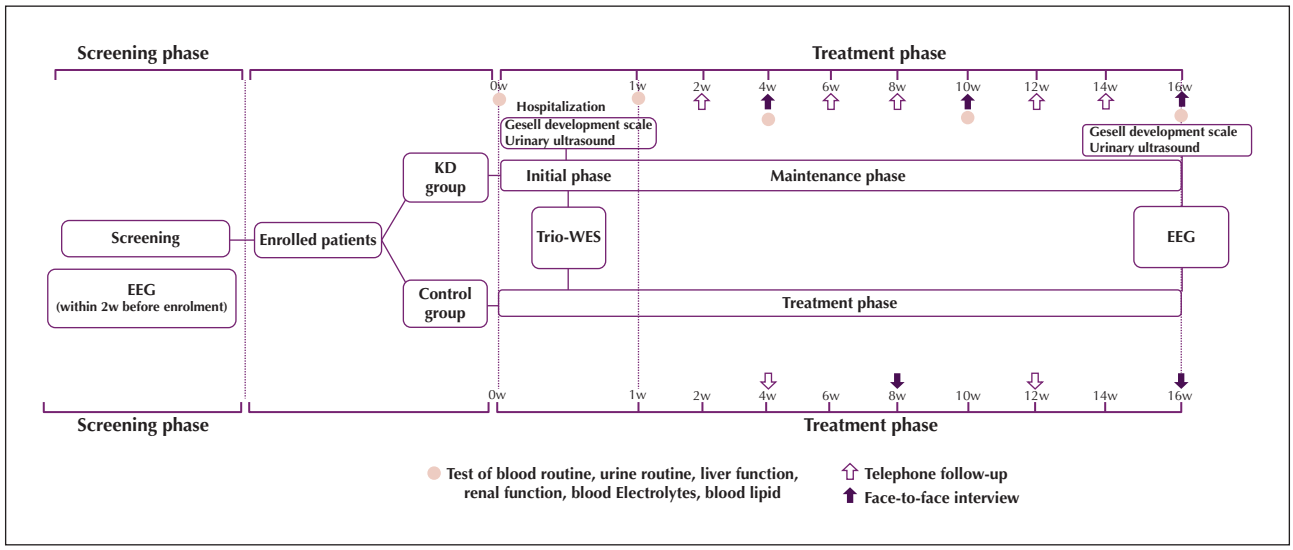
Outcome

Primary outcome

The reduction in spasms and remission of hypsarrhythmia on EEG at the 16th week was used to indicate efficacy. Patients were categorized as Grade I (electroclinical remission: epileptic spasms were completely controlled for at least one week with remission of hypsarrhythmia on EEG); Grade II (partially effective: the frequency of epileptic spasms was reduced by more than 50% and/or hypsarrhythmia had remitted on EEG); and Grade III (ineffective: the frequency of epileptic spasms was reduced by less than 50% with hypsarrhythmia).

Secondary outcome

(1) *Neurodevelopmental improvement in the KD group*. The Gesell development scale was compared



■ **Figure 1.** Study design. Patients were non-randomized to the KD or control group. The observation period was 16 weeks (treatment phase), which was divided into the initial phase (first week) and maintenance phase (2nd to 16th week). Patients in the KD and control groups were followed by telephone (white arrow) and face-to-face interview (black arrow). Routine testing for blood and urine, liver and renal function, electrolytes and lipid profile was regularly performed in the KD group (grey circle).

between the 16th week and baseline. Neurodevelopmental improvement was defined as the increase in development quotient (DQ) by more than 5 in at least one functional domain.

(2) *Adverse effects in the KD group*. Gastrointestinal reactions, moderate and severe metabolic acidosis (HCO_3- ≤13 mmol/L), hypoglycaemia (glucose ≤2.8 mmol/L), ALT ≥100 IU/L, hyperlipidaemia (triglyceride ≥1.7mmol/L or total cholesterol ≥5.2 mmol/L), hypokalaemia (K <3.5 mmol/L), hyponatraemia (Na <135 mmol/L), anomalous Ca/P/Mg, weight loss, and kidney stones were evaluated.

