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Short communication

Ketogenic diet treatment for pediatric super-refractory status epilepticus

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ABSTRACT

Purpose: We aimed to study whether ketogenic diet (KD) therapy leads to resolution of super-refractory status epilepticus in pediatric patients without significant harm.
Method: A retrospective review was performed at Phoenix Children's Hospital on patients with super-refractory status epilepticus undergoing ketogenic diet therapy from 2011 to 2015.
Results: Ten children with super-refractory status epilepticus, ages 2–16 years, were identified. 4/10 patients had immune mediated encephalitis, including Rasmussen encephalitis, anti-*N*-methyl-D-aspartate receptor encephalitis, and post-infectious mycoplasma encephalitis. Other etiologies included Lennox Gastaut Syndrome, non-ketotic hyperglycinemia, PCDH19 and GABRG2 genetic epilepsy, New Onset Refractory Status Epilepticus, and Febrile Infection-Related Epilepsy Syndrome. 4/10 patients' EEG features suggested focal with status epilepticus, and 6/10 suggested generalized with status epilepticus. Median hospital length was 61 days and median ICU length was 27 days. The median number of antiepileptic medications prior to diet initiation was 3.0 drugs, and the median after ketogenic diet treatment was 3.5 drugs. Median duration of status epilepticus prior to KD was 18 days. 9/10 patients had resolution of super-refractory status epilepticus in a median of 7 days after diet initiation. 8/9 patients were weaned off anesthesia within 15 days of diet initiation, and within 1 day of achieving ketonuria. 1/10 patients experienced side effects on the diet requiring supplementation.
Conclusion: Most patients achieved resolution of status epilepticus on KD therapy, suggesting it could be an effective therapy that can be utilized early in the treatment of children with super refractory status epilepticus.

1. Introduction

Super-Refractory Status Epilepticus (SRSE) is defined as status epilepticus (SE) continuing for at least 24 h after initiation of general anesthetic medications, including cases in which SE recurs with reduction of anesthesia [1]. It differentiates from refractory status epilepticus (RSE) by the failure of SE to resolve with anesthesia. SRSE is associated with various etiologies and carries a high risk of morbidity and mortality [2].

The ketogenic diet (KD) is a high-fat, low-carbohydrate, sufficient protein diet that mimics the fasting state, and is effective in some children with intractable epilepsy [1,3–5]. A number of pediatric case series of up to 9 patients with RSE or SRSE have been reported with variable efficacy [7–10,12]. In this single-institution case series, we investigated the use of KD for 10 children with SRSE, and explored whether this therapy can be both effective and safe.

2. Materials and methods

The Institutional Review Board at Phoenix Children's Hospital approved this study. A retrospective case review was performed on patients at Phoenix Children's Hospital between 0–18 years of age diagnosed with SRSE and treated with KD between 2011 and 2015. SRSE was classified as SE continuing for at least 24 h after initiation of general anesthesia (high-dose barbiturates, high dose midazolam or ketamine), including cases in which SE recurs with anesthesia reduction.

Data obtained included patient demographics, underlying conditions, length of hospitalization and ICU stay, EEG at initiation of KD, SE duration prior to KD, number of antiepileptic drugs (AEDs) used prior to status epilepticus and during KD, number and duration of anesthetic agents, alternative interventions used for SE during KD, KD formula, type of KD, KD ratio, KD duration, presence

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of ketones, and KD side effects (electrolyte imbalances, acidosis, etc.). Data also included SE resolution, disposition, KD therapy at disposition and follow-up, and seizure burden at most recent follow-up. Resolution of SRSE was determined by the absence of electrographic or convulsive seizures after discontinuation of anesthesia. Data was confirmed by review of physician notes and laboratory results. Means, medians, and interquartile ranges (IQR) were calculated for continuous variables and proportions for categorical variables.

The primary outcome used to demonstrate benefit of KD was the proportion of patients achieving resolution of SE after KD initiation. Secondary outcomes included the proportion of patients weaned off anesthesia within one day of achieving ketonuria, and the proportion of patients weaned off anesthesia within 15 days of KD initiation. Outcomes demonstrating harm included KD-related side effects.

