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Case report

A novel mutation in the *SLC5A2* gene causing benign renal glucosuria

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Abstract

Glucosuria is defined as a detectable amount of glucose levels in urine. It can be isolated or associated with other pathologies. In the presence of glucosuria in children and adolescents, it is important to perform an etiological study to exclude these conditions. Isolated renal glucosuria is a rare tubular disorder characterized by glucosuria without hyperglycemia or other glucose metabolism disorders. The inherited form of this disorder is called Familiar Renal Glucosuria (FRG). This is a rare condition caused by mutations in the *SLC5A2* gene (that encodes SGLT-2), which are responsible for the majority of cases. The long-term outcome of patients with FRG is very good, with no recorded mortality. The authors report a case of a 6-year-old girl with glucosuria that was found incidentally, without any symptoms or abnormalities in physical examination. Laboratory tests and urinalysis were normal, despite the presence of glucose in urine. The genetic test showed homozygotic missense mutation in the *SLC5A2* gene. With this case report, the authors would like to alert to this entity and to highlight the importance of pediatric renal glucosuria management and differential diagnosis.

Keywords

Benign glucosuria, genetics, kidney, mutation, *SLC5A2*.

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Introduction

Glucosuria is defined as a detectable amount of glucose levels in urine. Glucose is freely filtered through the glomerular basement membrane; however, under normal circumstances, the kidney reabsorbs almost 100% of filtered glucose [1-3]. Most glucose is reabsorbed in the proximal convoluted tubule (90%) and the remaining in the proximal straight tubule [4]. Glucose is absorbed at the luminal side of tubular cells by an active carrier sodium-mediated transport (SGLT) [3, 4]. The sodium electrochemical gradient driving glucose transport is maintained by sodium-potassium ATPase placed in the basolateral membrane [4]. Glucose is secreted at the tubular cell by facilitated diffusion transporter (GLUT) down glucose concentration gradient [2]. GLUTs are encoded by *SLC2* genes, and SGLTs are encoded by *SLC5* genes [3]. The expression of these transports does not vary, and the capacity to reabsorb glucose is constant [3]. SGLT-2 (expressed in proximal tubule) is the major contributor to renal glucose reabsorption [3].

The incidence of renal glucosuria varies between 0.16% and 6.3%, depending on population and screening criteria [1]. There is no predilection for race or gender reported. Several studies describe this condition in younger patients [3, 5].

Glucosuria can be isolated (with normal serum glucose level), or it can be associated with other pathologies [6]. In the presence of glucosuria in children and adolescents, it is important to conduct an etiological study to exclude other conditions [7].

We report a case of isolated benign renal glucosuria in a healthy girl with *SLC5A2* mutation.

Case report

The authors describe a 6-year-old girl with follow-up in neurodevelopment consultation beginning at 2 years old due to expressive language delay, with normal remaining neurodevelopment, normal growth rate and no other relevant personal history. There was no relevant familiar history. At 5 years old, she presented with glucosuria (500 mg/dL), which was found accidentally. There were no other symptoms reported, and she was not taking any medication. Vital signs and physical examination were normal.

Tab. 1 shows blood tests' results of investigation of glucosuria; all tests presented normal values.

Table 1. Blood test results.

Laboratory test	Result
Fasting glucose	81 mg/dL
Urea	39 mg/dL
Creatinine	0.26 mg/dL
Sodium	139 mEq/L
Potassium	4.97 mEq/L
Chloride	104 mEq/L
Calcium	9.4 mg/dL
Phosphorus	5 mg/dL
Magnesium	2.66 mg/dL
Ceruloplasmin	27.5 mg/dL
Uric acid	2.5 mg/dL
pH	7.31
Bicarbonate	18.8 mmol/L
Glycosylated hemoglobin	5.2%

Dipstick test showed 3+ glucose, pH 5.5 and urinary density 1,013. Urinalysis showed a glucose level of 456 mg/dL, osmolality 835.6 mOsmol/kg, amino acids within normal range. Fractional excretion of potassium was 8.5%, sodium was 2%, phosphorus was 15.6%, and uric acid was 9.36% (all normal). Urine culture and renal/bladder ultrasound were normal.

