CASE REPORT

Congenital glucose-galactose malabsorption due to SLC5A1 mutation: A case of hypernatraemic dehydration

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Abstract

Congenital glucose-galactose malabsorption (GGM) is an exceedingly uncommon autosomal recessive metabolic state defined by persistent diarrhoea along with serious dehydration. It is a disease that is difficult to consider in differential diagnosis and may be fatal if left untreated. This report details the clinical and diagnostic progress of a two-month-old Turkish infant exhibiting episodes of severe recurrent watery diarrhoea. Molecular testing revealed that the patient has a compound heterozygous variant in SLC5A1. The patient has been asymptomatic with fructose-based formula. Paediatricians should take into account unexpected congenital causes while looking for common causes in infants who present with chronic diarrhoea, particularly when accompanied by hypernatraemic dehydration. Early diagnosis and swift treatment is important in order to avoid major complications from undetected GGM. Genetic testing is highly encouraged as it helps in early identification of these patients, preventing major complications, and improving clinical outcomes.

Keywords: Diarrhoea, SLC5A1, Glucose-galactose malabsorption.

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Introduction

An abnormality in the transport of glucose and galactose throughout the intestinal brush barrier leads to an extremely rare autosomal recessive disorder known as glucose-galactose malabsorption (GGM). Patients with GGM exhibit neonatal onset of severe, almost fatal watery diarrhoea and dehydration.[1] Patients exhibit normal hydrolysis of sucrose, lactose, and maltose. The absorption of glucose and galactose is specifically low, whereas fructose absorption happens at a normal rate. GGM can frequently be devastating unless glucose and galactose have been eliminated from the diet.

Although there is no treatment for GGM, it may be controlled by removing lactose, glucose, and sucrose from the diet. Epidemiological data for GGM is insufficient, making it difficult for doctors to regard GGM as a primary diagnosis.

Case Report

A two-month-old male patient, born at term via caesarean section, weighing 3,625 grams, and the first and only living child of the family, was admitted to the paediatric emergency department of Bursa City Hospital, Türkiye, with restlessness, abdominal distension, fever, and decreased sucking. The case was seen in September 2024. There was a consanguineous relationship between the parents. There is no significant relevant family history. The patient had multiple emergency applications with complaints of abdominal distension, restlessness, and had been previously evaluated as having infantile colic.

On physical examination, his general condition was poor, turgor and tonus was decreased, and the child appeared sleepy, weak and pale. He appeared severely dehydrated. His blood pressure was 87/50 mmHg, saturation of peripheral oxygen 96%, pulse 230 beats per minute, temperature 39.5°C, weight was 5,100 grams and -0.81 standard deviation score (SDS). Other system examinations were normal. A severe hypernatraemic dehydration was documented with lab tests. The blood gas, complete blood count, and biochemistry results are provided in Table.

The patient was admitted to the paediatric intensive care unit due to hypernatraemic dehydration. During follow-up, oral intake was stopped, and hydration was maintained based on sodium levels. The patient continued to have watery diarrhoea and intermittent acholic stool was observed (Figure). A watery stool discharge was observed during digital rectal examination.

Pancreatic faecal elastase was 5.24 ug/mL (normally:>200 ug/mL), ammonia 54 µg/dL (11-51 µg/dL), zinc 0.82 ug/mL (0.6-1.2 ug/mL), alpha-1-antitrypsin 174 mg/dL (110-280 mg/dL), faecal fat 2.2 g/24 hours (normally:<12.9 g/24 hours), reducing substances 2+. In stool sugar

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chromatography, glucose was trace positive, while galactose, lactose, sucrose, and fructose were negative. Stool indicated acidity with a pH of < 6.

The severe combined immunodeficiency gene panel showed normal results. Fractionated sodium and urinary osmolality were normal.

Metabolic tests (amino acids, organic acids profile, lactate, pyruvate, biotinidase deficiency, tandem MS) were interpreted as normal. Stool culture showed no growth. Microbiological tests for adenovirus and rotavirus were negative. Abdominal ultrasonography did not reveal any pathology.