Statistical analysis

Comparison of primary outcome between KD and control groups

Intention-to-treat (ITT) analysis was carried out, and all of the enrolled patients were included in the statistical analysis. The primary outcomes for the patients who withdrew were filed according to worst outcome, and all were therefore defined as Grade III. The Cochran-Mantel-Haensel Chi-square of centre effect control was used to compare the primary outcome between the two groups in a bilateral test. Statistical difference was defined when p value < 0.05.

Analysis of the correlation between clinical factors and efficacy of KD

All of the patients in the KD group were regarded as the target population, and efficacy of seizure outcome was regarded as a dependent variable. The independent variables included sex (male or female), aetiology (genetic, structural, or unknown), number of AEDs (≤3 or >3), previous treatment with VGB (yes or no), ketogenic ratio (<3:1 or ≥3:1), level of serum ketone (≤3 or >3 mmol/L), age at enrolment, age at onset, and course of disease. If independent variables were categorical, then $\chi 2$ tests were used. If the average level and variability of continuous variables were inconsistent with normal distribution, then a non-parametric test (Kruskal-Wallis test) was used; otherwise, one-way ANOVA was used.

Analysis of the correlation between genomics and efficacy of KD

Patients in the KD group who finally completed 16 weeks of the KD with clear efficacy data were classified as responders (Grade I+II) or non-responders (Grade III). Based on WES, SNPs were obtained, and quality control was carried out. SNPs with a minor allele frequency of >0.01 and Hardy-Weinberg equilibrium of >0.001 which were detected in more than 90% of the samples in the cohort were reserved.

Correlations between SNPs or genetic data and efficacy were analysed. For comparison between responder and non-responder groups, statistical significance was defined at p <10-8. A focus was made on genes related to the generation and metabolism of ketone bodies. Statistical analysis was carried out using SPSS 23.0 and STAT software.

Results

Baseline data

The study was undertaken at 10 tertiary children's medical centres in mainland China from November 2017 to December 2018. A total of 227 patients were recruited, 135 and 92 of whom were assigned to the KD and control groups, respectively (*figure 2*). Baseline data were not statistically different between the two groups (*table 1*).

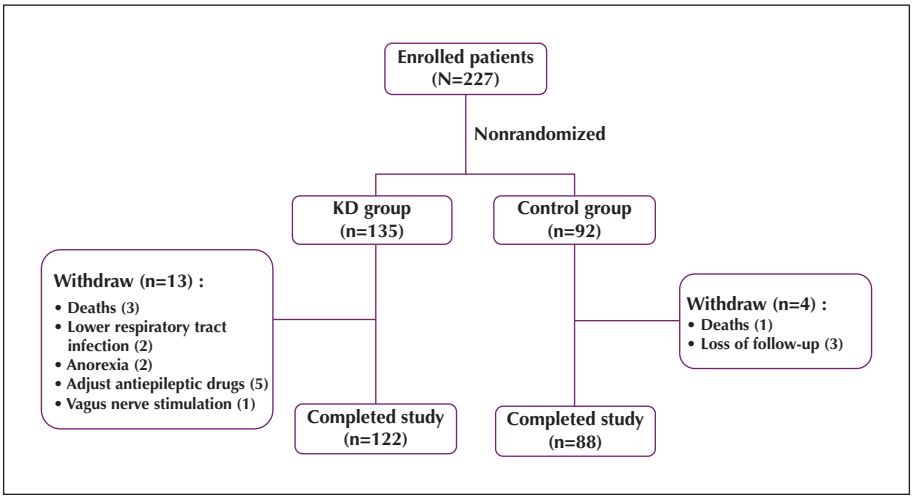
Genetic, structural, and unknown aetiology accounted for 18.5% (42/227), 22.5% (51/227), and 59.0% (134/227) of the 227 children, respectively. Twenty-eight genes with pathogenic or likely pathogenic variants were identified in 42 patients, including *CDKL5*, *ALG13*, *STXBP1*, *DNM1*, *PPP3CA1*, *CACNA1C*, *NF1*, *WDR45*, *TSC1*, *SLC35A2*, *SLC25A22*, *SETD5*, *SCN8A*, *NTRK2*, *NEXMIF*, *MTOR*, *KMT2A*, *KCNA2*, *IQSEC2*, *GRIN1*, *GNAO1*, *DYNC1H1*, *DEPDC5*, *CLCN4*, *CHD7*, *CACNA1E*, *ATP7A* and *ABCC8*.

