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Nephrolithiasis and Nephrocalcinosis in Children with Glucose-Galactose Malabsorption: Report of Five Cases

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Abstract Several reports described nephrolithiasis and nephrocalcinosis in children with glucose-galactose malabsorption (GGM). The etiology of renal stones in GGM is not known, but the chronic dehydration and concentrated urine complicating chronic diarrhea in GGM might be a possible mechanism. Few reports described nephrocalcinosis in association with hypercalcemia, hypercalciuria, and renal tubular defect. Both nephrolithiasis and nephrocalcinosis can present in the neonatal period at the time of diagnosis or manifest later during follow up. We are aware of eleven patients of GGM with nephrolithiasis reported worldwide, and eight patients of GGM with nephrocalcinosis. In this current report, we describe a total of five patients with GGM complicated with nephrolithiasis (three cases), and nephrocalcinosis (two cases). As far as we know, this series is the largest group of patients described with these complications in one report. We aim from this paper to deliver a message to the pediatricians and pediatric gastroenterologist to do regular ultrasonography of the kidneys in all patients of GGM at the time of diagnosis and during follow up to recognize these complications early and refer them in the right moment for management.

Keywords: *glucose-galactose malabsorption, nephrolithiasis, nephrocalcinosis, children*

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1. Introduction

Glucose-Galactose Malabsorption (GGM) is a rare metabolic disorder caused by a defect in glucose and galactose transport across the intestinal brush border [1]. The intestinal Na^+-glucose cotransporter (SGLT1) transports glucose into the enterocytes against its concentration gradients [2]. SGLT1 handles both glucose and galactose [3]. SLA5A1 gene codes for the intestinal brush border SGLT1, and mutations in this gene cause GGM [4]. The facilitated fructose transporter (GLUT5) is responsible for the transport of fructose across the intestinal brush border [3,5]. This private carrier is not affected by this disease, and therefore fructose is absorbed very well [5]. Replacing glucose and galactose by fructose usually, lead to the resolution of symptoms [6]. Nephrolithiasis and nephrocalcinosis rarely are reported in the literature as complications of GGM [7,8]. Here, we report three patients with nephrolithiasis and two patients with nephrocalcinosis.

2. Materials and Methods

We reviewed the health records of five patients with GGM complicated with nephrolithiasis or nephrocalcinosis retrospectively. These five patients were diagnosed between November 2011 and August 2017 and followed up at our center at King Fahd Central Hospital, Jazan, Saudi Arabia, which is the largest referral center in the southwestern part of the country. Data collected and included: Demographic information, age at presentation, age at diagnosis, family history, perinatal history, feeding history, clinical presentation, growth parameters, laboratory and radiological studies, treatment and outcome. Laboratory investigations included complete blood count (CBC), complete metabolic panel (CMP), arterial blood gas (ABG), urine examination and culture, stool examination and culture. We performed radiological imaging including renal ultrasound (US) and computed tomography (CT) scan of the abdomen.

We diagnosed GGM based on the unique clinical background, clinical evolution with different types of feeding and exclusion of the infectious causes of chronic diarrhea.

We utilized the renal US and CT scan of the abdomen to diagnose the renal complications of GGM such as nephrolithiasis and nephrocalcinosis. All patients continued their monitoring in pediatric gastroenterology clinics, and we referred them to a pediatric urologist or pediatric nephrologist based on the radiological findings.

3. Results

All patients were Saudi from Jazan province (southwestern of Saudi Arabia). Antenatal and perinatal history was unremarkable, and family history showed positive consanguinity in all five patients. There was a family history of GGM in the majority of the patients. The

clinical features, laboratory tests, radiological studies, treatment, and outcome, are individualized in details below for each case.

