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Clinical Report

Hypouricaemia and hyperuricosuria in familial renal glucosuria

Inês Aires[1,2], Ana Rita Santos[1], Jorge Pratas[3], Fernando Nolasco[1] and Joaquim Calado[1,2]

[1]Department of Medicine and Nephrology, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa-Hospital de Curry Cabral, Lisboa, Portugal, [2]Department of Genetics, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Lisboa, Portugal and [3]Department of Nephrology, Hospitais Universitários de Coimbra, Coimbra, Portugal

Correspondence and offprint requests to: Joaquim Calado; E-mail: jcalado@fcm.unl.pt

Abstract

Familial renal glucosuria is a rare co-dominantly inherited benign phenotype characterized by the presence of glucose in the urine. It is caused by mutations in the *SLC5A2* gene that encodes SGLT2, the Na^+-glucose cotransporter responsible for the reabsorption of the bulk of glucose in the proximal tubule. We report a case of FRG displaying both severe glucosuria and renal hypouricaemia. We hypothesize that glucosuria can disrupt urate reabsorption in the proximal tubule, directly causing hyperuricosuria.

Keywords: glucose; kidney; SGLT2; urate

Background

Familial renal glucosuria (FRG) is characterized by the presence of glucose in the urine in the absence of diabetes *mellitus* or generalized proximal tubular dysfunction. Mutations in the *SLC5A2* gene, encoding SGLT2, are responsible for the large majority of FRG pedigrees [1, 2].

Recently, SGLT2 was targeted as an innovative strategy for the treatment of hyperglycaemia in type 2 diabetes *mellitus* (T2DM). One interesting and consistent observation with SGLT2 inhibitors is the almost dose-proportional decrease in serum uric acid levels [3, 4], which is paradoxical in light of the associated diuretic effect of these compounds.

In the current report, we describe an FRG individual with increased urate renal excretion and hypouricaemia, and discuss renal hypouricaemia in the setting of severe glucosuria.

Case report

This study was part of the medical evaluation for glucosuria in a 35-year-old female individual. She presented with a urinary glucose excretion (UGE) of 487.8 mmol (87.8 g)/1.73 m^2/24 h.

The clinical data are detailed in Table 1. She took no medications. Mutation analysis was performed as previously reported [6]. The *novel* c.1033–1060del; p.V346AfsX17 *frameshift* mutation was identified in homozygosity (Figure 1A).

Owing to persistent low serum uric acid levels [113.01 µmol/L (1.9 mg/dL)], further evaluation was performed in order to exclude Fanconi syndrome. Urinary urate values were found to be raised, with an excretion of 7.33 mmol (1242 mg)/1.73 m^2/24 h or 0.13 mmol (21.5 mg)/kg of body weight and a fractional excretion of 20%.

Phosphorus (urinary and serum), bicarbonate (plasma) and immunoglobulin light chains (urine) were all within normal range (data not shown). By high-performance liquid chromatography, cystine was the only amino acid over-excreted: 639.3 µmol (153.3 mg)/24 h (reference range: 0–158.5 µmol/24 h). This latter finding is characteristic of a type non-I heterozygous cystinuric individual [7]. Accordingly, the over-excretion of cystine was considered an incidental finding and unrelated to the glucosuric phenotype.

On follow-up the patient got pregnant. At gestational week 24, she was hyperfiltrating with a serum creatinine of 35.4 µmol/L (0.4 mg/dL), but there were no further decreases in urate serum levels [130.8 µmol/L (2.2 mg/dL)], compared with her earlier non-pregnant condition. Fractional excretion for urate was now 12%.

Discussion

Under physiological conditions, SGLT2 is responsible for reabsorbing the majority of the filtered glucose [8]. The p.V346AfsX17 *frameshift* mutation in our patient likely leads to a truncated protein between SGLT2 transmembrane domains 8 and 9 and, therefore, fully accounts for the severe glucosuria. However, the hyperuricosuria with hypouricaemia points out to an associated renal hypouricaemia.

The handling of urate by the kidney is complex, involving both secretion (inhibited by pyrazinamide) and reabsorption (inhibited by probenecid) [9]. The pregnancy of our patient precluded additional testing with any of these compounds. Pregnancy induces an increase in both the

Table 1. Phenotype evaluation of case

Age	Country of origin	Weight (kg)	Height (cm)	Glucose excretion mmol/1.73 m^2/24 h (g/1.73 m^2/24 h)	Serum glucose mmol/L (mg/dL)	HbA1c (%)	Serum creatinine μmol/L (mg/dL)	Serum uric acid μmol/L (mg/dL)	Urinary urate mmol/1.73 m^2/24 h Ref: 1.5–4.4 (mg/1.73 m^2/24 h)	mmol/kg [a]0.04 ± 0.01 (mg/kg)	Fractional excretion [a]10%
35	Portugal	65	167	487.8 (87.8)	4.1 (74)	5.4	53 (0.6)	113.01 (1.9)	7.33 (1242)	0.13 (21.5)	20

