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Novel Mutation in the *SLC5A1* Gene Causing Glucose-Galactose Malabsorption

First Confirmed Case From Central America

*†Daphna T. Katz, MD, †Suzzette Curia, RD, *Amanda C. Fifi, MD, *Liz Febo-Rodriguez, MD, and *Alejandro Llanos-Chea, MD

Abstract: Congenital glucose-galactose malabsorption is a rare cause of life-threatening diet-induced diarrhea in infants. Mutations in the *SLC5A1* gene, which encodes for the sodium-dependent glucose transporter, result in large-volume diarrhea due to aberrant glucose and galactose transport across the intestinal brush border. The diagnosis can be made clinically based on the presence of diarrhea soon after birth, evidence of carbohydrate malabsorption in the stool, and resolution of diarrhea with dietary elimination of glucose and galactose. Genetic testing can confirm the diagnosis. Here we report the first confirmed case of glucose-galactose malabsorption in an infant from Central America due to a novel mutation in the *SLC5A1* gene. The patient began growing and thriving after being diagnosed and with the correct dietary interventions.

Key Words: carbohydrate malabsorption, congenital diarrhea, pediatric nutrition

INTRODUCTION

Congenital glucose-galactose malabsorption (GGM) (OMIM #606824) is a rare cause of life-threatening diet-induced diarrhea in infants (1). Mutations in the *SLC5A1* gene, which encodes for the sodium-dependent glucose transporter, result in aberrant glucose and galactose transport across the intestinal brush border (2). Consequently, unabsorbed glucose, galactose, and sodium remain trapped in the intestinal lumen driving an influx of water and resulting in large-volume diarrhea. Patients classically present with dehydration, weight loss, and electrolyte disturbances. Abdominal distention also occurs due to overgrowth of intestinal bacteria that ferment carbohydrates (3). In some patients, chronic dehydration and persistent electrolyte derangements result in renal calculi (2,4–6).

The true incidence is unknown due to the rarity of the condition, though there are believed to be between 200 and 300 cases worldwide (5). The diagnosis can be made clinically based on the presence of diarrhea soon after birth, evidence of carbohydrate malabsorption in the stool, and resolution of diarrhea with dietary elimination of glucose and galactose. Molecular confirmation of mutations in the *SLC5A1* gene can be obtained (7). The hydrogen breath test can also be used, though is less practical in infants (4).

GGM is primarily managed with dietary restriction of glucose and galactose (3,7). Children have normal growth and development once the diagnosis is made and with correct dietary interventions (8).

Here we report the first confirmed case of GGM in an infant from Central America due to a novel mutation in the *SLC5A1* gene. We review our patient's clinical and diagnostic course and discuss dietary management of the condition.

CASE PRESENTATION

A 10-month-old male from Honduras presented with severe malnutrition and chronic diarrhea. He was born full-term to a healthy 18-year-old mother, with a weight of 3.2 kg (38%, *z* score −0.3 on World Health Organization [WHO] boys 0–2 years). At birth, he was started on infant cow's milk-based formula and shortly after developed watery diarrhea, occurring up to 10 times daily. He had no feeding difficulty, yet required multiple hospitalizations for severe dehydration and electrolyte abnormalities. Family history was noncontributory. Due to persistent symptoms and worsening nutritional status, his mother brought him to the United States for further evaluation.

Upon presentation to our hospital, he weighed 5.2 kg (0%, *z* score −5.14 on WHO boys 0–2 years) and had a length of 58 cm (0%, *z* score −6.8 on WHO boys 0–2 years) (Fig. 1). On physical examination he had upper and lower extremity wasting, abdominal distention and global developmental delay. An abdominal ultrasound showed nephrocalcinosis.

An amino acid-based formula was introduced due to concern for cow's milk protein allergy, and concentrated to provide additional calories. This resulted in severe hypernatremic dehydration with sodium levels up to 166 mEq/L, acute kidney injury, and metabolic acidosis. Feeds were discontinued and a central venous catheter was inserted to start total parenteral nutrition. While feeds were held, he had significant improvement in his diarrhea. Upon restarting feeds, the diarrhea worsened.

Initial stool studies sent on admission were positive for multiple infections, which were presumed to be due to a chronic carrier state as per our infectious disease specialists. Additional stool studies resulted after 3 weeks of admission and showed low pH (4.2), normal alpha-1-antitrypsin, normal fecal elastase, and calprotectin. Stool-reducing substances and stool electrolytes were ordered but canceled by the laboratory.

An upper endoscopy and sigmoidoscopy were performed, given the severity of the patient's malnutrition and chronic nature of his symptoms, which were grossly and histologically normal. Electron microscopy and disaccharidase levels (including lactase, sucrase, isomaltase, and palatinase) were also normal.

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From the *Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of Miami Miller School of Medicine, Miami, FL; and †Department of Pediatrics, Holtz Children's Hospital/Jackson Health System, Miami.