Efficacy of KD and correlation factors

The ITT analysis showed that the efficacy in the KD group was superior to that in control group (Grade I: 13.4% vs. 10.9%; Grade II: 40.7% vs. 20.7%; Grade III: 45.9% vs. 68.9%, p=0.025) (*table 2*).

We further analyzed the clinical correlation factors of efficacy in the KD group. We found that children with ketogenic ratio of <3:1 had a higher rate of Grade I than those with ketogenic ratio ≥3:1 (66.7% vs. 33.3%, p=0.037), but the level of serum ketones was comparable. The efficacy of KD was not related to aetiology of IS, serum ketone level, age, and other clinical factors (*table 3*). The median time of response in 73 cases with Grade I and II was four weeks (1-14 weeks), and 50.7% (37/73) showed response within four weeks, corresponding to 45.2% (33/73) of the patients with ketogenic ratio of <3:1. Of the 18 patients with Grade I, 72.2% (13/18) showed response within four weeks, and 66.7% (12/18) showed a response with a ketogenic ratio of <3:1.

To explore whether the efficacy of the KD is related to genes involved in the synthesis and metabolism of ketone bodies, we used the WES data to analyse SNPs and gene-based correlation relative to the efficacy of the KD. For comparison between patients with Grade I+II and patients with Grade III, statistical significance was defined at p <10^{-8}. No SNPs or genes were confirmed to be related to the efficacy of KD. Only two SNPs (p <10^{-4}) were identified, corresponding to rs2272570 in *DRG2* (developmentally regulated GTP binding protein 2) (p=3.59×10^{-6}) and rs28417650



■ **Figure 2.** Study flow diagram. A total of 227 children with IS were recruited and non-randomly assigned to the KD group (n=135) and control group (n=92). A total of 17 children withdrew, including 13 patients in the KD group and four patients in the control group. Finally, 210 children (122 in the KD group, 88 in the control group) completed the 16 weeks of treatment.

▼ **Table 1.** Baseline demographic and clinical characteristics.

	KD group (*n*=135)	Control (*n*=92)	*p* Value
Gender *n* (%)		4	
Male	85 (63.0)	9 (53.3)	0.144[a]
Female	50 (37.0)	43 (46.7)	
Age/disease course (month)			
Age at enrolment, median (IQR), range	17.0 (12.0-23.0), 5.0-35.0	17.0 (13.0-26.0), 7.0-36.0	0.104[b]
Age at onset, median (IQR), range	5.0 (3.0-8.0), 1.0-30.0	6.0 (4.0-7.0), 1.0-22.0	0.553[b]
Disease course, median (IQR), range	10.0 (6.0-16.0), 2.0-32.0	11.0 (8.0-19.4), 0.5-35.0	0.059[b]
Aetiology *n* (%)			
Genetic	31 (23.0)	11 (12.0)	
Structural	30 (22.2)	21 (22.8)	0.101[a]
Unknown	74 (54.8)	60 (65.2)	
Numbers of AEDs *n* (%)			
≤3	66 (48.9)	55 (59.8)	0.106[a]
>3	69 (51.1)	37 (40.2)	
Previous treatment with VGB *n* (%)			
Yes	62 (45.9)	31 (33.7)	0.066[a]
No	73 (54.1)	61 (66.3)	

