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BRIEF COMMUNICATION

Use of the ketogenic diet in the neonatal intensive care unit—Safety and tolerability

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Summary

Drug-resistant epilepsy poses a challenge in neonatal patients, especially those in the neonatal intensive care unit (NICU), who have various secondary comorbidities. We present results of four children with a history of drug-resistant epilepsy for whom a ketogenic diet was initiated and used in the NICU. A nonfasting induction into ketosis over 1–2 weeks was utilized, with gradual increases in the ketogenic ratio every 2–3 days. Data were collected retrospectively from a database, which included medical history, daily progress notes, relevant laboratory data, and imaging and diagnostic information. The ketogenic diet was well tolerated in all cases. The most common side effects observed were constipation, hypoglycemia, and weight loss. Serum β-hydroxybutyrate levels demonstrated improved reliability as a marker of ketosis when compared to urine ketones in this population. Perceived benefits to the infants included improved seizure control, increased alertness, and decreased need for invasive respiratory support. These cases demonstrate that the use of the ketogenic diet for treatment of neonatal encephalopathy and refractory epilepsy can be undertaken safely in the NICU and is well tolerated by carefully screened neonates and infants.

KEY WORDS: Diet therapies, Neonatal intensive care unit, Refractory epilepsy, Nonpharmacologic.

The ketogenic diet is a high-fat, low-carbohydrate diet that is an effective treatment for reducing seizures in infants and children with drug-resistant epilepsy.[1,2] A 2012 Cochrane Review reported that the benefits of a ketogenic diet are comparable to those of modern antiepileptic drugs (AEDs).[2] The ketogenic diet has been studied previously in infants with refractory epilepsy and has been demonstrated to be safe and effective.[3–5] Klepper et al.[3] described the use of the ketogenic diet in four young infants, and Nordli et al.,[4] reported that the diet had equal efficacy in 32 infants, including medication weaning, when compared to previous studies of older children. Kayyali et al.,[5] described successful and efficacious use of the diet in 15 infants with refractory epileptic spasms. However, these studies have not described the use of ketogenic diet in critically ill hospitalized infants. Drug-resistant epilepsy poses a challenge in infant patients, especially those in the neonatal intensive care unit (NICU) who have various secondary comorbidities. There is a single published case report that includes one patient, 9 weeks of age, for whom the ketogenic diet was successfully used to treat refractory status epilepticus in the NICU.[6] Nonetheless, no other data have been published on the safety and tolerability of the ketogenic diet in infants being treated for epileptic encephalopathy and refractory seizures in the NICU. Thus, we present data on four infants with a history of drug-resistant epilepsy for whom the ketogenic diet was initiated and used in the NICU.

Methods

The Children's Mercy Hospital Institutional Review Board approved this study. Data were collected retrospectively from a database, which included medical history, daily progress notes, diet information, relevant laboratory data, imaging findings, and electroencephalography (EEG) monitoring. Frequency of clinical seizures, complications,

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and perceived benefits noted with ketogenic diet initiation were collected via caregiver and medical staff report. Patient demographics are presented in Table 1. All patients failed to respond to at least three AEDs prior to ketogenic diet initiation. Failure was defined as continued seizures despite appropriate doses of AEDs. Metabolic screening, including serum amino acids, urine organic acids, and acylcarnitine panel, was performed for all patients prior to diet initiation, as well as evaluation for contraindications to the ketogenic diet, as outlined previously by Kossoff et al.[7] All patients had EEG studies performed before and after ketogenic diet initiation, but there was no standard time for completion of EEG.

A nonfasting induction into ketosis over 1–2 weeks was utilized, with gradual increases in the ketogenic ratio every 2–3 days, starting with a ketogenic ratio of 1:1. Diet ratio was titrated until a blood ketone level >3,000 μmol/L was achieved. Diet ratio was adjusted further in response to perceived benefit to seizure control, infant alertness, or decreased need for respiratory support. The highest ratio utilized was 4:1. The following lab monitoring was performed during diet initiation: basic metabolic panels daily, urine dipstick for ketones with each void, and serum β-hydroxybutyrate every other day. Blood glucose was monitored with fingerstick four times daily or as needed based on clinical course. Frequency of laboratory blood draws were minimized to preserve infant blood volume. Ketogenic formulas (KetoCal 4:1 LQ, Nutricia North America, and Ross Carbohydrate Free, Abbott Nutrition) and modular products (MCT Oil, Nestle, and Liquid Protein Fortifier, Abbott Nutrition) were used to initiate the diet. In case 4, the patient's ketogenic formula was mixed with the mother's breast milk to the prescribed ketogenic ratio. All patients required additional vitamin and mineral supplementation to meet 100% of micronutrient requirements per Institute of Medicine recommendations.[8]

