Received: 14 October 2024 | Accepted: 1 February 2025

DOI: 10.1002/jpr3.70006

CASE REPORT

Gastroenterology

Carbohydrate malabsorption mimicking immune dysregulation: A histological challenge

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Funding information
None

Abstract

We report a case of neonatal-onset intractable diarrhea, where the patient's histologic findings suggested immune dysregulation. However, genetic testing revealed compound heterozygous variants in the *SLC5A1* gene. This case report adds to the existing literature by demonstrating that severe carbohydrate malabsorption can cause inflammatory histological features possibly secondary to small intestinal bacterial overgrowth.

KEYWORDS

chronic diarrhea, congenital diarrhea, glucose-galactose malabsorption, SIBO, *SLC5A1*

1 | INTRODUCTION

Glucose-galactose malabsorption (GGM; OMIM: 606824) is a rare autosomal recessive metabolic disorder caused by biallelic pathogenic variants in the *SLC5A1* gene. It impairs glucose and galactose transport across the intestinal epithelium, presenting with bloating and profuse watery diarrhea within days after birth.

2 | CASE REPORT

This patient was born full-term to nonconsanguineous parents after an uncomplicated pregnancy and delivery. He had a healthy older sibling, and family history was negative for intestinal or autoimmune disorders. His birth weight, length, head circumference, and physical exam were normal. Initially, he was exclusively breastfed. On day of life (DOL) 3, he developed yellow, watery diarrhea approximately every hour and one febrile episode (101.4°F). Despite feeding well, he lost 16% of his birth weight.

He was admitted to an outside hospital for evaluation and treated empirically with intravenous (IV) ceftriaxone and vancomycin for 48 h. Comprehensive infectious workup—cerebrospinal fluid, blood, respiratory, stool—was negative. He was trialed on various formulas for suspected milk protein allergy. A low-lactose formula (Similac Sensitive) did not improve the large stool volumes. An extensively hydrolyzed formula (Alimentum) slightly reduced stool volume but introduced mucus. An amino acid-based formula (Elecare) reduced stool volume but remained watery. Diarrhea improved with cessation of enteral feeds and resumed with reintroduction, necessitating total parenteral nutrition (TPN). Upon transfer to a tertiary center, breastfeeding was resumed ad lib, supplemented with a partially hydrolyzed formula (Gerber Extensive Hypoallergenic). After TPN was started,

small-volume breastmilk feeds were cautiously increased. However, persistent large-volume watery stools prompted a return to Elecare Infant formula without resolution.

Initial labs revealed hypernatremia (Na 164 mEq/L), normal anion gap metabolic acidosis (HCO_3 16 mmol/L), hypoalbuminemia (3.2 g/dL), and low total protein (4.6 g/dL). C-reactive protein was normal. Stool alpha-1-antitrypsin, fecal fat, and pancreatic elastase-1 were normal. A Hemoccult test was not performed, as no bloody stools had been reported. Stool osmotic gap was 247 mOsm/kg, suggesting diet-induced diarrhea. Simethicone provided some relief of gassiness; IV famotidine was given with TPN. No anti-diarrheals were used due to the uncertainty of infection.

At DOL 21, esophagogastroduodenoscopy and colonoscopy showed normal mucosal appearance. Disaccharidase assays revealed normal lactase and palatinase, but decreased sucrase (20.1 μM/min/g; ref 25–69.9) and maltase (73.5 μM/min/g; ref 100–224.4). Stool-reducing substances were positive at 2+ (0.75 g/dL). Antral biopsies showed focal chronic inflammation and focal increased eosinophils in lamina propria (Figure 1A); duodenal biopsies showed focal villous attenuation, acute duodenitis, and reactive epithelial changes (Figure 1B). Descending (Figure 1C) and sigmoid colon (Figure 1D) biopsies revealed focal architectural distortion, surface epithelial injury with intraepithelial lymphocytosis, and focal increased eosinophils in lamina propria. No features of microvillus inclusion disease or tufting enteropathy were identified. CD10 and periodic acid–Schiff–Alcian Blue staining highlighted thin, sharp linear brush borders; epithelial cell adhesion molecule and chromogranin staining were normal.

With biopsies suggesting possible immune dysregulation, immune studies and rapid trio whole-genome sequencing (WGS) with mitochondrial DNA analysis were pursued. Immune studies revealed normal T, B, and natural killer (NK) cell counts, as well as normal C-X-C motif chemokine ligand 9 (CXCL9) levels and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, but elevated soluble interleukin-2 (IL2) receptor (1820 pg/mL; ref ≤858.2), IL10 (8.1 pg/mL; ref ≤2.8), and IL6 (3.3 pg/mL; ref ≤2.0). Four days after sending samples, WGS identified compound heterozygous variants of uncertain significance (VUSs) in *SLC5A1*, inherited from each parent: NM_000343.4:c.404G>A (p.Arg135Gln) and c.312+5G>A p.?.

Although the variants were classified as VUSs, the patient's phenotype was consistent with GGM. Transitioning to a carbohydrate-free, fructose-based formula led to immediate and sustained improvement. The infant had no bowel movements for 4 days, then resumed normal stooling. This clinical response confirmed GGM and suggests these variants in the *SLC5A1* gene (or another undetected variant) are the underlying cause.

