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OLGU SUNUMU / CASE REPORT

A newborn with congenital glucose-galactose malabsorbtion and cardiac failure

Glukoz-galaktoz malabsorbsiyonu ve kalp yetmezliği olan yenidoğan olgusu

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Abstract
Glucose-galactose malabsorption is a life-threatening disease that starts in the newborn period. Due to SLC5A1 gene mutation in the sodium-dependent glucose transporter system, glucose and galactose are not absorbed in the small intestine mucosa, and this results in severe osmotic diarrhea. With early diagnosis and appropriate treatment, it is possible to prevent lethal complications, discontinue diarrhea and provide normal growth. We report here; a congenital glucose-galactose malabsorption diagnosed case with severe dehydration and shock table due to diarrhea during neonatal period, with which difficulty in diagnosis due to severe heart failure at the time of admission was also faced. To our knowledge, no cases of congenital glucose-galactose malabsorbtion complicated with heart failure have been published in the literature before.
Key words: Glucose-galactose malabsorption, heart failure, newborn diarrhea

Öz
Glukoz-galaktoz malabsorpsiyonu, yenidoğan döneminde başlayan ve hayatı tehdit eden bir hastalıktır. Sodyum bağımlı glukoz taşıyıcı sistemde SLC5A1 genindeki mutasyonlara bağlı olarak ince barsak mukozasında glukoz ve galaktozun emilmemesi sonucu ağır osmotik ishal ile seyreder. Erken tanı ve uygun tedavi ile ölümcül komplikasyonların önlenmesi, ishalin kesilmesi ve normal büyümenin sağlanması mümkündür. Burada, yenidoğan döneminde ishale bağlı ağır dehidratasyon ve şok tablosunda başvuran, konjenital glukoz-galaktoz malabsorbsiyonu tanısı konan, başvuru anında ciddi kalp yetmezliğinin olması nedeniyle tanıda zorluk yaşanan bir olgu sunulmaktadır. Konjenital glukoz-galaktoz malabsorbsiyonunun kalp yetmezliği ile komplike olduğu başka olguya literatürde rastlanmamıştır.

Anahtar kelimeler: Glukoz-galaktoz malabsorpsiyonu, kalp yetmezliği, yenidoğan ishali

INTRODUCTION

Glucose-galactose malabsorption (GGM) is a rare autosomal recessive disorder caused by a selective defect in the sodium-dependent glucose cotransporter (SGLT-1), a membrane protein that normally transports glucose and galactose across the intestinal brush border. Mutation in the Na^+/glucose cotransporter gene (SLC5A1, previously known as SGLT1) has been related to congenital GGM[1,2]. The SLC5A1 gene is located on 22q13.1 chromosome and encoding the SGLT1 membrane protein. The SGLT1 protein is located mainly in the intestine, but it also has been detected in the kidney, parotid and submandibular salivary glands and heart[3,4]. To date, 56 mutations at SLC5A1 gene have been reported as detailed by the Human Gene Mutation Database[5]. The Na^+/glucose cotransporter which is located in the brush border membrane of the intestinal epithelium, ensures normal glucose absorption. Cellular influx is driven by the transmembrane Na^+ electrochemical potential gradient. Glucose moves to the blood via the facilitated glucose carrier. Glucose-galactose malabsorption, secondary to a defect in this intestinal Na^+ /glucose cotransporter, causes accumulation of unabsorbed glucose and galactose within the neonatal gut and leads to osmotic diarrhea[6].

Congenital GGM is a very rare disease and diagnosis

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of GGM remains challenging for clinicians. It is characterized by life-threatening, intractable, watery acidic diarrhea; dehydration; and failure to thrive in neonates by several days of age. As GGM presents with an osmotic diarrhea, it disappears when feeding is interrupted. Elimination of glucose, galactose, sucrose and lactose from the diet resolves the diarrhea almost immediately, but it promptly resumes on feeding any of these sugars[6].

A premature infant admitted to our hospital with dehydration and shock and diagnosed GGM is presented in this case. Her severe cardiac insufficiency at the time of admission has caused difficulty in our diagnosis.

CASE

Healthy, 25 year old mother gave birth from first pregnancy to twins with vaginal delivery in 37 gestational week. It was learned that the mother and father were first cousins. There were no known diseases in the family. Babies were born as 1500 grams and 2000 grams. Twins stayed in a hospital for one week after delivery and they were discharged without any problems. They were breastfed at home. A few days after they were discharged, they had abdominal distension, foul smelling stools, coughing and unwillingness to suck. Postnatal day 11, they were brought to our hospital's Pediatric Emergency Service with these complaints. The first infant had shock symptoms, while the second infant had a moderate degree of dehydration findings. Physiological serum 20 cc/kg were given to them and they were taken to the neonatal intensive care unit.

In the physical examination of the first infant; her weight was measured as 1530 gr (<3%), height was 51 cm (90%) and head circumference was 35,8 cm (90%). Although her body temperature was 38^{0}C pulse was 89/min. Blood pressure was 42/22 (mean 32) mmHg. She had superficial respiration, skin was pale and cyanotic, skin turgor was reduced, mouth mucosa was dry, peripheral pulse was weak and capillary refill time was five seconds. No dysmorphic finding could be detected on general appearance. Neonatal reflexes were absent. Respiratory sounds were normal. No arrhythmia or murmur could be detected in heart, but it was bradycardic. Abdomen was distended; genital structure was normal. Anus, esophagus and choana were open.