3.1. Case 1

Four months and three weeks old Saudi girl admitted with a history of watery diarrhea, associated with vomiting since the age of one month. She was the first child of consanguineous parents. She was born at term, and her birth weight was 3.5 kg. There was no history of polyhydramnios. She was on artificial feed soon after birth. The child had recurrent admissions to local hospital with dehydration for fluid therapy. Examination revealed dehydrated child with dry mucous membranes and tachycardia. Her growth parameters for weight and height were below the 3rd percentile. She had no dysmorphic features. Systemic examination was unremarkable. Blood investigation showed serum sodium of 159 mmol/L. The results of serum potassium, phosphate, magnesium, and calcium were within the reference range. Her renal function test was normal. Arterial blood gas (ABG) analysis showed metabolic acidosis with a pH of 7.27, pCO2 18.8 mmHg, and serum bicarbonate (HCO3) 15 mmol/L. Stool culture and microscopic examination for ova, cyst, and parasite were negative. Urine analysis was cloudy in appearance, acidic reaction, blood 4+, no nitrite or protein, glucose 3+, no ketones, a specific gravity of 1.030, WBC 10-12 per HPF, no bacteria, no cast, epithelial cells, or crystals. Urine culture showed no growth. Imaging studies including kidneys ultrasound (US) and computed tomography (CT) scan of the abdomen showed multiple bilateral stones mainly in the lower calyces and renal pelvis of both kidneys [Figure 1 (A, B)]. We discontinued oral feeding and corrected the hypernatremic dehydration slowly. Diarrhea stopped during fasting but recurred again once she resumed her formula. We tried the child on lactose-free formula then amino-acid based formula with no improvement. Once we began the patient on fructose-based formula (Galactomin-19), she showed a dramatic improvement in stool consistency, frequency, and volume. We diagnosed GGM in this patient based on her presentation of chronic osmotic diarrhea with hypernatremic dehydration that responded only to fructose-based formula. The child achieved appropriate growth parameters on follow-up. She is also under follow-up by a pediatric urologist for renal stones.

2.2. Case 2

Three months old Saudi girl presented with a history of chronic diarrhea since birth. She was a full-term product with a birth weight of 2.5 kg. Parents are consanguineous. Two abortions complicated her previous pregnancies. One sibling died with undiagnosed chronic diarrhea at 15 days of age, and another sibling three years and five months old boy diagnosed to have GGM on fructose based formula (galactomin-19). Mother started her daughter on the same formula at home with the suspicion that her daughter has GGM like her brother and she noticed a marked improvement in stool consistency and frequency. The child had recurrent diarrhea again once the standard formula is resumed. Examination revealed a well-hydrated child. Her growth parameters showed weight on the 10th percentile and height on the 50th percentile. She had no dysmorphic features, and systemic examination was unremarkable. Blood investigation revealed normal values of complete blood count (CBC), serum electrolytes including sodium, renal and liver function tests, bone profile and blood sugar. Urine examination showed cloudy appearance, blood 3+, glucose 1+, epithelial cell 1+, other parameters of urine analysis were normal. Urine culture showed no growth. Stool culture and stool examination for ova, cyst, and parasite were negative. Imaging studies including abdominal ultrasound and CT scan showed renal stone measuring 16 mm at the renal pelvis of the right kidney [Figure 2 (A, B)]. The child was diagnosed as GGM and continued on galactomin-19. We referred the child to the urologist, and she had extracorporeal shock wave lithotripsy.