3. Theory

The primary research question was whether KD led to resolution of SRSE in pediatric patients.

4. Results

4.1. Clinical characteristics

Ten pediatric patients at Phoenix Children's Hospital were treated with KD for SRSE [Table 1]. Four patients were female and six patients were male. Ages ranged between 2–16 years of age (median 8; IQR 3.9–14.0; mean 8.7 ± 5.4). Five patients (50%) had a diagnosis of epilepsy before their hospitalization, and 3/5 patients (60%) had a known etiology. 4/10 patients (40%) were diagnosed with immune-mediated encephalitis (one with Rasmussen encephalitis, one with post-infectious mycoplasma encephalitis, and two with *N*-methyl-D-aspartate receptor (NMDA-R) encephalitis without an oncogenic source). The patient with Rasmussen encephalitis was diagnosed after admission with SRSE, and surgery was not considered given bilateral involvement. 1/10 patients (10%) had epilepsy of a metabolic etiology (non-ketotic hyperglycinemia). 1/10 patients (20%) had a known genetic epilepsy (mutations to PCDH19 and GABRG2). 2/10 patients (20%) had Febrile Infection-Related Epilepsy Syndrome (FIRES) and 1/10 patients (10%) had New Onset Refractory Status Epilepticus (NORSE). 4/10 patients (40%) had EEG features suggestive of focal SRSE, whereas 6/10 patients (60%) had generalized SRSE features. Hospital lengths ranged from 7 to 188 days (median 61.0; IQR 36.8–101.8; mean 74.5 ± 54.7) and ICU lengths ranged from 3 to 120 days (median 27.0; IQR 23.0–50.5; mean 39.0 ± 32.7). All patients were in SRSE prior to initiation of KD for 1–45 days (median 18.0; IQR 8.5–27.3; mean 20.4 ± 15.5). The number of AEDs used prior to status epilepticus ranged from 1 to 6 drugs (median 3.0; IQR 1.5–4.0; mean 3.1 ± 1.7). The number of anesthetic agents used prior to KD ranged from 1to 3 agents (median 2.0; IQR 2.0–2.8; mean 2.2 ± 0.6). 1/10 patients (10%) had a VNS placed 14 days prior to KD treatment.

4.2. Ketogenic diet initiation

All patients had baseline laboratory testing including serum carnitine, lactic acid, pyruvic acid, fatty acids, chemistries, lipids, electrolytes, complete blood counts, and vitamin A, D, E and K levels. These were evaluated by a neurologist prior to KD initiation. All patients were placed on the KetoCal (Nutricia®) formula. 9/10 patients (90%) were placed on a 4:1 KD ratio (fat to carbohydrates and protein grams) and 1/10 patients (10%) were placed on a 5:1 ratio. 9/10 patients (90%) received the diet via

Table 1
Patient characteristics and initial management.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (years)	3	15	16	3.5	11	2	7	5	15	9
Sex	F	M	F	M	M	M	F	M	M	F
Race	Caucasian	Caucasian	Caucasian	Hispanic	Native American	Hispanic	Caucasian	Caucasian	Hispanic	Hispanic
Diagnosis	Rasmussen encephalitis	Generalized epilepsy, intractable	Lennox-Gastaut syndrome	Non-ketotic hyperglycinemia	Mycoplasma post-infectious encephalitis	NORSE	FIRES; PCDH19 and GABRG2 mutations	FIRES	NMDA-R encephalitis	NMDA-R encephalitis
History of epilepsy	Yes	Yes	Yes	Yes	No	No	Yes	No	No	No
EEG features	L Hem Foc SE	Gen SE	L Hem Foc SE	Gen SE	Gen SE	Gen SE	Gen SE	Gen SE	L Hem Foc SE	L Hem Foc SE
Hospital length (days)	74	7	66	33	48	56	30	111	188	132
ICU length (days)	56	3	23	23	21	56	24	30	120	34
Duration of SE before KD (days)	25	1	25	7	11	44	8	10	45	28
AEDs used	LVM, FBM, PHB, VPA, CBZ	VLM, VPA, PHB, LTG, LYR, CBM	LVM, VPA, CBZ, CBM	TPM, FBM, LTG	LVM	LVM	LVM, TPM, CBM	LVM, VPA, LCM	LVM, ZNS	TPM, OXC
Anesthetic agents before KD	MDZ, PTB, KTM	MDZ	MDZ, PTB	MDZ, PTB, KTM	MDZ, HD PHB	MDZ, PTB	MDZ, PTB	MDZ, PTB, KTM	MDZ, PTB	MDZ, PTB
KD ratio	4 to 1	4 to 1	4 to 1	4 to 1	4 to 1	4 to 1	4 to 1	5 to 1	4 to 1	4 to 1
Type of KD	Enteral	Enteral	Enteral	TPN/IL	Enteral	Enteral	Enteral	Enteral	Enteral	Enteral