KD: ketogenic diet; IQR: interquartile range; AEDs: antiepileptic drugs; VGB: vigabatrin. [a] $\chi 2$ test.[b] Man-Whitney test.

in *PALM* (paralemmin) (p=3.8×10^{-5}). *DRG2* encodes a GTP-binding protein that regulates cell growth and differentiation. *PALM* encodes a palmitoylated phosphoprotein, paralemmin, related to the cytoplasmic face of plasma membranes. It is implicated in plasma membrane dynamics in neurons and other cell types, and may also be involved in the regulation of the cAMP signalling pathway in the brain.

In children with genetic aetiology, the efficacy of the KD was better in children with *CDKL5* encephalopathy. Four of five cases with *CDKL5* mutations were responders to the KD. However, the sample size was too small to draw any definitive conclusions, and the results should be further confirmed with a large sample size.

Neurodevelopmental improvement after 16 weeks of KD therapy

Of the 135 children in the KD group, 84.4% (114/135), 57.8% (78/135), 63.0% (85/135), 57.0% (77/135), and 68.2% (92/135) showed extremely severe delays in adaptability, gross motor skills, fine motor skills, communication, and personal-social skills at baseline, respectively. After 16 weeks of KD therapy, 102 children repeated the Gesell developmental scale and

▼ **Table 2.** Decrease in spasms and remission of hypsarrhythmia at 16 weeks after enrolment (ITT analysis).

	KD group (*n*=135) *n* (%) [95% CI]	Control (*n*=92) *n* (%) [95% CI]	*p* Value
Decrease in spasms and remission of hypsarrhythmia			0.025[a]
Grade I	18 (13.4) [7.6%-19.1%]	10 (10.9) [4.5%-17.2%]	
Grade II	55 (40.7) [32.5%-49.0%]	19 (20.7) [12.4%-28.9%]	
Grade III	62 (45.9) [37.5%-54.3%]	63 (68.5) [59.0%-78.0%]	

KD: ketogenic diet; ITT: intention-to-treat; Diff: difference; CI: confidence interval. [a]Cochran-Mantel-Haensel (CMH) $\chi 2$.

▼ **Table 3.** Correlation factors for seizure outcome in the KD group.

	Grade I (*n*=18) *n* (%)	Grade II (n=55) *n* (%)	Grade III (*n*=62) *n* (%)	*p* Value	*p* value (multivariate analysis)
Gender					
Male	6 (33.3)	28 (50.9)	16 (25.8)	0.018[a]	0.192[c]
Female	12 (66.7)	27 (49.1)	46 (74.2)		
Aetiology					
Genetic	4 (22.2)	17 (30.9)	10 (16.1)	0.021[a]	0.623[c]
Structural	0 (0.0)	13 (23.6)	17 (27.4)		
Unknown	14 (77.8)	25 (45.5)	35 (56.5)		
Prior treatment with VGB					
Yes	13 (72.2)	27 (49.1)	33 (53.2)	0.233[a]	-
No	5 (27.8)	28 (50.9)	29 (46.8)		
AEDs					
≤3	7 (38.9)	30 (54.5)	32 (51.6)	0.525[a]	-
>3	11 (61.1)	25 (45.5)	30 (48.4)		
Ketogenic ratio					
<3:1	12 (66.7)	21 (38.2)	18 (29.0)	0.015[a]	0.037[c]
≥3:1	6 (33.3)	34 (61.8)	44 (71.0)		
Serum ketone					
>3mmol/L	10 (55.6)	39 (70.9)	30 (48.4)	0.045[a]	0.303[c]
≤3mmol/L	8 (44.4)	16 (29.1)	32 (51.6)		
Age at enrolment					
Mean ± SD, month	18.3±7.8	17.5±7.4	17.9±7.8	0.883[b]	-
Age at onset					
Median (IQR), month	5.0 (4.0-6.3)	6.0 (3.0-9.0)	4.5 (3.0-7.3)	0.459[a]	-
Course of disease			1		
Median (IQR), month	10.5 (6.0-20.5)	9.0 (6.0-16.0)	2.0 (6.8-15.3)	0.361[a]	-

KD: ketogenic diet; IQR: interquartile range; SD: standard deviation; AEDs: antiepileptic drugs; VGB: vigabatrin. [a]$\chi 2$ test. [b]One-way ANOVA. [c]Logistic regression analysis.

