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Short communication

Initiating the ketogenic diet in infants with treatment refractory epilepsy while maintaining a breast milk diet

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ABSTRACT

Purpose: The ketogenic diet has been found to be safe and effective in the treatment of drug resistant epilepsy in childhood. The age range of children undergoing this treatment has steadily been going down. There is strong evidence that it is a safe alternative in infants with drug resistant seizures. The American Academy of Pediatrics strongly supports continuing a breast milk diet until infants are at least six months of age. The purpose of this study is to evaluate the safety and efficacy of the ketogenic diet in infants while maintaining a breast milk diet.
Method: This is a cohort study of 9 infants between the ages of 1 and 13 months with drug resistant epilepsy treated with the ketogenic diet while maintained on breast milk. The data from the first two patients was gathered retrospectively while the other seven were studied prospectively.
Results: We show that all nine infants achieved and maintained ketosis effectively. While one infant had no change in seizure frequency, three were seizure free at the first follow-up visit and four had a burden of seizure reduction greater than 50%. The diet was overall well tolerated, although one child required a hospital stay for dehydration and metabolic acidosis.
Conclusion: The ketogenic diet can be safely and effectively initiated in infants while continuing human breast milk feedings.

1. Introduction

Neonatal epilepsy remains a significant problem. Several large prospective studies have shown that up to 38% of infants with epilepsy were classified as drug resistant epilepsies [1]. Furthermore, the outcome for these infants remains rather poor, with 17% dying and 49% having an abnormal exam at the time of discharge [2]. Until recently there were no guidelines for the treatment of seizures in the newborn. The mainstay of treatment remains phenobarbital, with benzodiazepines generally used as second line [3]. In 2015 the International League Against Epilepsy published its recommendations for the management of infantile seizures [4]. In this publication the ketogenic diet was reported as possibly effective in the treatment of generalized seizures and as the treatment of choice for epilepsy in infants with glucose transporter deficiency type 1 syndrome and pyruvate dehydrogenase deficiency.

The ketogenic diet has been found to be both safe and effective in infants and children. Various retrospective studies have shown that most children tolerate the diet over prolonged periods of time [5,6]. Side effects are typically manageable but may include gastrointestinal disruptions, hypertriglyceridemia and nephrolithiasis. Several groups have published data showing that the ketogenic diet is an effective treatment for epileptic spasms [7,8]. One of the barriers that may influence the choice of the ketogenic diet as a treatment for infants with epilepsy is the desire for mothers to breastfeed. In 2012, the American Academy of Pediatrics reaffirmed its recommendation of exclusively breastfeeding infants for six months and asserted that breastfeeding should be considered a public health issue [9]. This prompted our group to design a protocol for initiating the ketogenic diet in breastfed infants. We present the clinical follow-up of nine infants who were successfully started on the ketogenic diet while maintaining human milk feedings.

2. Material and methods

This is a study of infants who received ketogenic diet therapy in the Comprehensive Epilepsy Center at Children's Mercy Hospital between May 2005 and January 2016. The patients reported in this study were part of a larger cohort of patients on the ketogenic diet followed at our

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institution. We included all of the infants who were continued on breastmilk at the time of diet initiation. The data from the first two patients was gathered retrospectively while the other seven were studied prospectively. The ketogenic diet was initiated per standard protocol (Charlie Foundation) during an inpatient admission. Patients were all orally fed and began the diet at a 3:1 ratio. Mothers expressed breast milk, which was subsequently mixed with ketogenic formula Ketocal 4:1(Nutricia North America) in eight of the nine patients, in patient 7 a soy-based ketogenic formula had to be used (Ross Carbohydrate Free ®) due to a milk protein allergy. Depending on the prescribed ketogenic ratio (typically 3:1 to 4:1), the formula contained approximately 5–10% calories from breastmilk, with more breastmilk in the 3:1 ratio and less breastmilk in the 4:1 ratio. The Dietary Reference Intakes (DRI) for protein for each subject was met for age and gender [10]. Seizure reduction (as reported by the parents in a seizure diary) and quality of life (as reported by parents in the form of a yes/no question to improved alertness, interactions, performance in school) were collected by means of self-report during scheduled clinic visits. Serum beta-hydroxybutyrate levels and standard labs were collected at baseline, at 1 month follow up and every 3 months thereafter. This study was approved by the local IRB.