All four patients were discharged home from the NICU on the ketogenic diet and were followed in the outpatient clinic every 3 months. Clinic visits consisted of anthropometric assessment, clinical evaluation, and discussion of diet efficacy with caregivers. Laboratory data collected at follow-up visits included basic metabolic panel, liver function tests, serum β-hydroxybutyrate level, lipid panel, and serum micronutrients.

Results

Ketogenic diet initiation was well tolerated in all infants studied. Ketosis was achieved in all cases as evidenced by serum ketone level (Fig. 1). Urine ketones were variable and did not correlate directly with serum levels of ketosis (Fig. 1). In case 1, the infant required continuous nasogastric feedings due to preexisting hypoglycemia that persisted, although did not worsen, with ketogenic diet induction.

Table 1. Patient demographics

	Medical history	Age at KD initiation (weeks)	Intubated at KD initiation (Y/N)	KD ratio required at initiation	Route of diet administration at KD initiation	Medications at time of KD Initiation	Epilepsy therapies to date	KD duration to date	Mean serum β-HBA since diet initiation	Outcomes to date
Case 1	*SCN2A* mutation, epileptic encephalopathy	10	Y	4:1	NG (continuous)	Phenobarbital Levetiracetam Topiramate Clobazam	Phenobarbital Topiramate Clobazam 4:1 KD	2.5 years	4,473 μmol/L	Daily seizures Severe DD Cortical visual impairment Dystonia
Case 2	Idiopathic Ohtahara syndrome	9	Y	4:1	NG	Levetiracetam Topiramate Phenobarbital	Vigabatrin 2.75:1 KD	2.25 years	4,314 μmol/L	Seizure-free × 2 years Severe DD
Case 3	*KCNT1* mutation, early infantile epileptic encephalopathy	9	N	3:1	PO	Phenobarbital Levetiracetam Clobazam Phenytoin	Phenobarbital Levetiracetam Clobazam 3.25:1 KD	10 months	4,123 μmol/L	Daily seizures Severe DD
Case 4	*KCNQ2* mutation, epileptic encephalopathy	6	N	3.5:1	PO/NG	Phenobarbital Levetiracetam Topiramate Clobazam	Phenobarbital Levetiracetam 3.75:1 KD VNS	2.25 years	6,950 μmol/L	Daily seizures Severe DD

NG, nasogastric; PO, by mouth; KD, ketogenic diet; β-HBA, β-hydroxybutyrate; DD, developmental delay.

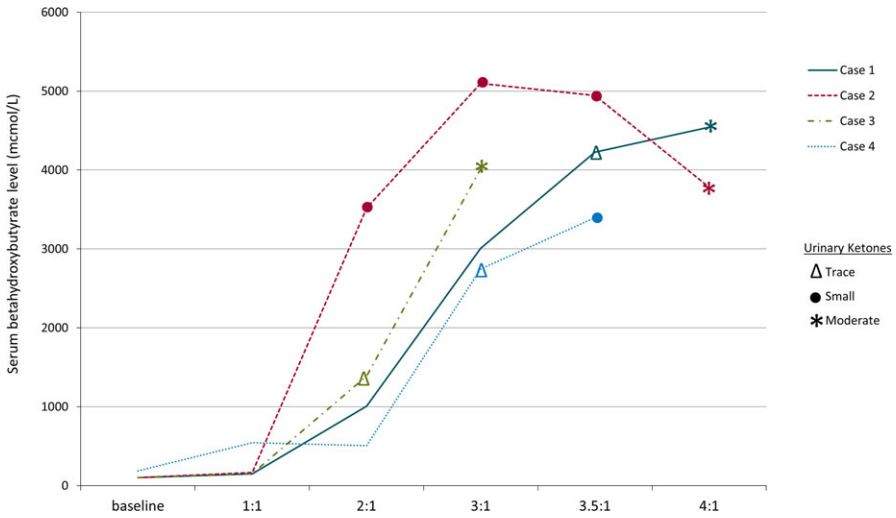

Figure 1.
Serum betahydroxybutyrate levels at each ketogenic diet ratio for cases 1–4 correlated with urine ketone measurements.
Epilepsia © ILAE

None of the infants in this series required intravenous fluids or intravenous nutrition support during diet initiation.

