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ORIGINAL ARTICLE

Long-term effectiveness and tolerability of ketogenic diet therapy in patients with genetic developmental and epileptic encephalopathy onset within the first 6 months of life

Tianyu Song | **Jie Deng** | **Chunhong Chen** | **Xiaohui Wang** | **Tongli Han** | **Xu Wang** | **Tie Fang** | **Xiaojuan Tian** | **Fang Fang**

Department of Neurology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing, China

Correspondence
Fang Fang, Department of Neurology, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, 56 Lishi Road South, Xicheng District, Beijing, 100045, China.
Email: fangfang@bch.com.cn

Abstract

Objective: To investigate the effectiveness and tolerability of ketogenic diet therapy (KDT) in patients with developmental and epileptic encephalopathy (DEE) associated with genetic etiology which onset within the first 6 months of life, and to explore the association between response to KDT and genotype/clinical parameters.

Methods: We retrospectively reviewed data from patients with genetic DEE who started KDT at Beijing Children's Hospital between January 1, 2016, and December 31, 2021.

Results: A total of 32 patients were included, involving 14 pathogenic or likely pathogenic single genes, and 16 (50.0%) patients had sodium/potassium channel gene variants. The median age at onset of epilepsy was 1.0 (IQR: 0.1, 3.0) months. The median age at initiation of KDT was 10.0 (IQR: 5.3, 13.8) months and the median duration of maintenance was 14.0 (IQR: 7.0, 26.5) months, with a mean blood β-hydroxybutyrate of 2.49 ± 0.62 mmol/L. During the maintenance period of KDT, 26 (81.3%) patients had a ≥50% reduction of seizure frequency, of which 12 (37.5%) patients achieved seizure freedom. Better responses were observed in patients with *STXBP1* variants, with four out of five patients achieving seizure freedom. There were no statistically differences in the age of onset, duration of epilepsy before KDT, blood ketone values, or the presence of ion channel gene variants between the seizure-free patients and the others. The most common adverse effects were gastrointestinal side effects, which occurred in 21 patients (65.6%), but all were mild and easily corrected. Only one patient discontinued KDT due to nephrolithiasis.

Tianyu Song and Jie Deng contributed equally to this study.

Significance: KDT is effective in treating early onset genetic DEE, and no statistically significant relationship has been found between genotype and effectiveness in this study. KDT is well tolerated in most young patients, with mild and reversible gastrointestinal side effects being the most common, but usually not the reason to discontinue KDT.

Plain Language Summary: This study evaluated the response and side effects of ketogenic diet therapy (KDT) in patients who had seizures within the first 6 months of life, and were diagnosed with genetic developmental and epileptic encephalopathy (DEE), a type of severe epilepsy with developmental delay caused by gene variants. Thirty-two patients involving 14 gene variants who started KDT at Beijing Children's Hospital between were included. KDT was effective in treating early onset genetic DEE in this cohort, and patients with *STXBP1* variants responded better; however, no statistically significant relationship was found between gene variant and response. Most young patients tolerated KDT well, with mild and reversible gastrointestinal side effects being the most common.

KEYWORDS

developmental and epileptic encephalopathy, genetic etiologies, ketogenic diet therapy, pediatric

1 | INTRODUCTION

Developmental and epileptic encephalopathies (DEEs) refer to a heterogeneous group of disorders characterized by early onset, usually severe epileptic seizures and electroencephalogram (EEG) abnormalities, in which both the frequent epileptic activity and the developmental impairment contribute to the worsening outcome.[1] DEEs are usually caused by genetic etiologies, which have been associated with variants in many genes involved in different functions.[2] Seizure control is difficult to achieve in many patients with DEE, even when antiseizure medications (ASMs) are optimized for the etiology, such as the sodium channel blockers used in *SCN2A*-related DEE.[3] However, patients who achieve seizure freedom often continue to have severe developmental impairments and other comorbidities due to the underline etiology.[4] While the future of precision medicine for genetic epilepsy seems bright, such as the use of ASO therapy for *SCN8A* encephalopathy in mouse following the discovery of *SCN8A* as a disease-causing gene ~10 years ago, precision therapies are not yet available for most genetic epilepsies.[5]

