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Keto-Bezoar: Adverse Event Related to Initiation of Ketogenic Diet in an Infant

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Abstract: The ketogenic diet is frequently used as part of the treatment regimen for pediatric patients with refractory epilepsy. This diet is generally well tolerated, with constipation being the most described side effect. This case highlights a previously undocumented severe complication of a "keto-bezoar" formation related to the initiation of the ketogenic diet in a young infant.

Key Words: epilepsy, pediatric, abdominal compartment syndrome, ketogenic diet

INTRODUCTION

The ketogenic diet (KD) is a widely accepted dietary treatment for refractory epilepsy in children and adolescents, with improvement in seizure control (1). As ketogenic formulas have become readily available, there has been an increase in KD use in infants, however, few studies describe adverse effects in this population (2). We present the case of an infant who developed severe fecal impaction after initiation of KD.

CASE REPORT

The patient is a 6-week-old term infant with drug-resistant epilepsy who experienced seizures hours after birth. Despite an escalating regimen of antiepileptic medications, the patient continued to experience refractory clinical seizures. There was high clinical suspicion for a BRAT1 gene mutation and associated epileptic encephalopathy syndrome. The patient's sibling, who also had BRAT1 gene mutation, had great success with KD, thus the patient was started on KD in the neonatal period, on day of life 27. Under the guidance of a KD dietician, the patient achieved ketosis on day of life 31 with a ketogenic ratio of 4.5 g of fat to 1 g of protein and carbohydrates.

Two weeks later, the patient developed feed intolerance with abdominal distention and nonbilious emesis. Abdominal radiograph demonstrated right-sided, nonspecific bubbly lucencies concerning for pneumatosis intestinalis. Enteral feeds were held, and ketosis was maintained through parenteral KD. A sepsis workup was initiated. At this time, he was noted to have abnormal stools, described as a combination of diarrhea and "rock hard pebbles."

Despite bowel rest and negative sepsis evaluation, the patient continued to have abdominal distention and passed blood-streaked mucus per rectum (Fig. 1). Abdominal radiographs showed persistence of bubbly lucencies in the right abdomen. An ultrasound showed a small amount of ascites but no bowel abnormality. With continued abdominal distention, the patient developed abdominal compartment syndrome and acute kidney injury, prompting an exploratory laparotomy. Operative findings were notable for copious clear ascites and normal bowel anatomy. No anatomic abnormalities leading to mechanical obstruction, signs of necrotizing enterocolitis, or external colonic obstruction were observed. The colon was severely impacted by an immobile and fixed bezoar at the hepatic flexure. This local impaction devascularized and circumferentially eroded the wall of the colon, thus a right hemicolectomy was necessary. The injury was too significant for a simple enterotomy with disimpaction. Due to his clinical instability, an end ileostomy was created, and the distal left colon was left diverted in situ.

Gross pathologic evaluation of the removed colon demonstrated a large stool bezoar and histologic evaluation demonstrated

FIGURE 1. Diaper with passage of blood-streaked mucus in absence of stool, indicative of proximal colonic impaction.

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The authors report no conflicts of interest.

Written consent from the patient's guardian to submit this case was obtained by Laura Hollinger, MD.

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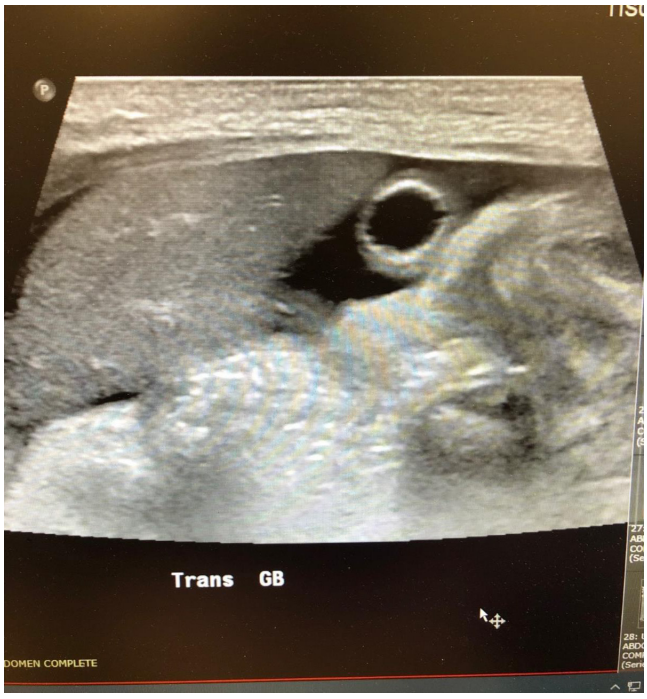

FIGURE 2. Bezoar visualized on ultrasound.

normal ganglion cells. Intraoperative frozen sections were not sent to evaluate for Hirschsprung disease due to patient's critical status. Permanent sections of the resected specimen confirmed the presence of ganglion cells. Unfortunately, the bezoar was not analyzed for chemical composition. In retrospect, the abdominal ultrasound appeared to have a large mass within the right hemicolon, adjacent to the liver (Fig. 2). A postoperative contrasted enema of the diverted left hemicolon revealed no obstructive pathology.