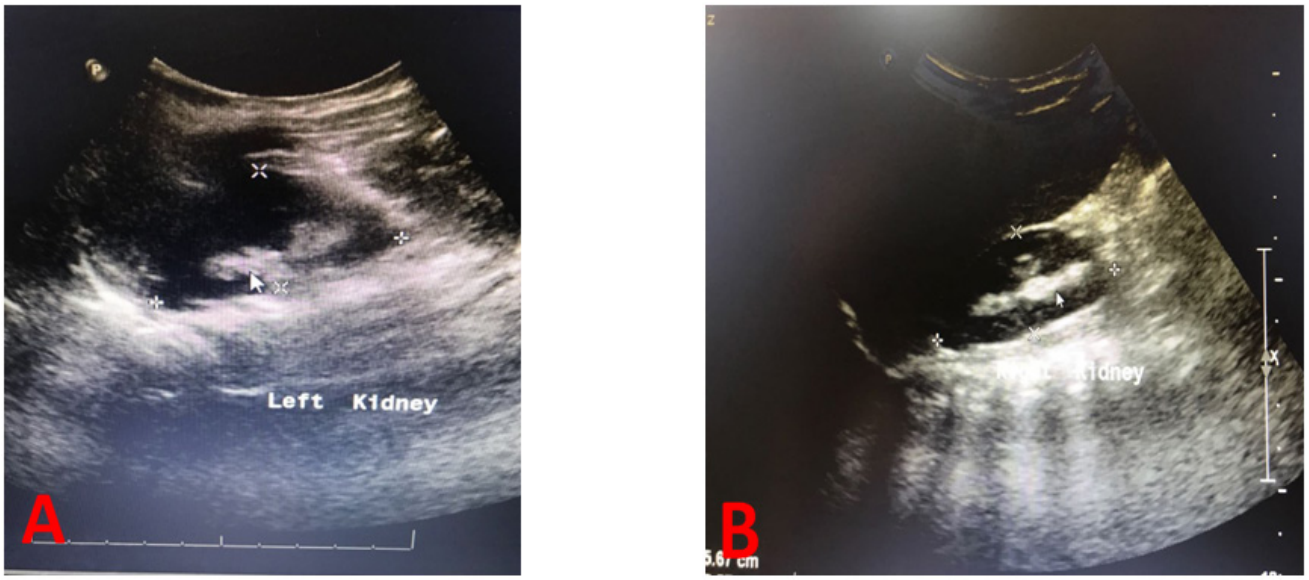

Figure 1. Renal Ultrasound. (A) Left kidney; (B) Right kidney, both showed multiple bilateral renal stones

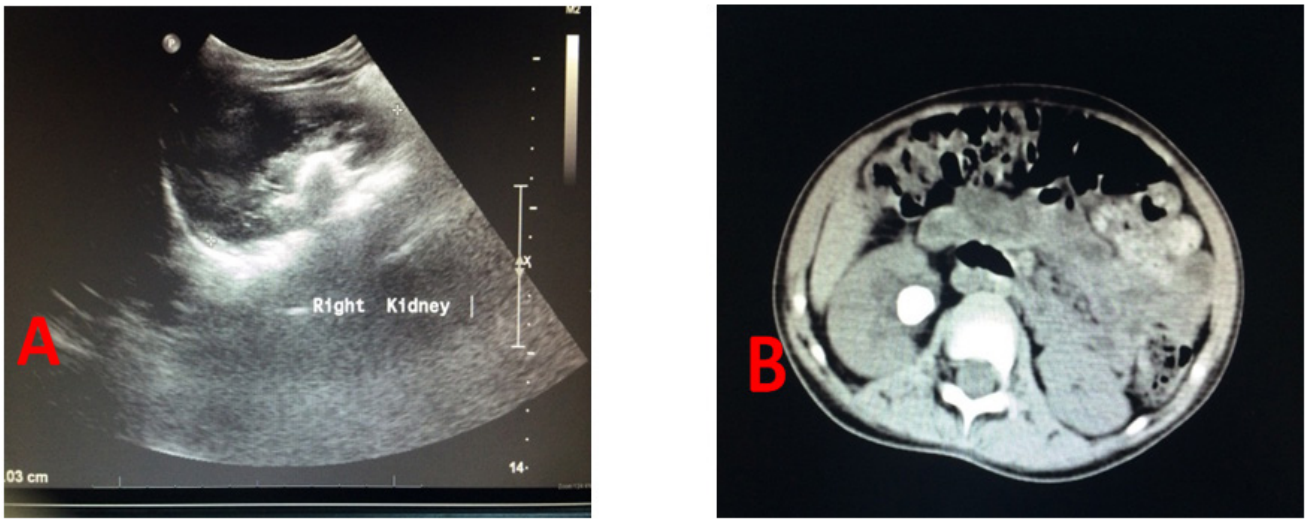

Figure 2. (A) Right kidney US; (B) CT scan of abdomen (cross section), both showed right kidney stone measuring 16 mm at the renal pelvis