Table: Blood gas, complete blood count and biochemical test results.

Test Name	Result	Unit	Reference Range
pH	7.13		7.35-7.45
pCO_2*	27	mmHg*	35-45
HCO_3*	9.1	mmol/L*	22-26
Lactat	3.8	mmol/L	0.5-1.6
Sodium	173	mmol/L	135-145
Chloride	144	mmol/L	98-106
White Cell Count	16.21	10^3/µL	6.51 - 13.32
Haemoglobin	12.5	g/dL	9.6 - 12.4
Platelet Count	447	0^3/µL	150 – 450
Urea	183	mg/dL	8.56 - 40.6
Creatinine	1.34	mg/dL	0.17 - 0.42
Sodium	171	mmol/L	136 – 145
Chloride	149	mmol/L	98 – 107
K	3.7	mmol/L	3.5 - 5.1
P	6.6	mg/dL	3.5 - 6.6
Ca	8	mg/dL	8.8 - 10.8
Total Protein	52.2	g/L	46 – 70
Albumin	36.3	g/L	38 – 54
AST	118	IU/L	0 – 40
ALT	138	U/L	0 – 41
Total billirubin	0.26	mg/dL	0.1 - 1.2
INR	INR 1.78	-	0.8 - 1.2

*pCO_2, Partial Pressure of Carbondioxide; HCO_3, Bicarbonate; mmHg, Millimeters of Mercury; mmol/L, Millimoles per Liter; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; INR, International Normalised Ratio; K, Potassium;P, Phosphorus; Ca,Calcium; IU/L, International units per litre; U/L, Units per litre; mmol/L, Millimoles per Litre; g/dL,Grams per decilitre; mg/dL, Milligrams per decilitre

Figure: Acholic stool.

Despite starting medium chain triglycerides-supported extensively hydrolysed formula and pancreatic enzyme replacement therapy (PERT), the patient's diarrhoea and hypernatraemia persisted. Lactose-free formula was introduced with a presumptive diagnosis of lactose intolerance. However, the patient's hypernatraemia and diarrhoea continued. He was empirically switched to fructose-based formula. After the introduction of fructose-based formula, diarrhoea attacks subsided, and sodium levels normalised. Diarrhoea continued for 14 days until a fructose-based formula was started. After the change of formula, the clinical condition improved within one day, allowing for transfer from intensive care to the ward within 48 hours. On day 20 of hospitalisation, the patient's weight percentile was 24.51, with an SDS of -0.69. The patient was then discharged.

Genomic DNA was isolated from peripheral blood and sent for whole exome sequencing (WES). Compound heterozygous mutation in the SLC5A1 gene: single mutation is c.583+2T>C variant likely pathogenic, and the other is c.899>A p.(Arg300His) classified as a VUS (OMIM: 606824).

The baby was started on a specialised formula (Galactomine® - fructose-based) with an appropriate dietary plan. The baby is currently thriving without diarrhoea attacks.

Nutritional therapy involved step-by-step trials of different enteral products. The patient did not respond to extensively hydrolysed formula or lactose-free formula. Consequently, carbohydrate malabsorption was considered in this patient.

In cases of severe dehydration of unknown aetiology, it is crucial to initiate targetted nutritional therapies for potential congenital causes of diarrhoea until advanced investigations and genetic testing are completed.

In light of the 25% recurrence risk, the parents were informed of their option of prenatal diagnosis and preimplantation genetic diagnosis. Another approach is to feed a formula that is high in fructose until a genetic diagnosis is reached.

Discussions

Congenital glucose-galactose malabsorption (OMIM: 606824) is an autosomal recessive disorder caused by a deficiency of the intestinal SGLT1 gene SLC5A1.