A reduction in clinical seizures was reported subjectively by caregivers and/or medical staff in three of four cases (cases 1, 2, and 4). However, only the EEG in case 4 demonstrated improved organization and decreased seizures after diet initiation. This patient became seizure-free within 2 weeks of starting the ketogenic diet. In case 3, caregivers did not report a reduction in seizure activity, and this observation was supported by continued seizures on EEG. None of the EEG findings demonstrated worsening of epilepsy; however, evolution of epileptic encephalopathy was observed in three of the four cases (cases 1–3).

Improved response to environmental stimuli was reported in all four cases by caregivers. Case 1 and case 2, who were intubated at baseline, were successfully extubated and weaned to either nasal cannula or room air after ketogenic diet initiation.

The most common side effects observed were constipation, hypoglycemia, and weight loss. Constipation was noted in cases 1 and 2. Constipation was successfully treated with glycerin suppositories and addition of MCT oil to the patients' formula. Case 1 experienced low blood glucose (defined as <40 mg/dl). Ten milliliters of juice was given acutely and progress of diet initiation was slowed, which resulted in improved blood glucose levels. Weight loss was a problem for case 1 initially, but resolved with calorie adjustments and the addition of MCT oil (5% of fat calories) to formula.

All four infants remain on ketogenic diet for management of epilepsy (Table 1). All infants were able to have at least one medication weaned after starting ketogenic diet, with two of the four infants having more than one medication weaned. No cases exhibited elevated cholesterol levels after ketogenic diet initiation.

Discussion

These cases demonstrate that initiation of the ketogenic diet for treatment of refractory epilepsy can be undertaken safely in the NICU and is well tolerated in carefully screened infants. Although the efficacy of the ketogenic diet for seizure control cannot be determined in this small population, the caregivers and medical staff reported reductions in numbers of clinical seizures, an observation supported by EEG findings in one patient. Unanticipated improvements in alertness and respiratory effort suggest additional benefit to support the use of this treatment option in infants in the NICU.

Serum β-hydroxybutyrate levels demonstrated improved reliability as a marker of ketosis when compared to urine ketones in this population, which has been noted previously.[3] Metabolic complications, including hypoglycemia, were consistent with previously reported side effects of the ketogenic diet in infants[3–6,9] and were easily managed with standard interventions. Acute weight loss, which was noted in case 1, was also reported previously in an infant started on the ketogenic diet by Goyens et al.[9] In both instances, weight loss was reversed successfully with the addition of MCT oil to the infant's formula. Hyperlipidemia is commonly reported with ketogenic diet use,[10] including in infants[4]; however, this was not observed in any cases at follow-up clinic visits.

Education of staff and caregivers is vital for successful use of this treatment option in the NICU. Initial obstacles to ketogenic diet initiation in the NICU included the following: staff inexperience with the metabolic effects and monitoring required for ketogenic diet initiation, concern by NICU physicians that use of the ketogenic diet would prevent infants from receiving appropriate nutrition and limit weight gain, incorrect ordering of formula, and

inappropriate administration of glucose to treat hypoglycemia. Written, verbal, and online education was provided for staff by the ketogenic diet team, which included physicians, nurse practitioners, and dieticians. The material provided has since been formalized into ongoing education offerings. Development of new order sets in the electronic medical record, specific to ketogenic diet initiation, allowed for accurate and streamlined patient management. Identification of dextrose in the electronic medical record as a cause of adverse reaction for all patients on the ketogenic diet improved institutional awareness to possible medication/infusion formulation errors.

Conclusion

In these cases, the ketogenic diet was safe and well tolerated as an adjunct therapy for intractable epilepsy in the NICU. Perceived benefits for the infants included improved seizure control, increased alertness and decreased need for invasive respiratory support. Careful attention to education of all caregivers and medical staff must be assumed prior to and during use of the ketogenic diet in the NICU to maximize benefit and limit risk to patients. Further study with a larger patient sample size is needed to determine if perceived benefits seen in this case series are statistically supported.

Disclosure of Conflict of Interest

Lindsey Thompson has served as a paid consultant for Nutricia North America. The remaining authors have no conflicts of interest to disclose. 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.

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