2.3. Case 3

Three years and eight months old Saudi boy is the brother of the previous patient (case 2). He presented initially to another hospital with a history of chronic diarrhea since birth. Diarrhea persisted in spite of multiple changes in the artificial formulas. He was diagnosed to have GGM and started on fructose-based formula (galactomin-19) with a dramatic improvement in his diarrheal illness. He also had Nephrolithiasis and subjected for extracorporeal shock wave lithotripsy and cystoscopy for stone crushing and removal. In the clinic, the general condition was stable and had no dysmorphic features. His growth parameters showed weight between 10^{th} and 25^{th} percentile and height between 25^{th} and 50^{th} percentile. Systemic examination was unremarkable. Blood investigation revealed normal values of complete blood count (CBC), serum electrolytes including sodium, renal and liver function tests, bone profile, uric acid and blood sugar. Urine examination was normal except blood 3+, and urine culture showed no growth. Abdominal ultrasound and CT scan showed multiple variable stones in both kidneys [Figure 3 (A, B)]. We referred the child to the urologist for lithotripsy.

2.4. Case 4

Two months and three days old Saudi girl admitted with a history of diarrheal illness since the age of 3 days. The diarrhea was watery with mucus but not mixed with blood and not offensive. She was a full-term product with a birth weight of 2 kg. Antenatal history was unremarkable with no polyhydramnios. She was the first sibling to consanguineous parents. No family history of chronic diarrhea or neonatal deaths. Mother started her on breast milk for three days then shifted to artificial formula. The child was admitted to peripheral hospital with gastroenteritis since two weeks. The lactose-free formula was introduced but with no significant improvement. On admission, the patient was lethargic, moderately dehydrated with dry mucous membranes, sunken eyes, depressed anterior fontanel, and tachycardia. Her growth parameters showed weight and height were both below the 3^{rd} percentile. She had no dysmorphic features, and systemic examination was unremarkable. Blood investigation revealed serum sodium of 176 mmol/L, potassium 4.1 mmol/L, blood urea nitrogen (BUN) 24.9 mmol/L, and creatinine 82 mmol/L. The results of phosphate, magnesium, and calcium were within reference ranges. Blood gas analysis showed metabolic acidosis with pH of 7.276, PCO2 26.1 mmHg, and bicarbonate (HCO3) 13.7 mmol/L. Stool culture and microscopic examination for ova, cyst, and parasite were negative. Urine analysis was unremarkable. Abdominal ultrasonography showed nephrocalcinosis of both kidneys. We treated hypernatremic dehydration, metabolic acidosis, and pre-renal azotemia with intravenous fluid. Based on chronic osmotic diarrhea with hypernatremic dehydration that did not respond to different feeding regimens, she was diagnosed to have glucose-galactose malabsorption (GGM). We started the patient on fructose-based formula (Galactomin-19) with a dramatic improvement in stool consistency, frequency, and volume.

2.5. Case 5

11 months old Saudi girl presented to pediatric gastroenterology clinic with a history of chronic diarrhea, abdominal distention, and vomiting since birth. Her primary physician started her on different formulas including lactose-free formula but without response. She responded very well to fructose-based formula (galactomin-19). Parents are consanguineous, with a positive family history of GGM. Based on her clinical presentation, strong family history of GGM and the response to fructose-based formula, she was diagnosed to have GGM. Her general condition was stable and vital signs were normal. No dysmorphic features. Her growth parameters showed weight on the 10^{th} percentile and height on 5^{th} percentile. Systemic examination was unremarkable. Blood investigation revealed hemoglobin (Hb) 12.8 g/dL, normal results of serum electrolytes including sodium, renal and liver function tests, bone profile and blood sugar. Urine examination was normal. Stool culture and stool examination for ova, cyst, and parasite were negative. Abdominal ultrasonography showed bilateral medullary calcification suggestive of nephrocalcinosis [Figure 4 (A, B)]. We referred her to a pediatric nephrologist who treated her with hydrochlorothiazide.

