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FAMILIAL RENAL GLUCOSURIA PRESENTING AS PAROXYSMAL GLUCOSURIA AND HYPERCALCIURIA DUE TO A NOVEL *SLC5A2* HETEROZYGOUS VARIANT

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ABSTRACT

Familial renal glucosuria (FRG) is a rare genetic disease characterised by isolated glucosuria in the absence of proximal tubular dysfunction. It usually occurs due to a mutation in the *SLC5A2* gene encoding the sodium-glucose cotransporter-2 (SGLT2), responsible for most of the renal glucose reabsorption. We report on a case of a patient presenting with paroxysmal glucosuria and hypercalciuria due to a novel *SLC5A2* heterozygous variant.

KEYWORDS

Familial renal glucosuria, SLC5A2 variant

LEARNING POINTS

- FRG usually presents with glucosuria but may also be associated with hypercalciuria and aminoaciduria.
- The amount of glucosuria is variable and can be normal in the same FRG patient because it is influenced by different glycaemia levels. This raises the question of whether the definition of FRG should be broadened to paroxysmal glucosuria.
- Having glucosuria does not prevent the development of insulin resistance.

CASE DESCRIPTION

A 47-year-old man was seen at the nephrology consultation presenting with chronic kidney disease (CKD) and arterial hypertension. The patient had no complaints. In particular, he did not suffer from polyuria, polydipsia, asthenia, slow-healing wounds, blurred vision or weight change. With perindopril 5 mg once daily, his blood pressure was well controlled. Clinical examination was reassuring with normal cardiac and pulmonary auscultation and no signs of peripheral or central venous congestion.

Biochemically, his serum creatinine (1.30 mg/dl) had been stable over the previous 12 months.

A 24-hour urine collection showed a glucosuria of 6.5 g glucose per 24 hours, in the absence of diabetes mellitus (DM; normal fasting glycemia and haemoglobin A1C). There was also a hypercalciuria present of 12.28 mmol calcium per 24 hours in the absence of hypercalcaemia or hyperparathyroidism *(Tables 1 and 2)*. Renal ultrasound showed a normal size of both kidneys and normal corticomedullary differentiation. There were no abnormalities of the medulla and the

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parenchyma was homogeneous, in particular there were no signs of lithiasis.

Given the patient's glucosuria without DM, genetic analysis was performed. Massive parallel sequencing of the exome panel showed that the patient was heterozygous for the mutation c.656-1G>A in the *SLC5A2* gene, coding for sodium-glucose cotransporter (SGLT) type 2 (SGLT2). Thus, the patient was diagnosed with familial renal glucosuria (FRG).

To optimise blood pressure control and to correct the asymptomatic hypercalciuria, a thiazide diuretic was added to his treatment (indapamide 2.5 mg once daily). The patient then developed limited hyperphosphatemia and hypermagnesmia. After 3 years, his weight (83 kg) and BMI (24.4 kg/m^2) remained stable, but his fasting glycemia was elevated to 115 mg/dl (HbA1c 6.0%), consistent with prediabetes.

DISCUSSION

The differential diagnosis of glucosuria is broad because it can occur in various circumstances: without hyperglycemia, due to a dysfunction in the proximal convoluted tubule (PCT), or with a hyperglycemia which exceeds the renal glucose reabsorption threshold. The dysfunction in the PCT can be general, with multiple abnormalities in the urine or with isolated glucosuria when there is a genetic mutation in the proteins responsible for glucose reabsorption such as SGLT type 1 (SGLT1, glucose-galactose malabsorption syndrome), SGLT2 (FRG) and glucose transporter 2 (GLUT2, Fanconi-Bickel syndrome)[1].

The patient in our case was diagnosed with FRG because he had a normal fasting glycaemia with isolated glucosuria and a novel heterozygous mutation in the *SLC5A2* gene. This mutation was not previously described in mutation databases ClinVar or LitVar[2] and only once in the normal population database gnomAD v2.1.1. This is a splice variant mutation and presumably results in partial or total loss-of-function of SGLT2. The mutation was classified as class 4 (likely pathogenic) according to the American College of Medical Genetics guidelines[2].

FRG is a rare genetic disease with a prevalence of 0.29% in the general Caucasian population[3]. It is characterised by the presence of persistent isolated glucosuria in the absence of proximal tubular dysfunction. However, hypercalciuria or aminoaciduria may also be present but the physiological mechanism is not yet fully known[4]. FRG usually arises from an SGLT2 deficiency caused by a mutation in the *SLC5A2* coding gene, mostly missense mutations[3]. This gene is

Parameter	Result (reference interval)
Haemoglobin	15.4 g/dl (13.5 – 17.5)
White blood cells	3.4 10^9/l (3.9 – 10.6)
Thrombocytes	22210^9/l (150 – 400)
Transferrin saturation	22% (20 – 50)
Ferritin	119.5 µg/l (23.9 – 336.2)
Fasting glucose	96 mg/dl (74 – 106)
HbA1c	5.7% (4 – 6)
Creatinine	1.30 mg/dL (0.67 – 1.17)
eGFR (CKD-EPI)	65 ml/min/1.73m^2 (≥ 90)
Uric acid	5.8 mg/dl (3.5 – 7.2)
Sodium (Na)	138.0 mmol/l (136 – 146)
Potassium (K)	4.4 mmol/l (3.5 – 5.1)
Chloride (Cl)	102 mmol/l (101 – 109)
Bicarbonate	25.6 mmol/l (22 – 32)
Calcium (Ca)	2.49 mmol/l (2.15 – 2.58)
Albumin	48 g/l (35 – 52)
AST	21 U/l (≤ 50)
ALT	19 U/l (≤ 50)
Gamma GT	18 U/l (≤ 55)
ALP	29 U/l (30 – 120)