Ketogenic diet therapy (KDT) is a well-established, nonpharmacologic treatment used for refractory childhood epilepsy.[6] It is based on a high-fat, adequate-protein, and low-carbohydrate diet. There are currently four main dietary therapies, all of which are effective in childhood drug-resistant epilepsy.[7] Many hypotheses about anticonvulsive and antiepileptogenic mechanisms of KDT have been proposed, such as the changes in neurotransmitter systems and channel regulation, enhancement of cellular bioenergetics and mitochondrial function.[8] The broad neuroprotective effects of KDT through the energy-sensing pathways and the cellular effects are also increasingly recognized.[9]

In recent years, KDT has been indicated in the treatment of patients with DEE and has been proven effective for patients with genetic etiology. However, there is no consensus on whether the effectiveness of KDT varies depending on gene function and type of variant, and in

Key Points

- KDT is effective in treating patients with genetic DEE onset within the first 6 months of life, and early initiation of KDT is more likely to be markedly effective.
- Patients with *STXBP1* variants may respond better to KDT, although no statistically significant relationship has been found between genotype and effectiveness.
- KDT is well tolerated in most young patients in this study. The most common side effects are mild and reversible gastrointestinal side effects.

which genotypes it is more effective.[10,11] Although a systematic review and meta-analysis showed that KDT used in infants with epilepsy is highly effective and well tolerated,[12] these studies rarely focused on the patients with early onset genetic DEE. Therefore, we aimed to evaluate the effectiveness and tolerability of KDT in patients with DEE caused by pathogenic variants and onset within the first 6 months of life.

2 | METHODS

2.1 | Participants

This single-center, retrospective cohort study was conducted on patients with epilepsy who were attended to Beijing Children's Hospital and received KDT between January 1, 2016, and December 31, 2021. This study was approved by the Institutional Review Board of Beijing Children's Hospital (ref No. [2023]-E-014-R).

Patients diagnosed with genetic DEE, which were caused by pathogenic or likely pathogenic variants of single genes and onset within the first 6 months of life were enrolled in the study. DEE was diagnosed according to the definition in the Epilepsies Position Paper of the International League Against Epilepsy (ILAE).[1] Classification and definition of epilepsy syndromes based on the position statement by the ILAE Task Force on Nosology and Definitions.[13] The syndromes in this paper were clinical phenotypes which diagnosed at the time of KDT initiation, including infantile epileptic spasms syndrome (IESS), early infantile DEE (EIDEE), epilepsy of infancy with migrating focal seizures (EIMFS), Dravet syndrome (DS), and non-syndromic epilepsy.

Genetic variants were identified by whole-exome sequencing (WES), and subsequently confirmed by Sanger sequencing. Clinical interpretation regarding pathogenic, likely pathogenic, or uncertain significance was based on the guidelines provided by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP).[14] Those with proven etiologies other than genetic etiology, such as structural, metabolic, immune, or with unknown etiology were excluded. Furthermore, patients with genetic variants related to the mTOR pathway were also excluded because of the functional complexity of the mTOR pathway, as tuberous sclerosis complex is characterized as a disease entity.[15,16]

Hospital records from The FUTang Updating medical Records Database were reviewed retrospectively,[17] including demographics, seizure type and frequency, neurodevelopment, urine organic acid profile, plasma amino acid and acylcarnitine profiles, EEG, and cranial magnetic resonance imaging (MRI) findings.

2.2 | Dietary protocol

Patients were evaluated by clinicians and nutritionists 10 days or more before receiving KDT (baseline). The pre-diet assessment consisted of nutritional evaluation including baseline weight and height, blood biochemical items including serum lipids and albumin, and urologic ultrasound to rule out contraindications to KDT. The type and ratio of dietary therapy were adjusted according to the decision of attending physician, and the data were recorded during the classic KDT or the modified Atkins diet (MAD) maintenance period. Patients on classic KDT had a lipid-to-nonlipid ratio from 0.8:1 to 4:1. Whereas patients on MAD received the ratio of approximately 1.5:1 according to Johns Hopkins protocol.[18] During the KDT, blood glucose, blood β-hydroxybutyrate (BHB), and urinary ketone bodies were measured. Patients were monitored for items such as the pre-diet assessment on a regular basis. Adverse effects were monitored, and the KDT regimen was adjusted accordingly. The KDT maintenance period was at least 1 month to assess effectiveness. The last follow-up was in October 2022.