The SGLT1 gene (SLC5A1) in humans is located on chromosome 22q13.1 and has 15 exons. It contains a 73 kDa hydrophobic protein that functions as a sodium-glucose cotransporter. This protein is predicted to have 14

transmembrane segments, which are integral for its role in transporting glucose and galactose across the intestinal and renal epithelial cells by coupling with sodium ion gradients.[2]

In congenital glucose-galactose malabsorption, malabsorption of glucose and galactose leads to osmotic diarrhoea, which causes a disproportionate loss of free water compared to sodium. This results in an elevation of serum sodium levels and development of hypernatraemic dehydration, as seen in this patient. The presence of severe hypernatraemia in an infant with persistent diarrhoea should, therefore, alert clinicians to the possibility GGM.

GGM patients usually present with symptoms due to carbohydrate malabsorption (severe osmotic type dehydration and diarrhoea). Symptoms manifest after feeding, including nausea, diarrhoea, and non-specific abdominal pain. In addition to constipation and weight loss, sometimes extra-intestinal symptoms such as headache can be observed. The transport of glucose, amino acids, vitamins, and a number of ions across the intestinal epithelium is carried out by SGLT1. In GGM, absorption of fructose and xylose is not affected.[3]

In the current patient, the diagnosis of GGM was considered after recurrent severe diarrhoea, hypernatraemic dehydration unresponsive to lactose-free or hydrolysed formulas, and resolution of symptoms with a fructose-based formula. Confirmation was provided by genetic testing, which revealed compound heterozygous mutations in SLC5A1.

The main differentials in infants with intractable diarrhoea and dehydration include congenital chloride diarrhoea, congenital sodium diarrhoea, cystic fibrosis, and cow's milk protein allergy. These conditions should be systematically ruled out. A recommended diagnostic approach involves: 1) careful evaluation of stool characteristics, 2) exclusion of infectious and metabolic causes, 3) stool biochemical testing including reducing substances and pH, and 4) genetic testing for congenital diarrhoeal disorders. This approach may assist clinicians in achieving early diagnosis.

Although its prevalence varies among populations, it is slightly more common in regions where consanguinity rates are high, supporting autosomal recessive inheritance.[4]

Results of a study by Saadah et al. showed that 87.5% of the parents of the study patients were consanguineous and that 37.5% had GGM-affected siblings.[5] In the current case too, the parents were consanguineous.

Valley et al.[6] presented the case of a-five-day-old girl with life-threatening dehydration, irritability and a remarkable weight loss. This case illustrates the typical clinical picture of GGM. In the present case, the clinical findings were not revealed in the neonatal period.

Lostao ve al.[7] significantly increased the ability to identify novel monogenic disorders, such as congenital diarrhoea and enteropathies in young infants, with next-generation sequencing.

The current patient identified a likely pathogenic heterozygous c.583+2T>C variant (OMIM:606824). WES also identified another heterozygous variant of uncertain clinical significance in the SLC5A1 gene c.899>A p.(Arg300His) (OMIM: 606824). The compound heterozygosity may have contributed to the patient's clinical condition.

Recent studies have aimed to record the clinical and laboratory characteristics of GGM patients and prevent malnutrition in the targetted populations.[8]

Iawama et al. reported a case of a new-born with typical GGM symptoms on the third day of life, accompanied by nephrological complications. The patient died at the age of four months due to complications such as intracranial haemorrhage, hydrocephalus, and seizures.[9] This case demonstrates how dramatic the course of the disease can be and how fatal it can be if left untreated.

Feeding a fructose-based formula is the most effective therapy for CGGM. GGM can be treated and children can grow up well if diagnosed and treated early. Therefore, it is important for medical professionals to consider this disease and make a quick and accurate diagnosis.[10]

Conclusion

Paediatricians should consider unexpected congenital causes when evaluating infants who present with chronic diarrhoea. In this patient, early recognition of glucose-galactose malabsorption and prompt dietary modification led to rapid clinical improvement. Early diagnosis and timely treatment are essential to avoid serious complications associated with undetected GGM. Genetic testing is strongly encouraged, as it facilitates early identification, prevents major complications, and improves clinical outcomes.

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HAA, HZT, AO & MT: Concept, design, data acquisition, analysis, interpretation, drafting, revision, final approval and agreement to be accountable for all aspects of the work.