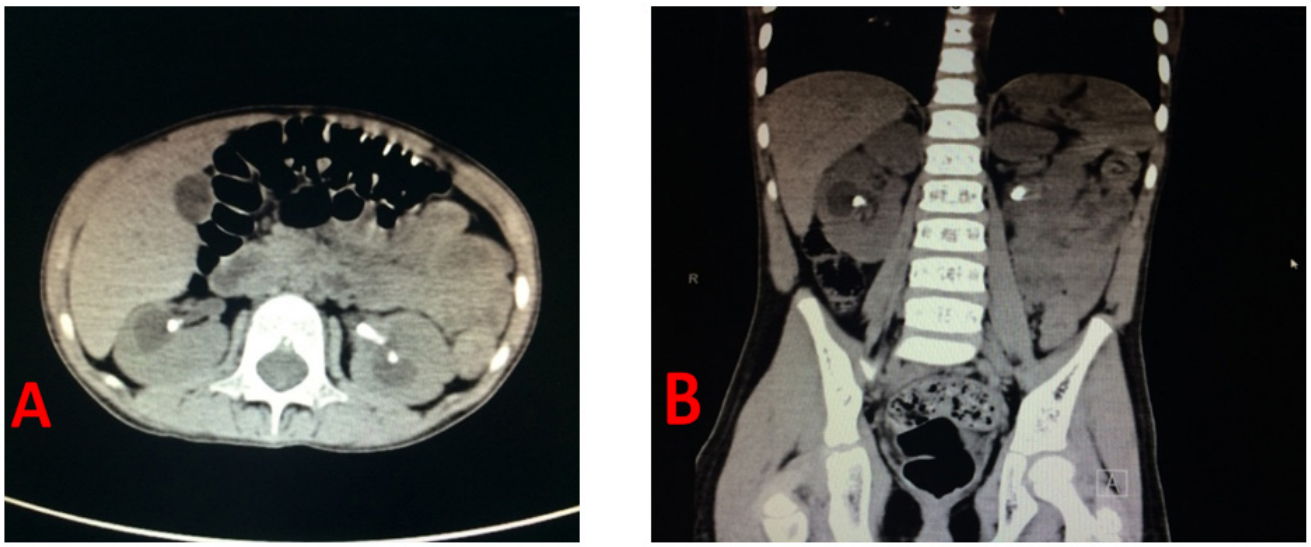

Figure 3. CT scan of the abdomen. (A) Cross section; (B) Longitudinal section, both showed renal stones in both kidneys