2.3 | Assessment of effectiveness

Response to KDT was assessed by seizure outcome, defined as the change in seizure frequency between baseline and the maintenance period of KDT, as recorded by the clinician in the hospital records. The outcomes were classified as Grade I when completely seizure-free for at least 6 month, Grade II when there was ≥75% and < 100% reduction in seizures, Grade III when there was ≥50% and <75% reduction in seizures, and Grade IV when there was ineffectiveness, which meant <50% reduction in seizures. The KDT was considered effective if the seizure reduction was ≥50% (Grade I + II + III), and significantly effective if the seizure reduction was ≥75% (Grade I + II).

2.4 | Statistical analysis

All the statistical analyses in this study were performed using SPSS Statistics version 26 (IBM). Continuous variables were presented as mean ± standard deviation (SD) or median and interquartile range (IQR), and categorical variables were presented as number (%). Differences of continuous variables between groups were assessed using Student's *t*-test or Mann–Whitney U-test.

Associations of categorical variables were assessed using Fisher's exact test. The significance level was set at p-value <0.05.

3 | RESULTS

3.1 | Patient characteristics

Between January 1, 2016, and December 31, 2021, 296 patients received KDT at the tertiary epilepsy center of Beijing Children's Hospital, 32 of whom met the criteria for inclusion in the study.

In our patient cohort ($n = 32$), there were 15 males and 17 females. The median age of seizure onset was 1.00 (IQR: 0.12, 3.00) months. Seventeen patients had single seizure type, while the other 15 patients had more than one types, including epileptic spasms, tonic seizure, and focal to bilateral tonic–clonic seizure. Twenty-two patients had at least one seizure per day, and 16 of them had a baseline seizure frequency of more than 10 times per day. Regarding the syndromic diagnosis, IESS was the most common, followed by EIDEE, EIMFS, and DS.

The characteristic interictal EEG findings were generalized or multifocal epileptiform discharges in 22 patients, hypsarrhythmia in seven patients, burst suppression in two patients, and diffuse slowing in one patient. All MRI findings were non-specific manifestation, including delayed myelination, lateral ventricle dilatation, and widened subarachnoid space, with no structural lesion. Three patients had a family history related to epilepsy, whose grandfather, cousin, and grandmother's brother had epilepsy, but the gene variants in these three patients were all de novo. All patients had drug-refractory epilepsy, and the number of ASMs before KDT ranged from 2 to 5, with a median of 3 (IOR: 3, 4), and the type of ASM did not change during the first 4 weeks of KDT. Baseline characteristics of the study population are described in Table 1.

The pathogenic or potentially pathogenic variants identified in 32 patients involved 14 different single genes. Sixteen patients (50.0%) had variants in ion channel genes, the most common of which was *SCN1A* ($n = 5$), followed by *SCN2A* ($n = 4$), *KCNT1* ($n = 3$), *KCNQ2* ($n = 2$), and *SCN8A* ($n = 2$). Five patients had variants in *STXBP1*, and four patients had variants in *CDKL5*. Other causative monogenic variants are listed in Table 2.

TABLE 1 Baseline characteristics of the study population.

Patient characteristics ($n = 32$)	Results at baseline
Gender, n (%)	
Male	15 (46.9%)
Female	17 (53.1%)
Age at seizure onset, median (IQR), months	1.00 (0.12, 3.00)
Seizure type	
Include epileptic spasms	16 (50.0%)
Exclude epileptic spasms	16 (50.0%)
Syndromic diagnosis	
IESS	10 (31.2%)
EIDEE	7 (21.9%)
EIMFS	5 (15.6%)
DS	3 (9.4%)
Non-syndromic epilepsy	7 (21.9%)
Number of ASMs before KDT, median (IQR)	3 (3, 4)

Abbreviations: ASMs, antiseizure medications; DS, Dravet syndrome; EIDEE, early infantile developmental and epileptic encephalopathy; EIMFS, epilepsy of infancy with migrating focal seizures; IESS, infantile epileptic spasms syndrome; IQR, interquartile range; KDT, ketogenic diet therapy.

