

# A Rare Cause of Intractable Diarrhea of Infancy

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## ABSTRACT

Intractable watery diarrhea presenting in the neonatal period is a relatively uncommon condition. Congenital disorders of malabsorption are among the major causes of prolonged watery diarrhea. This is the case report of a 3-month male infant born to consanguineous parents, who presented with intractable diarrhea since birth. He was failing to thrive and wasted. Persistent diarrhea lead to prolonged hospitalisation and recurrent hypernatremic dehydration. Relevant investigations clinched the diagnosis of "congenital glucose galactose malabsorption (CGGM)". The astute clinician should have a high index of suspicion regarding such rare causes of diarrhea in early infancy, as an appropriate rational diagnosis can lead to life-saving treatment as depicted in this case report.

**Key Words:** *Glucose-galactose-malabsorption, Chronic diarrhea, Hypernatremic dehydration.*

## INTRODUCTION

Diarrheal diseases are still among the leading causes of mortality and morbidity in children in developing countries with the prevalence of childhood diarrhoea being 51% in Pakistan.<sup>1</sup> A number of rare causes can lead to early onset persistent diarrhoea in infants. A number of such congenital malabsorptive disorders include glucose-galactose malabsorption, abetalipoproteinemia, congenital chloride diarrhea, primary intestinal lymphangiectasia, milk protein allergy, pancreatic insufficiency, cystic fibrosis, immunodeficiency, tufting enteropathy, and microvillous inclusion disease. These disorders pose significant diagnostic and therapeutic challenges. Among these disorders, CGGM is a rare disorder inherited as an autosomal recessive condition. The basic defect is in the sodium/glucose cotransporter, located in the intestinal epithelium and the renal tubules. There are six isoforms of sodium/glucose cotransporter, but the carrier genes SLC5A1 and SLC5A2 are the most important ones.<sup>2</sup>

## CASE REPORT

A 3-month male infant was admitted in the Hospital, with the problem of persistent diarrhea since birth. Diarrhea was profuse, watery and without any obvious blood or mucus in the stools. He was born through a spontaneous vertex delivery at full term, with immediate cry and had a birth weight of 3.4 kg. He was the third in order of birth, the parents being consanguineous. His two other siblings were healthy. There was no history of any early neonatal death in the family. This baby was exclusively breastfed. Initial clinical examination revealed

a baby weighing 2.8 kg with severe dehydration. He was obviously marasmic with normal temperature and no dysmorphic features. There was massive abdominal distention with mild perianal rash. He had partial neck control with an obvious social smile and good eye contact. Results of investigations done revealed the following: Hemoglobin 11.9 g/dl, total leukocyte count (TLC) 10000/cmm, platelets  $120 \times 10^9/L$  with neutrophils 65% and lymphocytes 30%; serum sodium 156 mmol/l, serum potassium 4 mmol/l, urea 14.9 umol/l, creatinine 68 umol/l, plasma ammonia 72 umol/l, plasma lactate 2.1 mmol/l and arterial blood gases were within reference range. Stool showed acidic reaction with no evidence of any ova or cyst on microscopy. Stool culture was reported negative and urinalysis revealed a specific gravity of 1.014, pH 5.0, protein and sugar nil reducing substance was nil, spot urine sodium 87 mmol/L and urine chloride was 90 mmol/l. Immunoglobulin levels, hepatitis B and C screening, HIV serology, 17OH progesterone levels, lymphocyte subset studies, CD4:CD8 ratio and sweat chloride test were all within reference range. The workup for autoimmune enteropathy was negative. After reviewing these results, the diagnosis of congenital chloridorrhea was also considered in the differential diagnosis. Barium meal follow-through, done at 3 months of age, was unremarkable with prominent ileal loops. Barium enema and rectal suction biopsy excluded the diagnosis of Hirschsprung enterocolitis. However, on intestinal biopsy, the histopathological report had raised the possibility of tufting enteropathy as one of the important differential diagnoses; and consequently, the expensive option of intestinal transplantation in such a situation was also one of the formidable challenges to be considered. During the course of illness, various types of infant formulae, including lactose-free formula and amino acid based elemental formula were used but the diarrhea persisted. The chronological age of the patient was exceeding the expected survival age for tufting enteropathy, making it a less likely possibility. Moreover, the improvement in the consistency of stools when the