3. Results

Nine infants with drug resistant seizures were included in this study (Table 1). The seizure etiologies were hypoxic ischemic encephalopathy (1 patient), glucose transporter deficiency type 1 [1], epileptic spasms [3], *KCNQ2* epileptic encephalopathy [1], *CDKL5* epileptic encephalopathy [1], Aicardi syndrome [1] and an infant with a generalized epileptic encephalopathy of unknown etiology. The average age at seizure onset was 3 month old with a range of 1–7 months of age. The average age at the time the diet was started was 6.7 months old with a range of 1 to 13 months of age. The infants had failed one to three antiepileptic drugs at the time of onset of the diet. Antiepileptic medications used included topiramate (6 patients), levetiracetam [5], clobazam [4], clonazepam [3], vigabatrin [2], zonisamide [2], clorazepate [1], ethosuximide [1], felbamate [1], lacosamide [1] and phenobarbital [1]. All of the patients were on a breast milk diet at the time of ketogenic diet initiation; one remained on a breast milk diet for six months, five for three months, and three for one month. All patients continued to be followed in clinic every three months for as long as they were on the ketogenic diet.

All of the patients achieved ketosis by the time of discharge (as assessed by urine ketones > 80 mg/dl and serum beta-hydroxybutyrate > 1000μmole/L) and were still in ketosis at the time of the first follow-up visit (Fig. 1). While on the diet and still on breast milk the infants gained an average of 9+/-19 points in weight percentiles (range -23 to +41, Table 1, all results are given as the average value +/- the standard deviation). We collected lipid profiles for all infants while on the diet. The average change in cholesterol was +8.9+/-33.8 mg/dl (Table 1) and the average change in triglycerides -18.6+/−113 mg/dl. However, not all infants had a repeat lipid profile at the time that breast milk was discontinued. In such cases we used next available lipid profile. We did not have enough data to ascertain the statistical significance of these changes. Serum glucose while on the diet was on average 73+/−10 mg/dl (range: 60–99 mg/dl). Serum bicarbonate was on average 21+/−4.3 mmol/L (range: 14–31 mmol/L).

Four infants were seizure free and on no antiepileptic medications at the time of breastmilk discontinuation. The parents of all but one infant reported an improvement in perceived quality of life. While the infants were maintained on breast milk the diet was generally well tolerated with the exception of one infant who developed gastrointestinal side effects resulting in a brief hospitalization for dehydration and metabolic acidosis.

Table 1
Clinical outcomes. QOL: Quality Of Life (parental perception of reported improvement in QOL), AED: Anti-Epileptic Drug, * all patients continued the ketogenic diet for at least three months after discontinuation of breastmilk (see Fig. 1), **Required hospitalization for dehydration. ***Expressed as the change in mg/dl between ketogenic diet initiation and last visit while still on breast milk (NA: data not collected at diet initiation for two patients whose ketogenic diet was initiated emergently in the NICU).

Patient	Age at seizure onset (months)	Age at diet onset (months)	# AEDs at onset	# AEDs at end of diet with breastmilk*	Diet ratio at onset	Adverse Events	Change in cholesterol***	% change in seizure frequency at 1st visit	% change in seizure frequency at last visit	QOL improved
1	1	3	1	2	3:1	None	19	> 50% reduction	< 50% reduction	Yes
2	7	9	2	0	3:1	None	45	> 90% reduction	Seizure free	Yes
3	1.2	12	2	0	3:1	Dehydration and metabolic acidosis**	−24	> 50% reduction	> 50% reduction	Yes
4	5	7	2	0	3:1	None	−13	< 50% reduction	Seizure free	Yes
5	1	5	3	4	3:1	Vomiting	−3	No change	No change	No
6	4	9	2	0	4:1	None	61	< 50% reduction	Seizure free	Yes
7	1.2	1.4	1	0	3:1	None	NA	Seizure free	Seizure free	Yes
8	0	1.2	3	3	3:1	Constipation	NA	Seizure free	> 50% reduction	Yes
9	6.5	13	3	1	3:1	Metabolic acidosis	−23	Seizure free	No change	Yes