3.2 | Dietary therapies

In our cohort, all patients started with classic KDT, and then seven of them were adjusted to MAD. The age at initiation of KDT ranged from 3 months to 31 months, with a median age of 10.00 (IQR: 5.25, 13.75) months. Twenty-nine patients (90.6%) started KDT in infancy, including 18 patients (56%) who started KDT before the age of 12 months. The median time interval between seizure onset and KDT initiation was 7.00 (IQR: 4.25, 11.75) months. During the maintenance phase of KDT, the lipid-to-nonlipid ratio ranged from 0.8:1 to 4:1, with a mean value of (2.659 ± 0.780):1, while the blood BHB ranged from 0.85to 3.65 mmol/L, with a mean value of 2.491 ± 0.616 mmol/L. In two patients, the 4:1 ratio was tried and was also well tolerated, as the lower ratio was well tolerated and without side effects, but not effective.

Follow-up time from 6 months to 75 months, with a median duration of 37 (IQR: 21, 52.5) months. The duration of KDT maintenance ranged from 1.5 months to 75 months, with a median duration of 14.00 (IQR: 7.00, 26.50) months. Regarding the retention rate, 29/32 (90.6%) maintained for 6 months, 19/32 (59.4%) for 1 year and 10/32 (31.3%) for 2 years. At the last follow-up, seven patients were still following the diet.

3.3 | Treatment effectiveness

In our cohort, KDT was effective in 26 patients (81.3%), including 12 (37.5%) in Grade I, 7 (21.9%) in Grade II, and 7 (21.9%) in Grade III. The median time to achieve seizure

TABLE 2 Responder rates to ketogenic diet therapy according to the pathogenic gene.

Causative gene	Grade I	Grade II	Grade III	Grade IV
($n=32$)	n (%)			
ACTL6B ($n=1$)	–	1 (100.0%)	–	–
ARX ($n=1$)	–	1 (100.0%)	–	–
CDKL5 ($n=4$)	1 (25.0%)	–	1 (25.0%)	2 (50.0%)
GABRB2 ($n=1$)	–	1 (100.0%)	–	–
KCNT1 ($n=3$)	–	1 (33.3%)	–	2 (66.7%)
KCNQ2 ($n=2$)	1 (50.0%)	–	–	1 (50.0%)
NF1 ($n=1$)	1 (100.0%)	–	–	–
PIGA ($n=1$)	–	1 (100.0%)	–	–
SCN1A ($n=5$)	2 (40.0%)	–	3 (60.0%)	–
SCN2A ($n=4$)	1 (25.0%)	2 (50.0%)	–	1 (25.0%)
SCN8A ($n=2$)	–	–	2 (100.0%)	–
SPTAN1 ($n=1$)	1 (100.0%)	–	–	–
STXBP1 ($n=5$)	4 (80.0%)	–	1 (20.0%)	–
RHOBTB2 ($n=1$)	1 (100.0%)	–	–	–

Note: Grade I when completely seizure-free, Grade II when seizures reduced by 75% to <100%, Grade III when seizures reduced by 50% to <75%, Grade IV when ineffective (seizure reduction <50%).

freedom was 1.50 (IQR: 1.00, 3.00) months in 12 Grade I patients, 10 of whom maintained seizure-free until the last follow-up, of which five patients had discontinued KDT more than 6 months. After discontinuation of KDT, one patient had a recurrence of seizures 6 months later and one was lost to follow-up.

The responder rates of patients with different pathogenic genes are shown in Table 1. Among them, KDT was highly effective in patients with variants in *STXBP1*, *SPTAN1*, and *RHOBTB2*.

The Grade I patients had many similar clinical characteristics to the others, with no statistically difference for gender ($p=0.726$), age at seizure onset ($p=0.454$), age at KDT initiation ($p=0.146$), interval between seizure onset and KDT initiation ($p=0.070$), mean BHB ($p=0.960$), type of genetic variant ($p=0.273$), seizure type including or excluding epileptic spasms ($p=0.273$), and syndromic diagnosis ($p=0.256$). However, patients who were completely seizure-free were more likely to have a lower lipid-to-nonlipid ratio during the maintenance period than other patients ($p=0.010$) (Table 3).

Clinical variables were also analyzed between patients with a significant effect of ≥75% seizure reduction (Grade I + II) and others (Grade III + IV). There was no statistically difference in gender ($p=1.000$), age at seizure onset ($p=0.448$), age at KDT initiation ($p=0.108$), lipid-to-nonlipid ratio ($p=0.094$), mean BHB ($p=0.209$), type of genetic variant ($p=0.149$), seizure type including or excluding epileptic spasms ($p=0.149$), and syndromic diagnosis ($p=0.189$) between the two groups. However, patients with a shorter time interval between seizure onset and KDT initiation were more likely to have a significant effect on KDT than the others ($p=0.022$) (Table 4).