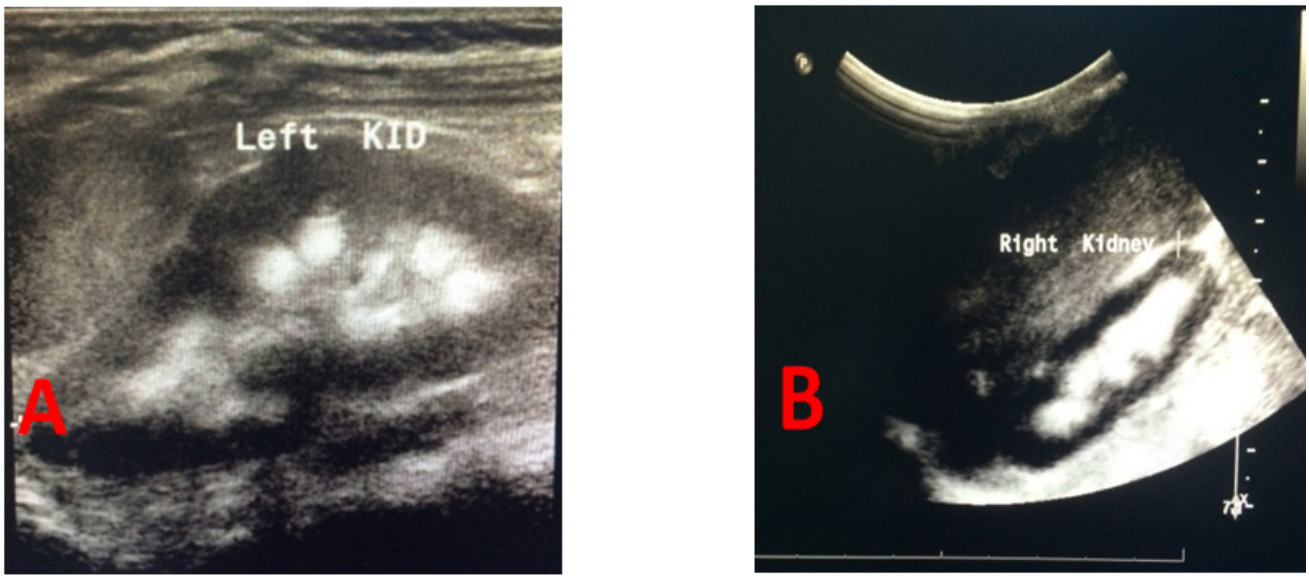

Figure 4. Renal Ultrasound. (A) Left kidney; (B) Right kidney, both showed bilateral nephrocalcinosis

4. Discussion

GGM is an autosomal recessive disorder, and consanguineous relationship plays an important risk factor in its inheritance [1]. All patients in this series showed a family history of consanguinity and the presence of GGM in the majority of them. There are only few hundred cases reported worldwide, and we are aware of about 45 patients with GGM described from Saudi Arabia [9].

The neonatal onset of severe watery diarrhea characterizes GGM [10]. Diarrhea is fatal unless we remove glucose and galactose from the diet [6]. Severe dehydration and metabolic acidosis among the frequent causes of death in these patients [5,11]. The diarrhea is osmotic, and stops with fasting but promptly resumes with the oral feeding of diets containing glucose or galactose [6]. The fructose-based formula is the only effective treatment for these patients [1,5,11]. All patients in this report presented with chronic diarrhea since birth. Diarrhea responded only to fructose-based formula. Two patients presented with other symptoms of Carbohydrate Malabsorption such as vomiting, abdominal distension, and flatus. Hypernatremic dehydration is considered to be one of the clues to the diagnosis of GGM. About 25% of children with GGM may develop hypernatremia [1]. Two patients presented to pediatric ER with signs of moderate hypernatremic dehydration and metabolic acidosis requiring appropriate fluid correction. Failure to thrive is one of the major clinical effect of chronic diarrhea in GGM [12]. We noticed that the undiagnosed patients had their growth parameters below the third percentile while those already diagnosed and on treatment had normal growth.

Stool sugar chromatography and oral glucose/galactose tolerance test may help in the diagnosis of GGM [1,11]. Recently the diagnosis is confirmed by the mutation analysis of SLA5A1 gene [4,13]. We were unable to do these tests because of a lack of facilities in our center. We diagnosed GGM based on the clinical ground and clinical evolution with different types of feeding.

Several reports described nephrolithiasis and nephrocalcinosis in children with GGM. Meeuwisse and Melin published in 1969 the first report of two patients

with GGM and renal stones [14]. The second report of GGM and nephrolithiasis was in 1992 from Saudi Arabia in 18-month-old Saudi girl [15]. Subsequently, Abdullah et al. reported eight cases with GGM; ultrasonography of the kidneys showed renal stones in two children [16]. Velibor Task from Macedonia described one girl with GGM complicated with renal stones at the age of 6 months [7]. There are two recent reports of GGM published from Saudi Arabia; Assiri et al. demonstrated two cases with renal stones in a group of five children with GGM, and Saadah et al. described two cases with nephrolithiasis in a cohort of 24 patients with GGM from the western region of Saudi Arabia [1,6]. The first report of GGM with nephrocalcinosis was in 1969 in an infant died at the age of 7 weeks due to severe dehydration, and on autopsy, the kidneys were macroscopically normal, but microscopic examination revealed nephrocalcinosis [14]. Since then eight cases were reported worldwide [6,8,17,18,19,20]. The most recent report of two cases with nephrocalcinosis described from Canada in 2017 [20]. We report here five cases of GGM which were complicated with nephrolithiasis in three patients and nephrocalcinosis in two patients. As far as we know, our report is considered the largest series of patients with GGM and renal complications.

