

## GLUCOSE-GALACTOSE MALABSORPTION SYNDROME PRESENTING AS CONGENITAL DIARRHEA

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### ABSTRACT

We describe the clinical history, diagnostic evaluation, and management of an infant who had congenital Glucose Galactose Malabsorption (GGM), a rare disorder thought to be inherited as an autosomal recessive trait. This infant experienced persistent diarrhea and hypernatemic dehydration during the first months of life and then renal stone on three months follow-up. Diagnosis is based on oral glucose tolerance test, stool reducing substances and rule out other diseases with use of laboratory investigations, small-bowel biopsy, and histology. Parental education about dietary management with fructose based formula and solid food feedings was important component of this patient's treatment.

**KEYWORDS:** Glucose galactose, Malabsorption, Chronic diarrhea, Child.

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### INTRODUCTION

Transport of water-soluble molecules across tissue barriers has attracted increasing interest since 1952, suggesting that the transport across the erythrocyte membrane required a carrier mechanism to facilitate diffusion.<sup>1</sup> Now it is established that transport and uptake of glucose can be rate-limiting in cells subject to large metabolic demands, as manifested by several disease states involving transport loss of function.<sup>2-3</sup>

Three types of concentrative Na<sup>+</sup>/glucose transporters have been identified: SGLT1 (locus 22q13.1) is responsible for glucose absorption from the intestinal tract. SGLT2 (locus 16p11.2), together with SGLT1, is responsible for glucose absorption in the renal tubules. SGLT3 (locus 22q12.2-q12.3) is localized to the plasma membrane of enteric neurons and skeletal muscle, and is incapable of functioning as a homo-oligomer.<sup>4</sup> Congenital glucose-galactose malabsorption (GGM), which is caused by defects of SGLT1, is an autosomal recessive disease characterized by the selective malabsorption of glucose and galactose.<sup>5,6</sup> Patients with GGM present with neonatal onset of severe, watery and acidic diarrhea while taking glucose-containing or galactose-containing diets. The condition is life-threatening if not diagnosed and treated. Only approximately 200 individuals worldwide are currently known to be affected by GGM.<sup>6,7</sup>

All studied patients carry mutations in their SGLT1 genes, while parents are Non manifesting carriers, speaking to the autosomal recessive pattern of inheritance of this disease. Many patients are the product of consanguineous parents, emphasizing this concept. Diarrhea in GGM is osmotic, being caused by accumu-

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lation of unabsorbed glucose and galactose in the intestine.<sup>2</sup> which stems from a defect in the active, transport mechanism of the two monosaccharide.<sup>8,9</sup> This condition leads to failure to thrive and severe malnutrition.

In this report, we describe a patient from Iran, who's clinical and laboratory findings confirmed diagnosis of GGM.

### CASE REPORT

A 2-months-old Iranian boy born to first-degree consanguineous parents was referred with a history of watery, acidic diarrhea noted on the third day of his life. His antenatal and natal histories were normal condition. He had been re-hydrated with intravenous fluids and had been taken off breast feeding at a local hospital when he was seven days old. The diarrhea resolved after withdrawal of breast feeding but re-started when breast feeding was resumed. He had three admissions in local hospital for dehydration and acidosis. When he was two months old, he was admitted in our hospital with apathy and severe dehydration. Laboratory findings were: Hb 8.1g/dL, WBC 8000/mm<sup>3</sup>, platelets 408,000/mm<sup>3</sup>, serum Na 190 mEq/L, serum K 3.2mEq/L, blood urea nitrogen 86mg/dL, serum creatinin 1.5mg/dL, arterial pH 7.1, serum HCO<sub>3</sub> 7.5mmol/L, urine specific gravity 1025 with glucosuria (++) . The stool pH was 5 and the stool was positive for reducing substances. At chromatography, the reducing substances were confirmed as glucose and galactose.