3.4 | Adverse effects and tolerability

Overall, 23 patients (71.9%) experienced adverse effects during KDT. The most common adverse effects involved the gastrointestinal system ($n=21$, 65.6%), including constipation ($n=13$, 40.6%), diarrhea ($n=6$, 18.8%), and vomiting ($n=4$, 12.5%). These gastrointestinal side effects tended to be mild and easily corrected with minimal interventions and did not lead to discontinuation of KDT. In addition, nephrolithiasis occurred in three patients, metabolic acidosis in three patients, and dyslipidemia in one patient. There was no significant weight loss or malnutrition, weight decreased slightly in three patients and did not increase in two patients.

During the follow-up, 25 patients had discontinued KDT for various reasons. Among them, seven patients because of achievement of seizure freedom, eight patients for family reasons, including financial stress, complicated dietary management, and disagreement among caregivers, six patients were dissatisfied with the degree of improvement in epilepsy, and one patient had difficulty continuing the diet after 1.5 months due to recurrent respiratory infections and hospitalization. In addition, two patients died for reasons unrelated to the diet, including one patient died of respiratory failure due to pneumonia, and another died of asphyxia due to epistaxis while

TABLE 3 The association between clinical parameters and seizure-free achieved with KDT.

Variables	Seizure-free		*p*-value
	Yes ($n=12$)	No ($n=20$)	
Gender, *n* (%)			
Male	5 (33.3%)	10 (66.7%)	0.726[a]
Female	7 (41.2%)	10 (58.8%)	
Age at seizure onset, median (IQR), months	1.50 (0.32, 4.00)	1.00 (0.08, 2.50)	0.454[b]
Age at KDT initiation, median (IQR), months	8.00 (5.00, 11.00)	12.00 (6.50, 15.00)	0.146[b]
Interval between seizure onset and KDT initiation, median (IQR), months	5.00 (4.00, 8.00)	9.00 (5.50, 13.00)	0.070[b]
Lipid-to-nonlipid ratio, mean ± SD	2.217 ± 0.732	2.925 ± 0.695	0.010[c]
Mean BHB, mean ± SD, mmol/L	2.483 ± 0.754	2.495 ± 0.538	0.960[c]
Type of genetic variant, *n* (%)			
Ion channel	4 (25.0%)	12 (75.0%)	0.273[a]
Others	8 (50.0%)	8 (50.0%)	
Seizure type			
Include epileptic spasms	8 (50.0%)	8 (50.0%)	0.273[a]
Exclude epileptic spasms	4 (25.0%)	12 (75.0%)	
Syndromic diagnosis			
IESS	6 (60.0%)	4 (40.0%)	0.256[a]
EIDEE	2 (28.6%)	5 (71.4%)	
EIMFS	0 (0.0%)	5 (100.0%)	
DS	1 (33.3%)	2 (66.7%)	
Non-syndromic epilepsy	3 (42.9%)	4 (57.1%)	

Abbreviations: BHB, β-hydroxybutyrate; DS, Dravet syndrome; EIDEE, early infantile developmental and epileptic encephalopathy; EIMFS, epilepsy of infancy with migrating focal seizures; IQR, interquartile range; IESS, infantile epileptic spasms syndrome; KDT, ketogenic diet therapy; SD, standard deviation.

[a]Assessed by Fisher's exact test.

[b]Assessed by Mann–Whitney *U*-tests.

[c]Assessed by Student's *t*-test.

sleeping. Only one patient discontinued KDT due to the adverse effect of nephrolithiasis.

4 | DISCUSSION

In our study, KDT was effective in 81.3% of patients diagnosed with genetic DEE with onset within the first 6 months of life, with a reduction in seizure frequency ≥50%. More importantly, 37.5% of patients were in Grade I, with a median time to achieve seizure freedom of 1.50 months, and most of them maintained seizure-free at the last follow-up. Interestingly, we found that these patients were more likely to have a lower lipid-to-nonlipid ratio during the maintenance period, with the caveat that the actual difference in median ratio was minimal, while their mean BHB was not significantly different from that of other patients. This suggests that patients who achieved seizure freedom were more likely to achieve an effective BHB level at a lower lipid-to-nonlipid ratio, and the effects of the diet were more sustained. This may be because patients with the specific etiology and genetic background are more sensitive to the KDT. Thus, patients may have good seizure control at lower ratios, whereas higher ketosis levels are not necessarily associated with seizure control, as reported in previous studies.[19] We also found that patients with a shorter time interval between seizure onset and initiation of KDT were more likely to be markedly effective with KDT, as observed in another study.[10] Therefore, early initiation of KDT may be considered for those infants who remain at greatest risk of neurodevelopmental compromise in the longer term.[12] A previous study has found a significant difference between KDT

TABLE 4 The association between clinical parameters and seizure reduction ≥75% achieved with KDT.