Taking into account the normal results of blood and urine tests, the authors hypothesized that the cause of glucosuria was genetic and it was performed a sequencing of the patient's *SLC5A2* gene that showed a homozygotic missense mutation of c.619G>T that resulted in the replacement of a valine with a phenylalanine at position 207 (p.Val207Phe).

Discussion

Glucosuria can occur in different clinical settings: associated with other disorders like diabetes mellitus and proximal tubular dysfunction; transient in the context of trauma or renal infections; or it can be a benign condition [1, 3, 7].

In diabetes mellitus, patients have elevated blood fasting glucose levels and increased glycosylated hemoglobin concentration [3].

Proximal tubular dysfunction includes several disorders characterized by the presence of low-molecular-weight proteinuria, glucosuria, phosphaturia, aminoaciduria and proximal renal tubular acidosis [8]. Many of the causes are inherited disorders, but it can also be idiopathic or associated with drugs [3, 8].

To exclude the presence of underlying conditions, it is important to perform a urinalysis with microscopic analysis, fasting blood glucose levels, serum electrolyte, bicarbonate and uric acid levels, glycosylated hemoglobin, urinary amino acids and fractional excretion of phosphorus, sodium, potassium and uric acid [3].

In our patient, all the laboratory tests were normal, despite the presence of glucose in the urine, and so we were able to exclude any of these disorders, which made us hypothesize this could be a case of benign renal glucosuria.

Benign glucosuria patients have normal fasting blood glucose, and glycosylated hemoglobin levels and other tubular abnormalities are absent [3]. Usually, they do not have any symptoms or signs in the physical examination, and this is discovered in routine urinalysis or accidentally, as happened in this case [1, 3, 5]. Nonetheless, dehydration or ketosis during fasting periods or intensive exercise can occur, and some patients have enuresis or mild pubertal/growth delay [1, 5]. There are reports of increased incidence of urinary tract infections and selective aminoaciduria associated with this disease [3].

The inherited form is called Familiar Renal Glucosuria (FRG) [3]. This is a rare disorder caused by mutations in the *SLC5A2* gene (that encodes SGLT-2), which are responsible for the majority of cases [3, 5, 7].

To date, there are 86 mutations of the *SLC5A2* gene associated with FRG described in different patients [5]. It can be transmitted as an autosomal recessive or dominant mode, and mutations are primarily missense, frameshift, splicing and nonsense [4, 5]. In general, patients with nonsense or missense mutations have mild glucosuria [3]. Our patient had a homozygotic missense mutation of the *SLC5A2* gene that leads to mild glucosuria, which is in accordance with the literature; however, to our knowledge, our patient's mutation has not yet been described as the cause of FRG.

Mutations of the *SLC5A2* gene have not been associated with other clinical abnormalities such as hypoglycemia, diabetes mellitus or kidney disease [7]. The renal abnormality is specific to glucose and no other monosaccharides, though extra-renal abnormalities have been described in patients with *SLC5A2* mutations such as complex intellectual disabilities, epileptic seizures, motor abnormalities and autism spectrum disorders [3, 9, 10]. In this case report, the patient was followed up in neurodevelopment consultation only because of expressive language delay; no further development delay or neurologic symptoms were observed. Literature reports of neurodevelopment impairment associated with *SLC5A2* mutations and renal glucosuria had described parental consanguinity [10, 11], which can be a possible feature contributing to neurodevelopment disorders, which was not verified in our patient.

The long-term outcome of patients with FRG is good, with no recorded mortality [3, 12]. Renal and extra-renal complications are rare, and no specific treatment is needed [3, 7]. Patients should have a routine medical follow-up; they must be counseled to avoid prolonged fasting periods and avoid eating glucose or other carbohydrates when they have intensive physical activity [1, 3].

With this case report, the authors would like to alert to this entity and to highlight the importance of pediatric renal glucosuria management and differential diagnosis, excluding other pathologies that require immediate treatment and have different prognoses. On the other hand, it is important to achieve the diagnosis of FRG to prevent future investigations and laboratory tests in the same patient and to reassure caregivers that this is a benign condition with a good prognosis.

Declaration of interest

The Authors have no conflict of interests relevant to this article to disclose. No funding was secured for this study.

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