Correspondence: Daphna T. Katz, MD, Pediatric Gastroenterology, Hepatology, and Nutrition, Department of Pediatrics, University of Miami Miller School of Medicine, 1601 NW 12th Avenue, MCCD Room 3005A, Miami, FL 33136. E-mail: DXK499@miami.edu.

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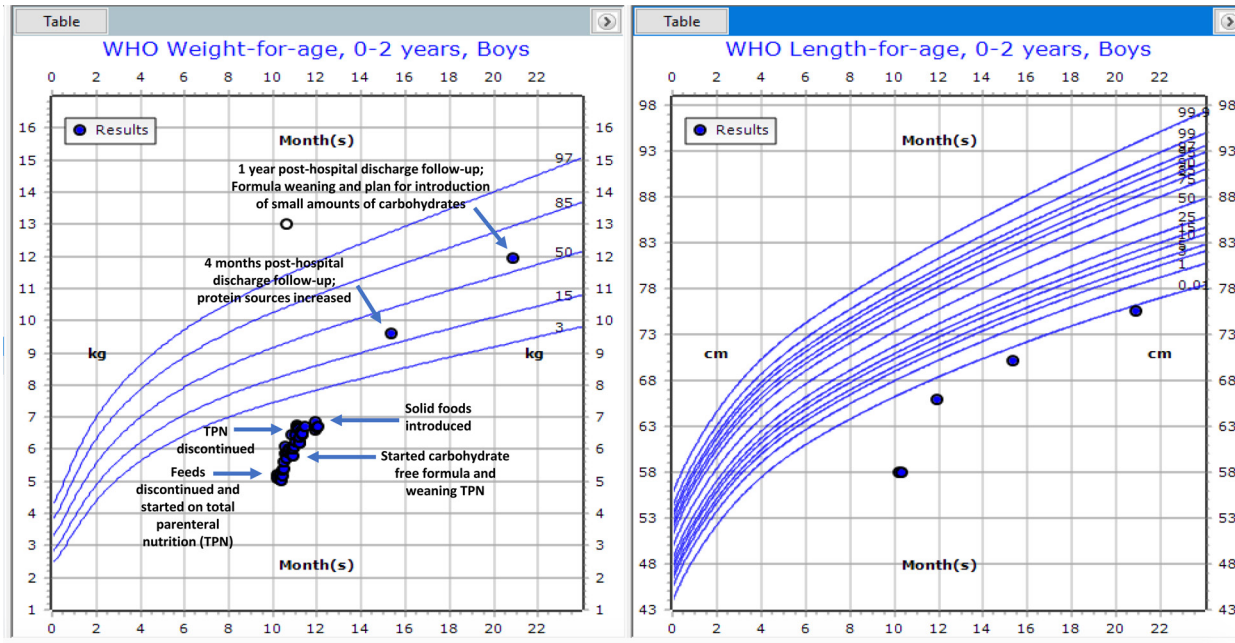

FIGURE 1. World Health Organization (WHO) growth charts displaying key nutritional interventions related to weight gain.

Given our high suspicion of carbohydrate malabsorption, he was started on carbohydrate-free formula, after which his diarrhea rapidly resolved. Fructose was added in increasing increments to meet his caloric requirements, and total parenteral nutrition was successfully weaned off. He was discharged after 6 weeks of hospitalization with a weight of 6.7 kg (0.08%, *z* score −3.18 on WHO boys 0–2 years). His discharge diet consisted of carbohydrate-free formula mixed with fructose powder to make 20 cal/oz formula, 8 oz per feed, 5 feeds per day (120 kcal/kg/day), and low carbohydrate-containing solid foods ad libitum. One week before discharge, results of genetic testing that had been sent on admission as part of the patient's initial workup, confirmed the diagnosis of GGM, revealing a homozygous c.1765G>T (p.Glu589*) variant on exon 14 of the *SLC5A1* gene.

Four months after hospital discharge, he presented for follow-up with a weight of 9.6 kg (24%, *z* score −0.7 on WHO boys 0–2 years) and developmentally thriving. His mother was encouraged to increase his protein intake to promote catch-up height. At 18 months of age, his weight-for-length was above 97%. Therefore, a plan was formulated to wean him off of the formula. Instructions were also given on how increasing amounts of carbohydrates could be slowly introduced.

DISCUSSION

We report the first confirmed case of GGM from Central America in an infant who experienced severe malnutrition before diagnosis, in part due to a lack of access to specialized care in his country of origin. Previously 1 case was reported from Colombia, though no genetic testing was performed, and 1 case was confirmed from Brazil with genetic testing (9,10).

Over 40 variants of the *SLC5A1* gene have been reported in the literature, with a large number from Amish and Arab populations where there were consanguineous unions (4,5,7,8). The novel sequence change found in our patient: SLC5A1, Exon 14, c.1765G>T (p.Glu589*), homozygous, creates a premature translational stop signal, which disrupts the last 76 amino acid(s) of the C-terminus of the SLC5A1 protein. This variant is not present in population databases, though other variants that disrupt this region have been observed in individuals with SLC5A1-related conditions (7,11).