Variables	Seizure reduction ≥75%		*p*-value
	Yes (*n* = 19)	No (*n* = 13)	
Gender, *n* (%)			
Male	9 (60.0%)	6 (40.0%)	1.000[a]
Female	10 (58.8%)	7 (41.2%)	
Age at seizure onset, median (IQR), months	1.00 (0.08, 4.50)	1.00 (0.13, 2.00)	0.448[b]
Age at KDT initiation, median (IQR), months	8.00 (5.00, 13.00)	12.00 (7.00, 22.50)	0.108[b]
Interval between seizure onset and KDT initiation, median (IQR), months	5.00 (4.00, 9.00)	10.00 (6.50, 21.00)	0.022[b]
Lipid-to-nonlipid ratio, mean ± SD	2.468 ± 0.763	2.938 ± 0.745	0.094[c]
Mean BHB, mean ± SD, mmol/L	2.376 ± 0.670	2.658 ± 0.504	0.209[c]
Type of genetic variant, *n* (%)			
Ion channel	7 (43.8%)	9 (56.2%)	0.149[a]
Others	12 (75.0%)	4 (25.0%)	
Seizure type			
Include epileptic spasms	12 (75.0%)	4 (25.0%)	0.149[a]
Exclude epileptic spasms	7 (43.8%)	9 (56.2%)	
Syndromic diagnosis			
IESS	8 (80.0%)	2 (20.0%)	0.189[a]
EIDEE	5 (71.4%)	2 (28.6%)	
EIMFS	1 (20.0%)	4 (80.0%)	
DS	1 (33.3%)	2 (66.7%)	
Non-syndromic epilepsy	4 (57.1%)	3 (42.9%)	

Abbreviations: KDT, ketogenic diet therapy; BHB, β-hydroxybutyrate; IESS, infantile epileptic spasms syndrome; EIDEE, early infantile developmental and epileptic encephalopathy; EIMFS, epilepsy of infancy with migrating focal seizures; DS, Dravet syndrome; IQR, interquartile range; SD, standard deviation.

[a]Assessed by Fisher's exact test.

[b]Assessed by Mann–Whitney *U*-tests.

[c]Assessed by Student's *t*-test.

responders and nonresponders regarding the syndromic diagnosis,[11] whereas no statistically significant difference was found in our study, perhaps due to the small sample size.

The effects of KDT may differ according to the type of genetic variant. It has been reported that ion channel regulation plays a crucial role in the mechanism underlying the antiepileptic nature of KDT.[9] For example, ketones and the reduction in glycolytic flux during KDT may activate ATP-sensitive potassium (K_{ATP}) channels.[8] In addition, previous studies have also shown that KDT is particularly effective in patients with variants in *SCN1A*, *SCN2A*, and *KCNQ2*.[11] However, patients with pathogenic variants in the ion channel genes did not perform better than those with other gene variants in our cohort. The small number of cases with the relevant gene variants in this and the above studies is insufficient to evaluate the effectiveness of KDT in patients with ion channel gene variants, and further cases need to be collected for observation and follow-up.

We found that patients with several specific gene variants responded better to KDT, particularly the *STXBP1*. Previous studies have shown inconsistent effects of KDT in patients with *STXBP1*-DEE,[10,11,20–23] while one study has reported that KDT is highly effective in patients with late onset.[24] In our study, four out of five patients with *STXBP1*-DEE achieved seizure freedom, suggesting that KDT is highly effective not only in those with late onset, but also in those with early onset, and providing further evidence that KDT is most effective in maintaining seizure freedom.[23] The STXBP1 gene encodes a syntaxin-binding protein that facilitates neurotransmitter release between

neurons by regulating vesicle fusion.[25] KDT actions on synaptic transmission have been reported,[8] which could theoretically explain why patients with *STXBP1* variants respond better to KDT.