Parameter	Result (reference interval)
CK	125 U/l (≤ 171)
PTH	36 ng/l (12 – 88)
ASLO	44.0 IU/ml(≤ 200)
ANA	Negative
PLA2R autoantibodies	< 14 U/ml (≤ 14)
HBsAb	Negative
HBsAg	Negative
HBcAb	Negative
Aldosterone	11.7 ng/dl (1.8 – 23)
Renin	159.2 mIU/l (4.4 – 46.1)
Aldosterone/renin ratio	2.0
CH50	36.9 U/ml (36 70.7)
C3	1.25 g/l (0.9 – 1.8)
C4	0.33 g/l (0.1 – 0.4)
IgG	8.10 g/l (7 – 16)
IgA	1.35 g/l (0.7 – 4)
IgM	0.44 g/l (0.7 – 4)

Abbreviations: **ALP:** alkaline phosphatase, **ALT:** alanine transaminase, **ANA:** antinuclear antibody, **ASLO:** antistreptolysin O, **AST:** aspartate transaminase, **C3:** complement 3, **C4:** complement 4, **CH50:** complement activity, **CK:** creatinine kinase, **CKD-EPI:** Chronic Kidney Disease Epidemiology Collaboration formula, **eGFR:** estimated glomerular filtration rate, **gamma GT:** gamma glutamyl transferase, **HbA1c:** haemoglobin A1c, **HBcAb:** hepatitis B virus core antibody, **HBsAb:** hepatitis B virus surface antibody, **HBsAg:** hepatitis B virus surface antigen, **IgA:** immunoglobulin A, **IgG:** immunoglobulin G, **IgM:** immunoglobulin M, **PLA2R:** phospholipase A2 receptor, **PTH:** parathyroid hormone.

Table 1. Patient's blood values at presentation.

Parameter	Result (reference value)
Volume	2390 ml/24h (1000 – 1500)
Sodium (Na)	189 mmol/24h (40 – 220)
Potassium (K)	58 mmol/24h (25 – 125)
Chloride (Cl)	174 mmol/24h (110-250)
Calcium (Ca)	12.28 mmol/24h (2.5 – 7.5)
Phosphate (P)	28 mmol/24h (13 – 42)
Magnesium (Mg)	5 mmol/24h (3-5)
Ureum	26.3 mg/24h (26 – 43)
Uric acid	774 mg/24h (200 – 1000)
Protein	0.07 g/24h (0.04 – 0.15)
Cortisol free	4.56 µg/24h (≤ 51)
Albumin	3.82 mg/24h (≤ 30)
Urinary microscopy	1 red blood cell/µl (0 – 17), 1 white blood cell/µl (0 – 28). No cylinders, crystals or epithelial cells

Table 2. Patient's urine values of a 24-hour urine excretion at presentation.

located on chromosome 16p11.2 and consists of 2019 base pairs with 14 exons encoding 672 amino acids, forming 14 transmembrane helices. SGLT2 is mainly located in the S1 and S2 segments of the PCT and reabsorbs glucose by using the electrochemical Na^+ gradient created by the basolateral Na^+/K^+ ATPase pump. As a result, glucose and Na^+ move into the cell via secondary active transport. SGLT2 transports most of the glucose (90%, the so-called high-capacity cotransporter), but has a low affinity. SGLT1 transports a smaller proportion (10%, the so-called low-capacity cotransporter) in the S3 segment, but has a higher affinity[1].

The inheritance of FRG was initially thought to be autosomal dominant or recessive, however, based on cohort studies the inheritance was found to be co-dominant with incomplete penetrance[3]. Heterozygous patients would present with mild glucosuria and, in addition, there are discrepancies in the amount of glucosuria between siblings with the same mutation[1]. One explanation for this may be that different mutations and inheritance patterns affect the decrease in glucose reabsorption threshold differently. Glycaemia levels within the normal range can thus be below or above the new glucose reabsorption threshold and thus give no glucosuria, or a difference in the amount of glucosuria in the same patient[3]. This may explain the paroxysmal glucosuria in our case. Despite SGLT2 inhibition playing an important role in the treatment of type 2 DM, CKD and heart failure today, it does not address the causative pathophysiological mechanism of DM. Previous literature has already shown that FRG is not protective for DM[5]. This is compatible with our case. Nevertheless, FRG patients are still responsive to SGLT2 inhibitor treatment[5].

FRG is currently considered a benign inherited disorder without significant clinical consequences. It usually arises due to a mutation in *SLC5A2* (SGLT2 coding gene). It is inherited in a co-dominant manner and with incomplete penetrance. This case shows, as previously described, that FRG can also be associated with and that glucosuria can be missed due to fluctuating glycaemia levels[3,4]. Moreover, FRG patients are not protected against insulin resistance and may still benefit from treatment with SGLT2 inhibitors[5].

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