Abbreviations: female, F; male, M; New Onset Refractory Status Epilepticus, NORSE; Febrile Infection Related Epilepsy Syndrome, FIRES; Protocadherin 19, PCDH19; gamma-aminobutyric acid type A receptor gamma 2, GABRG2; *N*-methyl-D-aspartate receptor, NMDA-R; left, L; generalized, Gen; focal, Foc; hemispheric, Hem; status epilepticus, SE; levetiracetam, LVM; felbamate, FBM; phenobarbital, PHB; valproate, VPA; carbamazepine, CBZ; lamotrigine, LTG; lyrica, LYR; clobazam, CBM; topiramate, TPM; lacosamide, LCM; zonisamide, ZNM; oxcarbazepine, OXC; midazolam, MDZ; pentobarbital, PTB; ketamine, KTM; high-dose, HD; antiepileptic drugs, AEDs; ketogenic diet, KD; total parental nutrition, TPN; intralipids, IL.

enteral feeds, and 1/10 patients (10%) received the diet via total parental nutrition and intralipids (TPN/IL). The KD formula was initiated at 50% of recommended dietary allowance for 20 h/day, and increases in calorie intake of 10% were titrated each day anesthesia was tapered. Electrolytes, arterial blood gases, and daily urine ketones were checked during KD therapy.

4.3. Primary outcome

9/10 patients achieved resolution of SRSE, occurring 1–19 days (median 7.0; IQR 7.0; mean 7.9 ± 6.1) after KD initiation (Table 2).

4.4. Secondary outcomes

8/9 patients with SRSE resolution were weaned off anesthesia within 15 days of KD initiation (median 5.5; IQR 0.75–9.0; mean 5.6 ± 5.3), and within one day of achieving ketonuria. One patient required 44 days to be weaned off anesthesia after KD initiation. Time to ketonuria ranged from 0 to 13 days (median 5.5; IQR 2.0–8.0; mean 5.9 ± 3.8), with the patient receiving TPN/IL KD requiring the longest duration. One patient had a vagal nerve stimulator (VNS) activated four days after KD initiation and was weaned off anesthesia the following day. The four patients with immune mediated encephalitis received immunosuppressive therapy (methylprednisolone, intravenous immunoglobulins, ACTH, and/or plasma exchange) before and during KD therapy. One patient with NMDA-R encephalitis achieved SRSE resolution without achieving ketonuria. The one patient receiving KD via TPN/IL was transitioned to enteral KD feeds after SRSE resolution. All patients achieving SRSE resolution were discharged to a rehabilitation unit. One patient failed to achieve resolution of SRSE despite 3+ ketonuria, and died in hospice care. 9/10 patients (90%) had no side effects with KD. One patient experienced side effects including ketoacidosis, hypophosphatemia, and hypokalemia which were corrected with bicarbonate and electrolyte supplementation. The number of AEDs used at hospital discharge ranged from 3 to 5 drugs (median 3.5; IQR 3.0–4.0; mean 3.6 ± 0.7).