Laboratory examination was performed; hemoglobin 9.3 g/dl, white blood cells 19,500/mm^3, platelet count 820,000/mm^3, C-reactive protein 1.2 mg/L, procalcitonin 1.39 ng/mL, urea 70mg/dl, creatinin 0.3 mg/dl, sodium 123 mEq/L, potassium 6.5 mEq/L, chlorine 96 mEq/L, calcium 7.1 mg/dl, glucose 13 mg/dl, albumin 2.2 g/dl, AST 92 U/L, ALT 71 U/L, total bilirubin 0.4 mg/dl, direct bilirubin 0.2 mg/dl, free T4 1ng/dl, TSH 2.6μIU/mL. After the first supportive treatment blood gases were taken; pH 7.29, pCO2 32 mmHg, pO2 44 mmHg, BE -10 mmol/L and HCO_3 16 mmol/L. The weight of the second infant was 1850 gr (<3%), height was 51 cm (90%), head circumference was 36 cm (90%). Skin turgor was reduced, mouth mucosa was dry, peripheral pulse was normal and capillary refill time was two seconds. Neonatal reflexes were decreased. Other physical examination findings were normal and laboratory findings were close to normal.

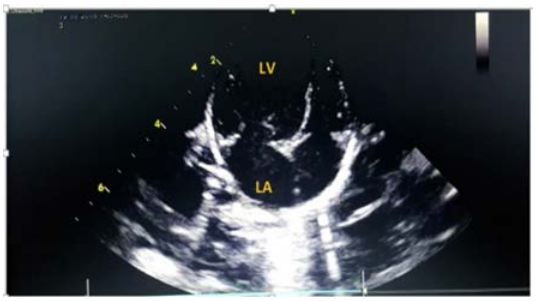

Figure 1A. Reduction in movement of mitral valves, left ventricular dilatation and right deviation in interventricular septum in systole

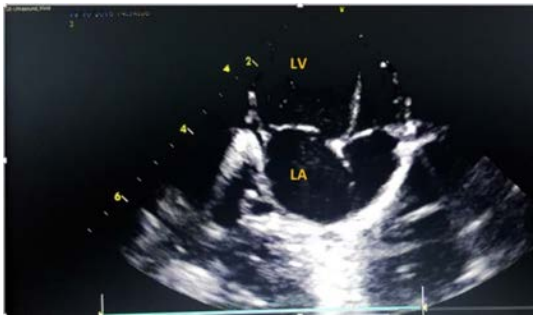

Figure 1B. In diastole, mitral valve can not close completely and left ventricular dilatation.

First baby was intubated due to insufficient and superficial respiration. For dehydration and hypoglycemia, appropriate fluid treatment containing maintenance fluid with sodium and

glucose was given. Treatment with vancomycin 10 mg/kg/dose every eight hours and cefotaxime 50 mg/kg/dose every eight hours was started. Free air was detected under diaphragm in direct abdominal graph. Operation was scheduled subsequent to correction of vital signs. When the patient was examined with echocardiography; reduced ventricular function and second degree mitral insufficiency were detected. Ejection fraction was measured as 48% and shortening fraction as 21% (Figure A and B).

Treatment with dopamine 10 μg/kg/min and dobutamin 10 μg/kg/min was started. Erythrocyte suspension was given. Having relatively better general condition, patient was taken to surgery on the 48th hour after admission; she had gastric perforation and primary repair was performed. After operation, antibiotic treatment with vancomycin, meropeneme 20 mg/kg/dose every eight hours and metronidazole 7.5 mg/kg/dose every 12 hours was continued. On the 5th day after admission, patient was separated from mechanical ventilation; hematologic and biochemical tests and blood gases were normal. However, systolic function was not completely corrected in echocardiography. Dopamine and dobutamin were reduced and finally, discontinued as cardiac functions were corrected according to echocardiographic examination. Treatment was continued with captopril and furosemide.

On the 7th day after operation, nutrition was started with low volume and it was increased gradually. However, watery stool was detected. In faecal examination, no blood or infection finding was observed and reductant was detected to be positive. Nutrition was discontinued. Renutrition started with lactose free formula; but, watery stool restarted. Nutrition was discontinued once more. Glucose and galactose free formula (Galactomin19®, Nutricia) was used during renutrition, and diarrhea was recovered and did not happen again with enteral feeding completely.

During this time, her twin sister also received appropriate fluid treatment and treatment with vancomycin and cefotaxime. During nutrition, same problems were also observed in twin sister, and same nutrition protocol started for her as well. After 15 days of hospitalization, the twin sisters were discharged without problem. The family was informed about the disease and their verbal consent was taken to publish this case.