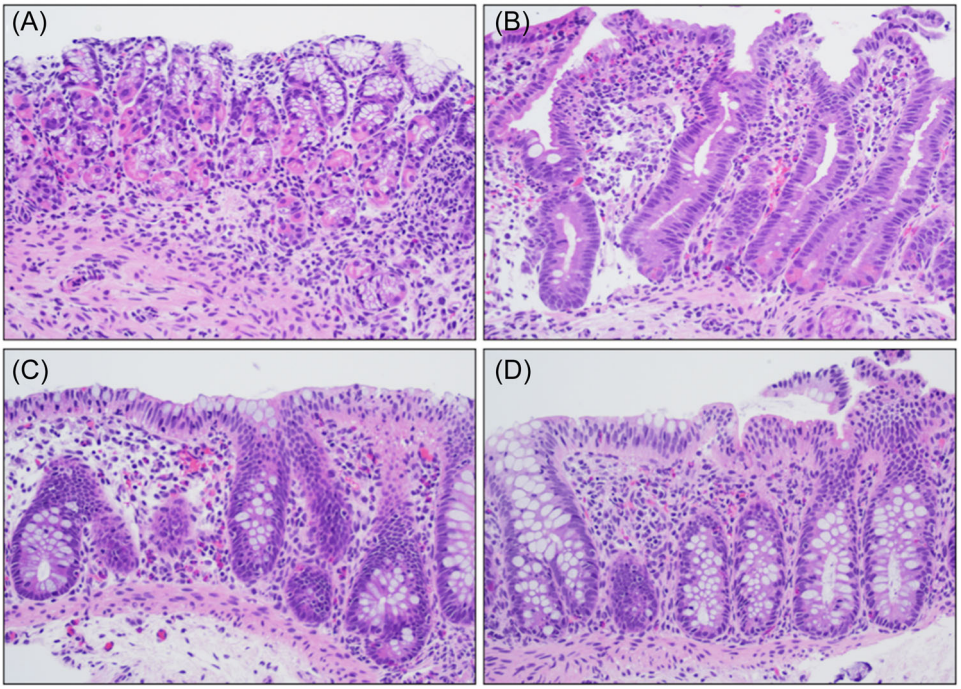

FIGURE 1 Histologic findings of congenital glucose-galactose malabsorption. (A) Stomach. Transitional mucosa with focal chronic inflammation and focal increased eosinophils in lamina propria. (B) Duodenum. Duodenal mucosa with focal villous attenuation, acute duodenitis, and reactive epithelial changes. (C). Descending colon. Colonic mucosa with focal architectural distortion, surface epithelial injury with intraepithelial lymphocytosis, and focal increased eosinophils in lamina propria. (D) Sigmoid colon. Colonic mucosa with focal architectural distortion, surface epithelial injury with intraepithelial lymphocytosis, and focal increased eosinophils in lamina propria.

By discharge, most labs normalized except for mild anemia (likely physiologic nadir) and slightly low albumin and total protein. He was discharged on the same oral regimen, and by 10 weeks of age, his weight had improved to the 30th percentile.

3 | DISCUSSION

This infant's neonatal-onset chronic diet-induced diarrhea and pathology findings showing an inflammatory infiltrate with architectural distortion initially misled the diagnostic process. Such changes may reflect nonspecific ontogenic responses but can also occur in disorders of inflammation and immune dysregulation,[1] which was the initial diagnosis. The findings in the duodenum—focal villous attenuation, acute duodenitis, and reactive epithelial changes—can also be seen in small intestinal bacterial overgrowth (SIBO), which we speculate may have been occurring due to excessive luminal carbohydrate in the context of GGM. Histological features of SIBO can range from normal to those resembling inflammatory bowel disease.[2] Thus, GGM cannot be confirmed or excluded by histopathology alone.

Patients with GGM often present with severe dehydration due to diarrhea and may develop fever, mimicking infection, or inflammatory disorders.[3] Diagnosis typically emerges after multiple unsuccessful feeding trials and is supported when stabilization occurs on a fructose-based formula.[3] When diarrhea resolves upon fasting, GGM should be considered. Ultimately, fasting trials and genetic testing are key diagnostic methods.[4]

This case underscores the importance of genetic testing in the diagnostic process. Identifying the genetic cause guided a switch to a fructose-based, carbohydrate-free formula, promptly resolving diarrhea and improving growth. In severe neonatal-onset intractable diarrhea, rapid comprehensive sequencing (e.g., whole-exome sequencing or WGS) can establish or eliminate a host of diagnoses and obviate the need for invasive testing.[5]

In resource-limited regions, diagnosing GGM is particularly challenging, necessitating heightened vigilance when repeated attempts to transition from parenteral to enteral feeding fail. Upon suspicion of GGM, immediately eliminating glucose and galactose may yield dramatic improvement, serving as a preliminary diagnostic tool.[4] Educating healthcare providers in these settings, improving diagnostic capabilities, and ensuring access to specialized formulas are essential measures that can significantly improve survival and outcomes.

Overall, this case illustrates the critical role of genetic testing, where pathology alone may be misleading. It also highlights the value of a multidisciplinary team approach—including gastroenterologists, geneticists, and pathologists—to achieve an accurate diagnosis and initiate timely management for optimal patient outcomes.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ETHICS STATEMENT

Written informed consent was obtained from the parent.

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How to cite this article: Eroglu S, Nandolia S, Zhang Y, Voltaggio L, Guerrerio AL. Carbohydrate malabsorption mimicking immune dysregulation: A histological challenge. *JPGN Rep*. 2025;6:174-176. doi:10.1002/jpr3.70006