Among surviving patients, 8/9 (89%) patients were regularly followed in outpatient neurology clinics, and 1/9 (11%) was lost to follow-up. Follow-up duration from time of discharge ranged from 1 to 39 months (median 17.5; IQR 11.0–32.5; mean 19.3 ± 14.6). Among those followed, 5/8 (62.5%) remained with intractable epilepsy, ranging from 1 seizure weekly to 10 daily seizures. 5/8 patients (50%) remained on KD at their most recent clinic visit, all of whom were not on KD therapy prior to SRSE. Four of the nine surviving patients (44%) tapered off KD all had immune-mediated encephalitis, three of which were tapered off KD therapy prior to hospital discharge. Those three patients did not progress to intractable epilepsy, and the remaining patient with immune-mediated encephalitis (Rasmussen encephalitis) was discontinued from KD therapy one year after discharge.

5. Discussion

In our experience, most of our patients (90%) had resolution of SRSE with KD therapy, and the therapy was tolerated well with minimal side effects.

The utilization of KD as a treatment for RSE has been reported. Several groups have reported on children with RSE treated with KD, of whom many have had a beneficial response [6–9]. Nine children with RSE secondary to FIRES had been reported, of whom seven had resolution of SE within four days of treatment [10]. With respect to SRSE, a series of 10 adult patients was reported [11]. 9/10 patients had resolution of SE within a median of three days after KD initiation, seizure resolution occurred in 7/10 patients within one week of KD initiation, and the only patient without

Table 2
Clinical outcomes.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Resolution of SE	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Length of SRSE after KD initiation (days)	5	1	2	9	10	12	7	15	19	3
Length of anesthesia after KD initiation (days)	5	1	0	9	9	12	6	15	44	Anesthesia weaned before KD
Time to ketonuria (days)	6	0	2	13	8	8	5	2	Ketosis not achieved	6
Side effects with KD	No	No	No	No	No	No	Yes	No	No	No
Steroids while on KD	Yes	No	No	No	Yes	Yes	No	No	Yes	Yes
AEDs at hospital discharge	ATV, CBM, PHB, TPM	LVM, LTG, PHB	LVM, CBM, FBM, CHZ	TPM, FBM, LTG	LVM, VPA, CBZ	N/A	LVM, TPM, PHB	LVM, CBM, FBM, LCM, PHB	LVM, ZNS, FBM	LVM, TPM, PHB
Duration of follow-up after discharge (months)	39	10	12	29	Lost to follow-up	Deceased	1	4	36	23
Seizure burden at most recent follow-up	15 seizures/day	1 seizure/week	Seizures during menses	3 seizures/week	Lost to follow-up	N/A	Daily seizures	No seizures	No seizures	No seizures
KD at most recent clinic visit	No	Yes	Yes	Yes	Not at discharge	N/A	Yes	Yes	No	No

Abbreviations: left, L; generalized, Gen; focal, Foc; hemispheric, Hem; status epilepticus, SE; levetiracetam, LVM; felbamate, FBM; phenobarbital, PHB; valproate, VPA; carbamazepine, CBZ; lamotrigine, LTG; lyrica, LYR; clobazam, CBM; topiramate, TPM; lacosamide, LCM; zonisamide, ZNM; oxcarbazepine, OXC; midazolam, MDZ; pentobarbital, PTB; ketamine, KTM; high-dose, HD; antiepileptic drugs, AEDs; ketogenic diet, KD; ativan, ATV; chlorazepate, CHZ; N/A, not applicable.

SRSE resolution failed to reach ketosis. A pediatric series was reported of four children with SRSE treated with KD, of whom all were weaned off anesthesia with variable residual seizure burdens [12].

Our study is limited by its retrospective nature, a small sample size, the lack of consistent acquisition of serum beta-hydroxybutyrate levels, and the concomitant use of other agents while KD was utilized. In some patients receiving concurrent therapies directed at an underlying diagnosis, resolution of SRSE cannot be directly attributed to the KD. Prospective trials are needed to directly link the effectiveness of KD to SRSE, identify predictors of treatment responsiveness, and determine a dose-responsive relationship of treatment to SRSE. This, however, may be difficult to achieve given how critically ill most of these patients are.

6. Conclusion

The majority of patients with SRSE achieved resolution of SE on KD therapy, suggesting that it could be an effective therapy that can be utilized early on in the treatment of children with SRSE.

Conflicts of interest

None.

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