DISCUSSION

Among the causes of chronic diarrhea during neonatal period are; microvillus atrophy, tufting enteropathy, congenital GGM, autoimmune enteropathy, sucrase-isomaltase deficiency, cow's milk allergy, congenital short bowel syndrome, IPEX (Immune dysregulation; polyendocrinopathy; enteropathy; X-linked), congenital lactase insufficiency, congenital chloride and sodium malabsorption, bile acid malabsorption and congenital enterokinase insufficiency. Congenital GGM, caused by a selective defect in the glucose and galactose transport mechanism across the intestinal brush border. Mutations in the Na^+/glucose cotransporter gene (SLC5A1) have been linked to congenital GGM.[1] This Na^+/glucose cotransporter couples glucose or galactose to Na^+ gradients across the brush border membrane of the cells lining the small intestine and ensures normal glucose absorption. Cellular influx is driven by the transmembrane Na^+ electrochemical potential gradient. Glucose then moves to the blood across the basolateral membrane via the facilitated glucose carrier.

Glucose– galactose malabsorption is an autosomal recessive disease secondary to a defect in this intestinal Na^+/glucose cotransporter. Accumulation of unabsorbed glucose and galactose within the neonatal gut leads to life-threatening, watery, acidic diarrhea and dehydration whilst taking a glucose or galactose-containing diet. The disease can be lethal if these newborns are not diagnosed and treated in a timely manner[6,7]. Faeces may be foul smelling and fatty, because fatty acids are produced by fermenting glucose in intestinal bacteria. Although glucose and galactose absorption may not be ensured, fructose absorption is normal. Lactose in breast milk is degraded by lactase enzyme which is found in brush borders from epithelial cells of intestine. If generated glucose and galactose cannot be absorbed, they cause osmotic diarrhea[8]. Watery diarrhea, dehydration and hypernatremia and metabolic acidosis are typical findings in neonatal period. As GGM presents with an osmotic diarrhea, it disappears when feeding is interrupted. The only oral feeding tolerated is a carbohydrate-free formula. Elimination of glucose, galactose, sucrose and lactose from the diet resolves the diarrhea almost immediately, but it promptly resumes on feeding any of these sugars[6]. Some other criteria can be used to establish the diagnosis of GGM: glucose–galactose

malabsorption evidenced by glucose and galactose in stool, a flat plasma glucose/galactose response following an oral glucose/galactose tolerance test, no response to lactose-free diet and a normal intestinal biopsy[6].

Diagnosis may be made by correction of diarrhea with eliminating glucose and galactose from nutrition and by not observing diarrhea with fructose containing baby food.[9] If there is no known mutation in family history, verification with genetic tests are not required for diagnosis.[10] Since genetic tests had to be performed in another centre and diagnosis was verified clinically, no genetic study was performed in our patient.

During treatment, elimination of glucose and galactose from nutrition will generally result in positive results. We utilized fructose containing Galactomin 19® in our case. It was reported that adequate weight gain and normal neurological development could be provided with appropriate nutrition[8]. During neonatal and early infant period, fructose containing formula should be utilized. When changing to supplementary food, it is recommended that nutrients rich in fructose such apple and pear puree, carrot, green bean and zucchini should be consumed; however, nutrients rich in glucose and sucrose such as peach, banana, pea, sweet potato and corn should not be consumed[8,11]. It is known that since a small amount of glucose may be absorbed in the large intestine as the patients age, such patients may consume glucose containing nutrients in low amounts[8,11]. However, as nutrients are consumed, gastrointestinal complaints should be monitored closely, they should be consumed in small amounts and new nutrients should be added with 5-7 days' intervals to nutrition. Babies may consume meat on the 8th month and egg in the 11th-12th months. Containing 40-45% of fructose, honey may be utilized as a sweetener later[8,11].

In literature, there are cases of GGM associated with nephrocalcinosis, rickets and nephrogenic diabetes insipidus[12]. Urine test and kidneys in ultrasonography examinations of our patient were observed to be normal.

Because of its rarity, the diagnosis of GGM remains challenging for clinicians. Severe acidosis was observed in our case on admission and unexpected ventricular systolic dysfunction was detected in echocardiography. The main reason for cardiac compromise in our case was acidosis. It's well known that acidosis decreases the contractility of cardiac muscle in the excitation-contraction coupling pathway, including both the delivery of Ca^{+2} to the myofilaments and the response of the myofilaments to Ca^{+2}. Management of the underlying pathology may be required to allow rapid normalization of the metabolic state. Acidosis also could induce a negative inotropic effect in the heart, through alteration of electrical activity, pumps and channels and modifications of myofilament sensitivity to calcium. As the duration of acidosis exposure increases, the severity of cardiac dysfunction is expected to increase[13]. Since hyponatremia, acidosis and ventricular systolic dysfunction were present during admission, sepsis was considered for diagnosis; as diarrhea was observed in twin sister by nutrition, our patient was fed more carefully during postoperative period. Hyponatremia condition at admission of patient was considered to be related to third-space fluid and electrolyte shift associated with gastric perforation. After discharge weight gains and neurological developments of twin sisters were monitored and they were observed to be normal. We would like to express that in the presented case it is difficult to diagnose GGM due to its complications with cardiac insufficiency and gastric perforation.

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