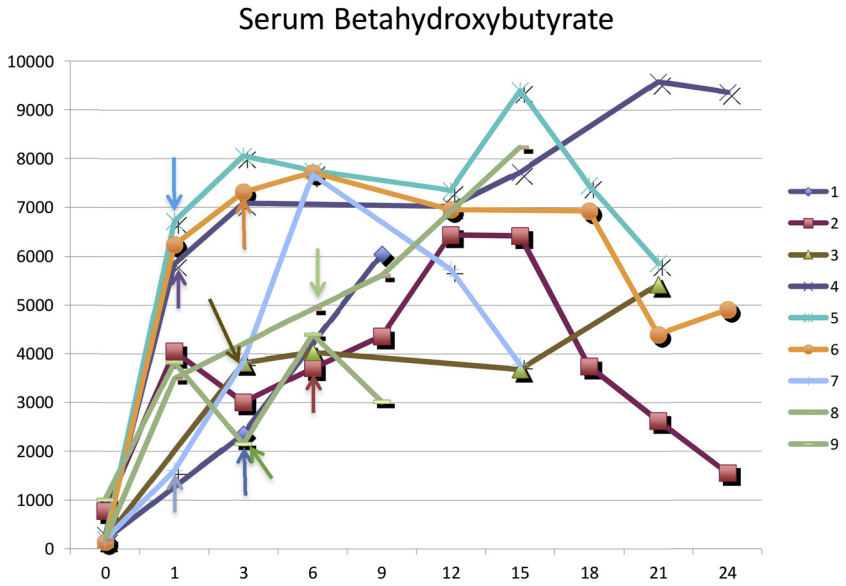

Fig. 1. Serum betahydroxybutyrate levels after initiation of the ketogenic diet. The arrows indicate the end of the breast milk diet. X-axis: Treatment length in months, Y-axis: Beta-hydroxybutyrate serum levels in μmol/L. Note that the one-month labs were not available for patients 1 and 3.

4. Discussion

In this study we report nine breastfed infants with drug resistant epilepsy treated successfully with the ketogenic diet. At the time of diet initiation they were 1 to 13 months of age (average 6.7 months). All nine infants were able to continue on a diet of breast milk for at least 1 month. The reasons for discontinuing breastmilk included a combination of factors, including reaching 6 months of age (AAP recommended minimum length of time on breastmilk), loss of supply or decreased interest in expressing breastmilk (see supplemental Table 1 for details). All of the infants achieved ketosis prior to discharge (as measured by urine ketones and serum beta-hydroxybutyrate levels) and maintained ketosis (as measured by serum beta-hydroxybutyrate levels) at subsequent visits. No significant side effects were reported. Four of the infants were seizure free and three had a greater than 50% seizure reduction. None of the infants had significant side effects from the treatment. This is the largest reported cohort of breastfed infants treated with the ketogenic diet. Two groups previously reported [11,12] respectively five and four infants treated with the ketogenic diet while on breast milk. The infants in both studies were slightly older on average than our patients. Both groups showed a significant decrease in seizure burden. In the present study we expand on this experience. We present a larger group of infants, all with treatment refractory epilepsies. We show that in this group of infants the diet was effectively initiated while maintaining a breast milk diet. The results of the laboratory and biometric data support the effectiveness and the safety of the diet.

Drug resistant epilepsy in infants remains a significant problem [2]. The use of the ketogenic diet in infants has been shown to be safe and effective and the International League Against Epilepsy now recognizes it as a treatment option for these infants [4]. Given the American Academy of Pediatrics' strong endorsement of breast-feeding infants and given the increased use of the ketogenic diet to treat drug resistant epilepsy in infants, finding a solution that allows for maintenance of a diet of breast milk while on the ketogenic diet is of importance. The present report adds evidence supporting the safe and effective use of the ketogenic diet in breastfed infants with drug resistant epilepsy.

Conflict of interest disclosure

J.B. Le Pichon has no conflicts of interest to disclose.

Lindsey Thompson has served as a paid consultant for Nutricia North America.

Megan Gustafson has no conflicts of interest to disclose.

Ahmed Abdelmoity served as consultant for Livanova and Lundbeck. Served on the speaker bureau of Livanova, Lundbeck, UCB, Sunovion, and Eisai.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.03.017.

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