The blood glucose and galactose levels were measured by glucose oxidase reagent. Other data collected and tests included urine osmolality, analysis and urine electrolytes, renal ultrasound, and clinical response to special formula. Small-bowel biopsies were obtained from the duodenojejunal junction. Two biopsies were obtained and sent for histology. The child had hypernatremia, with a mean serum sodium level of 165mEq/L in the second time after hydration (range 160-190). All the investigations like serum calcium, phosphate, alkaline phosphatase, potassium, magnesium, chloride, blood urea nitrogen, immunoglobulin, albumin, sweat chloride, urine electrolytes, com-

plete blood count, prothrombin time, and partial thromboplastin time were normal. Stools were positive for reducing substances, which were confirmed by sugar chromatography to be glucose and galactose; but negative for rotavirus and cryptosporidiosis. Stool culture showed no pathogens, and stool electrolytes were normal. Small-bowel aspiration for giardia was negative, and the culture showed no growth. Histology of the small-bowel biopsies was normal. Urine analysis showed glucosuria in our patient. The hypernatremic dehydration was treated with intravenous fluids and, after discontinuing enteral feeding, his diarrhea stopped. Diarrhea reoccurred after introducing lactose, dextrinmaltose or glucose-containing formulas. There was no diarrhea after starting a fructose-supplemented, carbohydrate-free formula. Child responded clinically to fructose-based formula, and he is thriving at follow-up. He grew normally and was discharged from the hospital at 3.5 months of age. Three months later, there was renal stones in his renal ultrasound. Based on clinical course and laboratory findings his diagnosis was GGM.

### DISCUSSION

To the best of our knowledge, this is the first reported case of GGM from Iran. More than 40 mutations of SGLT1 responsible for GGM have been identified so far and fewer than 300 patients have been identified worldwide. This is inherited as an autosomal recessive trait.<sup>10,11</sup> The family histories were positive for consanguinity and infantile death from chronic diarrhea in 50% of this case. The disease commonly affects girls, a finding that we didn't observe in our study.<sup>3</sup> The cause of female predominance in this disorder is unknown, but it might be related to genetic susceptibility. The high rate of consanguinity in our population and the occurrence of symptoms stemming from compound heterozygous mutations in autosomal recessive diseases suggest that the prevalence of genetically related disease may be higher in this area.

The initial symptom of GGM is watery diarrhea after initiation of milk feeding within a few days after birth, but other gastrointestinal

symptoms are rare. The major clinical effect of chronic diarrhea on our child was failure to thrive, a finding that is in agreement with the literature.<sup>12</sup>

GGM might be associated with renal glycosuria due to renal tubular reabsorption defect, this condition was noted in our patient.<sup>13</sup> Another association with GGM is renal stones, which was reported by Meeuwisse in 1969.<sup>14</sup> The cause of renal stones in GGM is unknown.<sup>14,15</sup> An interesting finding in GGM is hypernatremia from recurrent dehydration, which was noted in our patients.<sup>14,16</sup> However, GGM may stem from acute gastroenteritis caused by rotavirus, which was not noted in our patient.<sup>3</sup> Infants with GGM have impaired glucose and galactose absorption and normal fructose absorption.<sup>17</sup> Treatment with lactose free milk, partial hydrolysate, and amino-acid formulas was not effective and continued watery diarrhea. However, it is important to exclude congenital disaccharidase deficiency (especially lactase), which appears as watery diarrhea from birth and low lactase levels.<sup>18,19</sup> Diagnosis of GGM may also be made by measuring sugar and amino acid evoked potential differences in the jejunum in vivo, this last investigation was not made in our patient.<sup>20</sup> Children with GGM usually respond dramatically to fructose-based formula with improvement in their diarrhea and growth, as seen in our patient.<sup>2</sup>

In summary, GGM is an important cause of chronic diarrhea in infants, particularly if it starts within a few days of milk feeding. Hence, treating physicians need to be vigilant in looking for this treatable cause of chronic diarrhea and to study the genetic basis of the disease in the Iranian children.

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