The etiology of renal stones in GGM is unknown [1]. Nephrolithiasis secondary to hyperoxaluria is a well-known complication in patients with Malabsorption syndromes [7]. This finding is due to impairment of fatty acid absorption, in the sense that intraluminal fatty acids will compete with oxalate for calcium binding and increase the availability of intraluminal oxalate for absorption and excretion in the urine [21]. Impairment of fatty acid absorption is not a feature of GGM. Hence we do not think this mechanism plays a role in renal stone formation in this condition. There is epidemiological evidence that high fructose intake is a risk factor for kidney stones formation [22]. Many reports described GGM with nephrolithiasis at the time of diagnosis before starting fructose-based formula which makes this hypothesis unlikely. All reported cases of GGM with nephrolithiasis did not show any predisposing infectious, metabolic, or anatomical factors [1,7]. In our report, we did not identify any developmental abnormalities of the urinary tract, and no evidence of urinary tract infection (UTI). Urine examination did not show any significant crystals in the urine. We think like other reports that chronic dehydration and metabolic acidosis complicating GGM are possible risk factors for renal stones formation [6].

The term nephrocalcinosis describes the deposition of calcium salts in the renal parenchyma and tubules [24]. Several reports described the association of hypercalcemia and renal tubular defect with the nephrocalcinosis in children with GGM [8,17,19,20]. Recently, Fiscaletti et al. described two cases with GGM and nephrocalcinosis, he demonstrated hypercalcemia and hypercalciuria in one child and high levels of 1,25 $(OH)_2D_3$ in both of them [20]. He hypothesized that the upregulation of epithelial calcium channels (TRPV6) and 1,25$(OH)_2D_3$ are possible factors involved in the pathophysiology of nephrocalcinosis sometimes seen in GGM. In a group of 11 infants with carbohydrate malabsorption in the form of congenital lactase deficiency, the authors described a similar finding of hypercalcemia and nephrocalcinosis with an unclear mechanism [23]. Calcium levels were within normal range in our patients with GGM and nephrocalcinosis.

SGLT1 is found mainly in the apical membranes of enterocytes and renal proximal straight tubules (S3 cells) [3]. The mutation of SGLT1 gene in GGM might be the cause for mild impairment of tubular glucose transport and presence of glucosuria in some children with GGM [1]. There is no clear evidence that glucosuria predisposes children with GGM to UTI and subsequent renal calculi formation. None of the two patients with glucosuria in our group of GGM developed UTI [7].

It is recommended to do renal ultrasonography in all patients with GGM to identify these renal complications; this will allow early referral and management [6,7]. It is our policy in pediatric gastroenterology division to do radiological imaging in all cases of GGM. In this group of patients, urine examination showed microscopic hematuria in all three patients with nephrolithiasis, and sterile leukocyturia in the first patient. Both two cases with nephrocalcinosis did not develop urinary symptoms, and urine examination was entirely normal. We identified nephrolithiasis and nephrocalcinosis by doing kidneys US. We did renal CT scan in all cases of GGM with nephrolithiasis for detailed study of the renal system to exclude any developmental abnormalities.

Extracorporeal shock wave lithotripsy (ESWL) uses shock waves to fracture the stones [15]. We refer all three patients with nephrolithiasis to a pediatric urologist. Two patients had ESWL while the other patient is still under observation and follow-up in a urology clinic. Crystallization inhibitors; mainly citrate and magnesium; are an effective treatment option for nephrocalcinosis [24]. Hydrochlorothiazide can be used to treat hypercalciuria; it increases calcium uptake in the distal tubule and stimulates calcium reabsorption in the proximal tubule [24]. Our pediatric nephrologist started one of the nephrocalcinosis patients on hydrochlorothiazide while the other patient moved to another area soon after discharge. Soylu et al. reported that hypercalcemia and nephrocalcinosis associated with GGM might improve on a glucose-galactose-free diet [19]. Saarela et al. described a similar observation in the past in reported cases of congenital lactase deficiency on a lactose-free diet [23].

In conclusion, We report these cases to alert pediatricians to the nephrolithiasis and nephrocalcinosis as potential complications of GGM in children. Therefore, physicians should perform renal ultrasonography regularly in all patients with GGM to recognize and manage these complications early. On the other hand, we should include GGM in the differential diagnosis of all patients with neonatal onset of chronic diarrhea and renal ultrasonographic findings of nephrolithiasis or nephrocalcinosis.

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