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Nephrolithiasis in a child with glucose-galactose malabsorption

Received: 22 April 2003 / Revised: 20 August 2003 / Accepted: 26 August 2003 / Published online: 11 December 2003
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Abstract Glucose-galactose malabsorption (GGM) is a rare autosomal recessive disorder of intestinal transport of glucose and galactose, leading to watery diarrhea, dehydration, failure to thrive, or early death. We report a female newborn with GGM, whose clinical diagnosis was confirmed by mutational analysis of the *SGTL1* gene. Bilateral nephrolithiasis was discovered after an episode of hematuria. Metabolic causes of nephrolithiasis were not found. The most likely explanation for the development of nephrolithiasis is chronic diarrhea leading to dehydration and highly concentrated urine. High fluid intake and rigorous prevention of dehydration is therefore advised for these patients. Furthermore, life-long monitoring of their renal status, including regular ultrasound examinations, is warranted.

Keywords Nephrolithiasis · Glucose-galactose malabsorption · *SGTL1*

Introduction

Glucose-galactose malabsorption (GGM) is a rare autosomal recessive disorder of intestinal transport of glucose and galactose. It results in watery diarrhea, dehydration, failure to thrive, or even early death in the neonatal period, without early diagnosis and appropriate dietary measures. The disease was first reported in 1962 by Lindquist and Meeuwisse [1] from Sweden and Laplane et al. [2] from France. Since the gene that encodes the intestinal sodium-dependent glucose transporter (*SGLT1*) has been characterized, diagnosis of GGM is now possible by mutation analysis [3]. In this report, we describe a patient from Macedonia whose clinical diagnosis was confirmed by DNA analysis and who developed bilateral nephrolithiasis as a complication of the disease.

Case report

This girl is the second child of healthy, non-consanguineous parents. She was born after an uneventful pregnancy with a birth weight of 3.2 kg (50th percentile), a height of 51 cm (50th percentile), and an Apgar score of 8 and 9 at 1 and 5 min, respectively. On the 4th day of life, soon after breast-feeding was begun, she developed watery diarrhea. She became severely dehydrated (>15% of body weight) with a distended and hyperactive abdomen. Blood chemistry revealed severe metabolic acidosis and hypernatremia (178 mmol/l); her stool pH was below 5. Microbiological investigations did not demonstrate any infectious agents. There was intermittent glucosuria (up to 1+). Termination of breast-feeding and the introduction of a lactose-free formula did not result in any clinical improvement. An oral glucose tolerance test was abnormal, resulting in a flat curve. The presence of watery diarrhea with hypernatremic dehydration in a breast-fed neonate, along with the finding of intermittent glucosuria, raised the clinical suspicion of GGM [4]. Therefore, the child's feed was switched to a fructose-based formula (Galactomin 19, Nutricia). After introducing this formula there was a dramatic resolution of the diarrhea, with a weight gain of 3 kg within 2.5 months.

Analysis of the 15 exons of the *SGLT1* gene in a DNA sample prepared from peripheral blood of the patient confirmed the clinical suspicion of GGM. The index case was found to be a compound heterozygote carrying a nonsense mutation in exon 2 and a 1-base pair deletion at the acceptor splice site of intron 13. The exact designations of the mutations are c.197 C>T and IVS 13 -2 del a.

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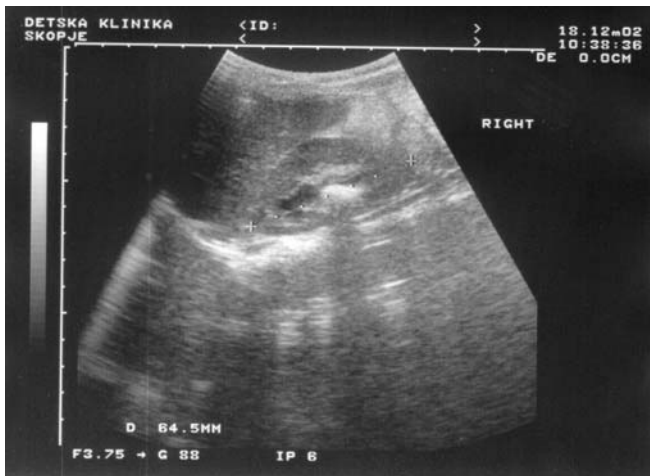


Fig. 1 Ultrasound scan of the right kidney revealing a solitary calculus in the renal pelvis

The first maternal allele results in a premature termination of translation (R63X) and the second paternal allele predicts a truncated glucose transporter protein.