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infant was kept nil by mouth, strongly suggested the possibility of an osmotic cause of diarrhoea. However, an important clinical observation was the worsening of diarrhoea on administration of oral rehydration salt. This important clinical clue led us to consider the diagnosis of CGGM as the most likely underlying cause of this patient's intractable diarrhoea. Consequently, the infant was started on a carbohydrate-free formula, which resulted in a dramatic clinical response with the stool consistency becoming normal for the first time. This was followed by a rapid weight gain and no further episodes of dehydration. Weight gain was noted from 2.8 kg to 5 kg within 2 months of starting carbohydrate-free formula. Currently, the child is thriving well on this formula and is 15 months old weighing 10 Kgs. Finally, the genotype analysis was done and the results revealed frameshift mutation for c496-497insG in exon 6 of SLC5A1 gene, which confirmed the diagnosis of CGGM.

### DISCUSSION

The diagnosis of intractable diarrhea of infancy with onset in the neonatal period is definitely an important challenge for the clinician.<sup>3</sup> However, the number of causes are few and relatively uncommon. Important causes include congenital microvillus atrophy, tufting enteropathy, CGGM, congenital lactase deficiency, congenital malabsorption of chloride and sodium, bile acid malabsorption, and congenital enterokinase deficiency.<sup>4</sup> Only a few hundred cases of CGGM have been identified worldwide.<sup>5</sup> It is an autosomal recessive condition, first reported in Sweden and France in 1926. In CGGM, the basic defect is in the SGLT1 intestinal transporter which results from mutation in the SLC5A1 gene (182380). This gene is located on chromosome 22q13.1.67. Lactose is the milk sugar present in both breast and formula milk. It is broken down to glucose and galactose on the intestinal brush border. The sodium/glucose cotransporter (SGLT1), then transports glucose and galactose across the brush border into the enterocyte. SGLT1 is responsible for absorption of these monosaccharides by tight coupling of two sodium ions and one sugar molecule leading to their movement across the membrane.<sup>6</sup>

In CGGM, osmotic diarrhea results from malabsorption of glucose and galactose. These sugars are fermented in the colon by the bacterial flora leading to the production of short chain fatty acids. Consequently, the stools become acidic. Infants suffering from this disorder present with profuse diarrhea, hypernatremic dehydration and metabolic acidosis in the early neonatal period.<sup>2</sup> Since, the diarrhea is osmotic in nature, it tends to ameliorate once the enteral feeding is withheld. The stool pH is generally <5.3 and the reducing substance is

positive in the stool. The stool osmotic gap is of the order of >40 mosm. In this patient, parental consanguinity, the osmotic nature of diarrhea and the worsening of the diarrhoea with the administration of ORS, strongly suggested the diagnosis of CGGM on clinical grounds, which was finally confirmed by gene mutation analysis. Prognosis of CGGM in the short- and medium-term with administration of the special milk formula is generally good. As these children grow up, most of them can tolerate small amounts of glucose to some extent with no deleterious consequences. However, the main issue with this group of children is the compliance with the special formula milk and the exorbitant cost of the treatment. In the long-term, the problems related to the relatively higher intake of proteins and fats in the diet can have significant health consequences. As patients grow older, most can tolerate some amount of glucose with no diarrhea.<sup>7</sup>

It is important to have a high index of suspicion for rare congenital malabsorptive disorders while managing infants with intractable diarrhea of infancy. This, to the authors' knowledge, is the first reported case of CGGM from Pakistan. Previously, there has been a case report from Iran in this region.<sup>8</sup>

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