The patient improved slowly after surgery and tolerated slow advancement to goal feeds of maternal breast milk. Ketogenic feeds were not resumed given the concern that the high fat content of the ketogenic formula contributed to the bezoar formation and fecal impaction. Genetic testing confirmed a BRAT1 gene mutation. The patient's seizures were controlled on a regimen of seven antiepileptic medications. He underwent ileostomy takedown two months later and was successfully discharged home on an enteral feed regimen of term formula and maternal breast milk.

DISCUSSION

International guidelines include the usage of KD in infants and children with drug-resistant epilepsy or underlying metabolic disease. A recent systematic review concluded that its usage is safe for infants <23 months of age; however, KD is rarely used in the first weeks of life as pharmacologic treatment is considered first line for refractory seizures in the newborn period (3, 4). Although previous reports demonstrate mild feed intolerance related to KD in infants (Table 1) (2–6), this case exemplifies a previously undocumented adverse event of bezoar formation with bowel obstruction. Specific aspects of our patient's case may have contributed to the bezoar formation. Due to strong clinical suspicion for an underlying genetic epilepsy syndrome, and patient's similarly affected sibling's positive response to KD, our patient initiated KD at 6 weeks of age, younger than most documented reports of KD initiation (3, 4). Additionally, the patient required a high ketogenic ratio (4.5:1) to achieve ketosis, which is above the ratio of 3:1 primarily reported for use in infants (2, 3).

While necrotizing enterocolitis has not been described in the literature as an adverse effect of KD use in neonates or infants, animal studies show enteral lipids to be inflammatory to the intestinal mucosa. Triglycerides contribute to oxidative stress and inflammation that can lead to the development of necrotizing enterocolitis (7). Premature infants and newborns have inadequate fat absorption due to low carboxylic ester lipase, and therefore decreased fat emulsification leads to gut inflammation. Due to immature lipid metabolism in neonates, it is postulated it may be difficult to achieve ketosis (8).

As a potential sequelae of our patient's young age, concern for decreased fat absorption, and high KD ratio, we suspect the KD to be the cause of bezoar formation leading to intestinal obstruction, bacterial translocation, and culture negative sepsis. After gross and histopathological analysis, no alternative mechanical or anatomical cause was identified. We considered other differential diagnoses, such as Hirschsprung disease, small left colon syndrome, anorectal malformation, and meconium ileus. Ultimately, these diagnoses were ruled out with surgical, pathologic, and radiographic evaluations. Therefore, we hypothesize that the KD was the most likely cause of the stool bezoar.

Although the specimen was not sent for chemical composition, the clinical significance of a severe fecal impaction associated with this KD remains important and contributes to the literature as a safety warning for providers prescribing this diet. While the KD may improve seizure control in infants with refractory epilepsy, it is a diet that should be initiated with caution in very young patients, weighing benefits and risks on an individual patient basis.

TABLE 1. Common side effects associated with the ketogenic diet

Author	N-sample size	Common side effects noted (frequency)	Less common side effects noted (frequency)	Age patient population
Dressler 2020	Literature review of 20 studies	Constipation, high ketosis, elevated triglycerides	Hypoglycemia, emesis, nephrolithiasis, growth deficits	<12 months
Falsaperla 2020	4	Constipation (50%)	Weight loss (25%)	6 to 10 weeks age
Kim 2019	109	Constipation (32%), decreased bicarbonate (33%), emesis (20%)	Low free carnitine level (8%), feeding difficulty (5.5%), nephrolithiasis (2.8%), hypoglycemia (6.4)	3 weeks to 3 years age (mean age 1.4±0.8 years)
Ismayilova 2018	29	No statistically significant adverse effects reported		2.5 weeks to 23 months
Wirrell 2018	27		Hypoglycemia (7%), emesis (7%), dehydration and ketoacidosis (3.7%)	5 to 11 months (median 7 months)

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