At the age of 6 months, the girl presented with colicky pain, irritability, and bloody urine. Ultrasonography revealed a non-obstructive stone (5 mm) in the lower pole of the right kidney. There were another three small calculi, with a diameter of up to 3 mm, in the contralateral kidney. At the time of this presentation, serum electrolytes, uric acid, and acid-base status were normal. Urinary molar ratios were as follows: calcium/creatinine 0.42 (normal <2.2), uric acid/creatinine 0.39 (normal <1.0), oxalate/creatinine 0.107 (normal <0.36), and citrate/creatinine 0.142 (normal >0.129). Nitroprusside reaction as an investigation for cystinuria was negative. The parents were advised to increase her fluid intake and regular ultrasound examinations of the urinary tract were recommended.

At the age of 23 months, the child had another episode of renal colic and macroscopic hematuria. This time, the ultrasound examination revealed a solitary calculus in the right renal pelvis measuring 15 mm, with moderate dilatation of the pelvicalyceal system (Fig. 1). In the left kidney, there were three small non-obstructive stones, as identified by previous ultrasound examinations. Excretory urography confirmed the findings of the ultrasound examination and excluded congenital abnormalities of the urinary tract. The child was referred to a pediatric urologist for extracorporeal shock wave lithotripsy. The calculus in the right renal pelvis was successfully disintegrated. Spectroscopic analysis of the fragments revealed the presence of weddellite ($\text{CaC}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$).

Discussion

There are three reports of nephrolithiasis in children with GGM in the literature [5, 6, 7]. Three patients have been reported by Meeuwisse and Melin [5]. Their first patient was a 4-month-old female baby who was found to have a small calculus. At the age of 3 years, after an attack of pyelonephritis, four stones were detected. The stones were composed of calcium oxalate and calcium phosphate. The second patient, who was the sister of the previous patient, died at the age of 7 weeks due to severe dehydration. On autopsy, the kidneys were macroscopically normal, but microscopic examination revealed crystalline material within the distal tubules and adjacent

interspaces (nephrocalcinosis). The third patient was a 38-year-old woman with GGM who had a first attack of colic during the passage of a small renal calculus. On a second occasion the stone was collected and analyzed; it contained calcium, ammonium, oxalate, and phosphate. As in our patient, excretory urography was normal.

Abdullah et al. [6, 7] reported a group of eight Arabian children with GGM. In two children ultrasonography of the kidneys revealed renal stones; in one child nephrolithiasis was discovered at the first clinic visit, while in another patient it was detected after 1 year of follow-up.

Recently Pahari et al. [8] reported a baby with neonatal nephrocalcinosis associated with GGM. Their patient had hypercalcemia that was not mediated by hyperparathyroidism and promptly responded to fructose-based formula. The authors believe that the mechanism responsible for hypercalcemia is similar to that in congenital lactose deficiency; additional risk factors for nephrocalcinosis are metabolic acidosis and chronic dehydration.

We were unable to demonstrate any metabolic or anatomical factors responsible for the bilateral nephrolithiasis in our patient. Although nephrolithiasis secondary to hyperoxaluria is a well-known complication in patients with malabsorption syndromes, we do not consider that this mechanism plays a role in patients with GGM, since absorption of fatty acids is not impaired. The disease was well controlled until the 6th month, because the baby had been exclusively fed with Galactomin 19. After this period introduction of new foods resulted in an eventual glucose and galactose load with watery stools. During fevers, infections, and oral antibiotic administration (sugar content!) the water loss from the stools increased, resulting in highly concentrated urine.

It is well known that the *SGLT1* gene is expressed in renal tubular cells and its mutation might be responsible for mild impairment of tubular glucose transport [4]. It is possible that glucosuria, which is found in some children with GGM, may be a predisposing factor for the development of urinary tract infections and for a subsequent risk for stone formation. Although we documented glucosuria on several occasions, there was no evidence for any urinary tract infection in our patient.

We would like to emphasize that among GGM patients with renal stones or nephrocalcinosis only our patient has had molecular genetic confirmation of the disease with mutational analysis of the *SGLT1* gene. This is of particular importance for further phenotype-genotype studies investigating the relationship between the mutation type and the severity of the disease.

In conclusion, nephrolithiasis may be found in children with GGM. Therefore, renal ultrasonography should be regularly performed in these children. High fluid intake and rigorous prevention of dehydration should be advised for these patients along with a life-long monitoring of their renal status.

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