There were also several patients with rare gene variants, such as *SPTAN1* and *RHOBTB2*, who were highly responsive to KDT. The SPTAN1 gene encodes an α spectrin that is specifically expressed in nonerythrocytic cells, and the aggregation and failure of heterodimerization of α and β spectrins may contribute to the severe infantile epileptic encephalopathy.[26] The RHOBTB2 gene encodes one of the Rho-related BTB-domain-containing proteins, which constitute a subfamily of atypical Rho GTPases, and may play a crucial role in seizure susceptibility.[27] However, it was difficult to evaluate the effect of KDT in a few cases in both our study and the previous studies.[26–28]

Adverse effects are common in KDT, but most do not lead to discontinuation of the diet and the risk of serious adverse events is low.[6] Overall, 71.9% of patients in our study experienced adverse effects during KDT. The most common adverse effects were related to the gastrointestinal system (65.6%), including vomiting, constipation, and diarrhea. However, the diet may not fully explain the high incidence of gastrointestinal symptoms. In patients with DEEs, gastrointestinal symptoms may be part of the disease itself, rather than a result of immobility, medication, or other factors.[29] In addition, constipation is the most common adverse event prior to diet initiation in infants with drug-resistant epilepsy.[30] Therefore, the importance of a comprehensive pre-diet assessment of complicating comorbidities, including gastrointestinal symptoms, should be emphasized to accurately assess the incidence of adverse effects, especially in young patients with DEE.

The KDT was well tolerated in most of our patients, with 19 of 32 patients maintaining the diet for 1 year and 10 patients for at least 2 years. Most patients discontinued KDT due to lack of compliance, ineffectiveness of the diet, death from other causes, and achievement of seizure freedom as reported in the previous study.[30] However, one patient had to discontinue the diet due to nephrolithiasis. As this appears to be a common adverse effect of KDT,[31] given that the possibility of discontinuation and lithotripsy treatment, monitoring and possibly initiation of prophylaxis may be necessary to prevent the development and progression of nephrolithiasis once KDT is initiated.[32] There was also one patient who had to discontinue the diet due to recurrent respiratory infections and hospitalization. A web-based survey showed that 15% of children were admitted to the emergency room for respiratory problems, which is comparable to the rate of KDT side effects.[33] Respiratory infection may be a common event in patients on KDT and requires more attention. However, it is unclear whether the diet increases the risk of respiratory infections, as the physiological role of ketogenesis in the immune response remains elusive.[34]

As a retrospective, single-center research, this study has several limitations. The main limitation is the small sample size, which is also due to the rare nature of genetic DEEs, and no adjustment was made for multiple testing with association analyses. Further prospective studies with larger sample sizes are needed to confirm these findings. Another limitation is the lack of assessment of improvements in developmental outcomes. In addition, as our center is a tertiary children's hospital, patients with more severe DEEs may be admitted. On the other hand, the advantage of this study is that it provides an overview of both the effectiveness and tolerability of KDT in patients with genetic DEE within the first 6 months of life.

5 | SIGNIFICANCE

Our study shows that KDT is effective and well tolerated in patients with early onset genetic DEE. Patients with *STXBP1* and several rare gene variants responded better to KDT. Adverse effects are common but tended to be mild and easily corrected, and few patients need to interrupt their diet as a result.

AUTHOR CONTRIBUTIONS

TS and JD: conception and design of the study, data acquisition, data interpretation, and writing of the original draft. CC, XW, TH, XW, TF, and XT: data acquisition. FF: design and supervised the conduct of the study, critically revising the manuscript. All authors read and approved the submitted version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study are available from the corresponding authors on reasonable request.

ETHICS STATEMENT

This study was conducted in accordance with the principle of the Declaration of Helsinki and was approved by the Institutional Review Board of Beijing Children's Hospital (ref No. [2023]-E-014-R). Informed consents were given by the guardians of the patients.

PATIENT CONSENT STATEMENT

All the patients and their families consented to participate in the study and to have subsequent follow-up visits. Informed consents were given by the guardians of the patients.

ORCID

Tianyu Song https://orcid.org/0009-0000-4599-5660
Jie Deng https://orcid.org/0000-0001-5391-7451
Fang Fang https://orcid.org/0000-0001-6362-7896

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