29.4% (30/102) of them showed neurodevelopmental improvement. In the 14 children with Grade 1 seizure outcome, 50.0% (7/14) showed neurodevelopmental improvements. In the 46 children with Grade II seizure outcome, 32.6% (15/46) showed improvements.

Adverse effects of KD therapy

In the 135 children in the KD group, the adverse effects in the initial phase (first week) were gastrointestinal reactions (23.7%; 32/135), hyperlipidaemia (12.6%; 17/135), hypoglycaemia (11.9%; 16/135), and metabolic acidosis (10.4%; 14/135). The adverse effects in the maintenance phase were abnormal levels of Ca/P/Mg (23.0%; 28/122), weight loss (22.1%; 27/135), hyperlipidaemia (22.1%; 27/122), and gastrointestinal upset (18.9%; 23/122). In the 13 patients who withdrew from the study in the KD group, three patients died, and four patients withdrew due to adverse events. The causes of death were cardiovascular accident (with congenital heart disease at baseline) in one, and severe pneumonia in two cases. Among the four children who withdrew due to adverse events, two had recurrent lower respiratory tract infection, and two had poor feeding during the initial phase.

Discussion

In this study, the remission of infantile spasms and hypsarrhythmia on EEG at the 16th week was regarded

as an indicator of seizure outcome. The results show that the efficacy in the KD group was superior to that in the control group for children with ACTH- or corticosteroid-resistant IS, with electroclinical remission in 13.4% and partial efficacy in 40.7% after KD therapy. Previously published studies on the KD as for treatment of ACTH- or corticosteroid-resistant IS were non-controlled. One study included 15 children with IS refractory to first-line treatment (oral corticosteroids, ACTH or VGB). After three months with the KD, 40% of the patients were seizure-free for more than 15 days, and hypsarrhythmia had disappeared on EEG [18]. Another study included 17 children with steroid- and VGB-resistant IS. After three months of follow-up, 65% were seizure-free, and hypsarrhythmia had disappeared [14]. In a retrospective study involving six children, five cases showed an absence of hypsarrhythmia, and two cases were seizure-free after one month of KD treatment [19]. Two case reports revealed that treatment with various AEDs and ACTH was ineffective; one case with glucose transporter 1 (GLUT1) deficiency and another with *SCN2A* mutation, however, the patients were seizure-free after KD treatment [20, 21].

Predicting which patients may be responders to KD therapy is difficult, except for patients with specific metabolic disorders, such as GLUT1 deficiency. For this reason, we analysed possible correlations with clinical factors of KD efficacy, including aetiology, ketogenic ratio, serum ketone levels, age at onset, number of oral AEDs, and other clinical factors.