Though genetic testing ultimately confirmed the diagnosis in this case, the key to arriving at the diagnosis was resolution of diarrhea with fasting, which pointed to diet-induced diarrhea (Fig. 2). Low stool pH, positive reducing substances, and high stool osmolar gap (290 − 2 × (Stool Na^+ + K^+) >100 mOsm) generally confirm carbohydrate malabsorption (12). In this case, stool studies were limited. However, the positive fasting test, low stool pH with normal alpha-1-antitrypsin and fecal elastase, lead to a high clinical suspicion for carbohydrate malabsorption. This patient underwent a broad workup initially due to the severity of his symptoms and lack of access to specialized testing before admission to our hospital. In retrospect, endoscopy/ colonoscopy and genetic testing were not needed to arrive at the diagnosis.

Initial treatment of GGM involves dietary elimination of glucose and galactose. Infants can be fed a fructose-based formula, as fructose undergoes facilitated transport via GLUT-5 transporters (2,3,6). Alternatively, a carbohydrate-free formula supplemented with fructose powder to meet the energy requirements of an infant can be used (2). Fructose may be added in increments of 3 cal/oz every 2–4 days as tolerated until the desired cal/oz is achieved (13).

As solid foods are introduced, calories should be provided mostly in the form of fats and proteins, and cardiovascular health should be monitored (2,4,7,13). These patients should receive adequate calcium and vitamin D supplementation due to a lack of dairy intake (10). Glucose-containing suspensions should be avoided (4). Improved tolerance to glucose and galactose may be observed in some patients over time, though the mechanism is unclear (5); slow introduction may be attempted, with intake adjusted based on stool weight (2,10).

CONCLUSIONS

GGM is a rare potentially fatal autosomal recessive disorder caused by mutations in the *SLC5A1* gene. We diagnosed the first patient from Central America based on resolution of diarrhea with

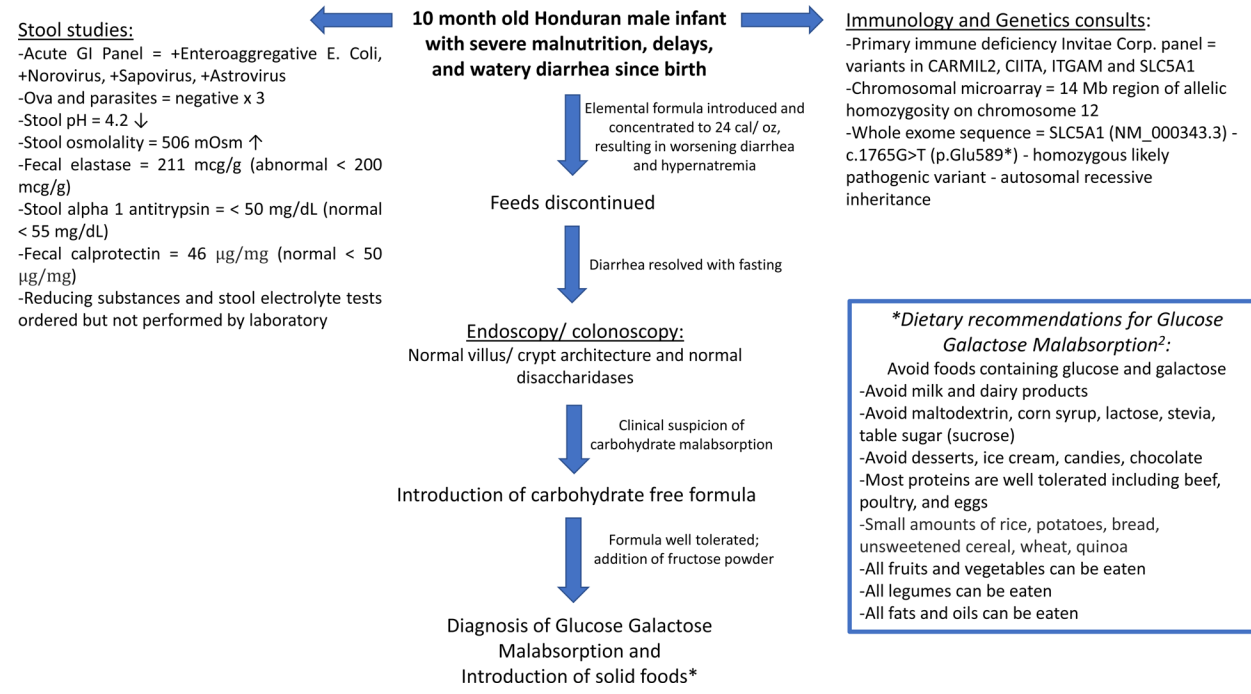

FIGURE 2. Diagnostic and intervention timeline, including dietary recommendations for glucose-galactose malabsorption.

dietary elimination of glucose and galactose before obtaining genetic confirmation of a novel mutation. Patients with GGM can be managed lifelong with dietary interventions.

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Written informed parental consent was obtained for this report.

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