We did not find a correlation between the level of serum ketosis and efficacy of the KD. Disputes exist about whether the efficacy of the KD is related to serum ketone level. Gilbert *et al*. retrospectively analysed 74 children treated with KD, and found that children with blood beta-hydroxybutyrate levels >4mmol/L were more likely to have decreased seizure frequency [22]. A retrospective study involving 63 children reported that older age at onset, female gender, a high ketogenic diet ratio, and non-fasting induction were associated with good odds of improved seizure outcome [23]. Numis *et al*. analysed 36 children treated with KD, and showed no correlation between the level of β-hydroxybutyrate and seizure control [24]. This may suggest that the effective mechanism of the KD for IS may not be entirely due to the direct effect of ketones but through complicated signal pathways, to achieve seizure control. We found that the responder rate in children with a ketogenic ratio <3:1 was significantly higher than that in children with a ratio of ≥3:1, which was surprising. In the present study, the ketogenic ratio was adjusted according to seizure outcome and ketone level. In patients with seizure control, once the level of serum ketone was appropriate and seizures were controlled, the ketogenic ratio was no longer increased. Therefore, seizures were controlled at a relatively low ketogenic ratio in some patients. However, in patients with uncontrolled seizures, the ketogenic ratio continued to increase according to tolerance and serum ketone level. This may be one of the reasons why the patients with a ketogenic ratio <3:1 demonstrated better efficacy. However, this result does not directly suggest that a low ketogenic ratio is preferable, but indicates that for patients with poor effects of KD therapy, routinely increasing the ketogenic ratio may not be helpful when serum ketones reach a certain level. In a previous study, Raju *et al*. also showed, in a randomized trial of 38 infants, that a 2.5:1 ratio for KD was as effective as a 4:1 ratio, but with less side effects [25]. According to the KD guidelines in 2016, a classic KD with 3:1 ratio is recommended in infancy (under the age of two years) [26].

In the present study, we were unable to confirm a correlation between KD efficacy and aetiology of epilepsy. We preliminarily observed that in patients with genetic aetiology, 80% (4/5) of patients with *CDKL5* encephalopathy were responders to the KD, consistent with the results of a previous study. Lim *et al*. retrospectively analysed 104 children with *CDKL5* mutations after KD therapy; 88% of them showed improved seizure control [27]. Children with *CDKL5* encephalopathy may have a good response to the KD, but further study is needed.

Considering that the efficacy of the KD may be related to pyruvate metabolism, fatty acid degradation, methyl butyrate metabolism, glycolysis, and other signal pathways, and that efficacy is probably influenced by specific genetic backgrounds in different individuals, we used WES data to analyse SNPs and determine possible correlations between genotype and efficacy of KD. However, no SNPs or genes related to KD efficacy were identified. In the future, the sample size should be expanded, and analysis should be combined with biochemical, genetic, and proteomic methods in order to further clarify the genomic factors involved in the response to the KD.

The study has the following limitations.

– The efficacy evaluation was based on remission of epileptic spasms and hypsarrhythmia on EEG at the 16th week, and the evaluation time was short.
– The criteria were relatively vague for Grade II regarding the efficacy evaluation and included patients with remission of hypsarrhythmia but whose epileptic spasms were not decreased by more than 50%, leading to an over-estimation of the efficacy of KD therapy to a certain degree. The target population comprised patients with ACTH- or corticosteroid-resistant IS, and spasms in most of the patients were intractable, thus either a reduction in the frequency of epileptic spasms or remission of hypsarrhythmia on EEG were important

regarding the prognosis of these patients.
– Based on ethical considerations, the enrolled patients were non-randomized, which may have introduced a certain selective bias. However, the baseline data were not statistically different between the KD group and control group, thus the selective bias may have been minimal.

Conclusion

In conclusion, this prospective controlled study provides evidence that the efficacy of the KD is superior to adjustment of oral antiepileptic drugs in children with ACTH- or corticosteroid-resistant IS. After 16 weeks of KD therapy, 13.4% of the patients achieved electroclinical remission, and 40.7% showed ≥ 50% reduction in frequency of seizures and/or remission of hypsarrhythmia. Neither the level of serum ketones nor the aetiology of epilepsy were shown to play a major role in the efficacy of the KD, and we were furthermore unable to confirm an association between SNPs in genes involved in the ketone metabolic pathway and efficacy. ■

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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TEST YOURSELF

(1) How did the efficacy of KD therapy compare with that of adjustment of oral antiepileptic drugs in children with ACTH- or corticosteroid-resistant IS at age 3-36 months?

(2) What were the clinical factors that correlated with efficacy in the KD group?

(3) Is KD therapy safe for children with IS, aged 3-36 months? What are the common adverse effects of KD therapy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".