Ref, reference range for urinary urate.
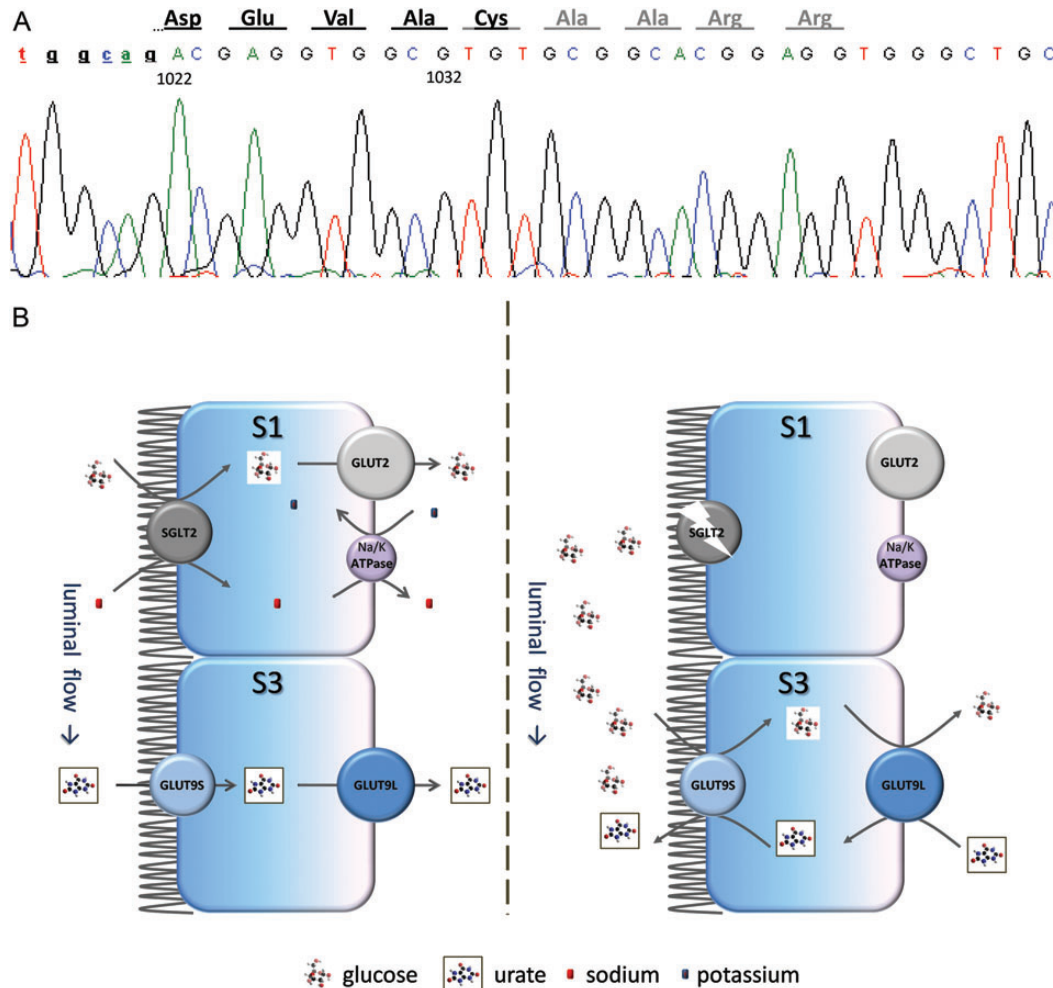[a]Values detail average (and standard deviation when specified) in an adult population [5].

Fig. 1. (**A**) The c.1033–1060del mutation. The splice acceptor site for intron 8 is included (small caps). Nucleotides are numbered according to the *SLC5A2* cDNA accession number NM_003041. The wild-type amino acid sequence is represented in black; in light gray, the new ORF. (**B**) Suggested mechanism for the renal hypouricaemia associated with defects of SGLT2. In the presence of normally functioning SGLT2 (left side) all the glucose is reabsorbed in the early segment (S1) of the proximal tubule, while in the late S3 segment GLUT9 is normally reabsorbing urate. If SGLT2 is disrupted (right side), either by genetic defects or pharmacological inhibition, the presence of significant amounts of glucose in the late segments of the proximal tubule reverses the direction of urate transport, with GLUT9 exchanging luminal glucose for intracellular urate and actively promoting urate secretion.

urate glomerular filtration and in its tubular reabsorption, with proportionally greater increments observed with the former and, hence, the lowering of serum urate usually observed in the first 24 gestational weeks [10]. Since our case did not display such a decrease in serum levels (and even improved its fractional excretion) with pregnancy, we can assume the urinary urate over-excretion seen with glucosuria to be a consequence of enhanced secretion rather than impaired reabsorption. Two solute carriers that reabsorb urate are known to be expressed in the proximal tubule, URAT1 (*SLC22A2*), the target of probenecid, and GLUT9 (*SLC2A9*), mutations of which are responsible for an isolated renal hypouricaemic phenotype [11, 12]. Interestingly, GLUT9 was also shown to exchange extracellular glucose for intracellular urate [13]. Two GLUT9 isoforms, GLUT9S (expressed at the apical side) and GLUT9L (at the basolateral side), act concertedly to reabsorb uric acid from the glomerular filtrate. We can hypothesize that

in the presence of a high glucose concentration in the late proximal tubular lumen, the direction of urate transport could be reversed, with glucose being exchanged for urate and leading to excessive urinary excretion and secondary hypouricaemia (Figure 1B).

To our knowledge, only one report addressed the urinary urate excretion in FRG [14]. All six individuals were homozygous for the p.K321R mutation, had a UGE of 460.7–938.1 mmol (83–169 g)/1.73 m^2/24 h and displayed generalized aminoaciduria. In one case, uricosuria was within the upper limit of the reference range. Although we have not pharmacologically detailed the involved pathway or screened our patient for mutations in URAT1 and GLUT9, our findings are in line with previous reports describing renal hypouricaemia in cases of hyperglycaemia induced glucosuria. Not only in T2DM [15], but also in maturity-onset diabetes of the young (MODY) [16], in particular, in HNF1α-mutated cases (MODY3), who are characterized by a paradoxically low renal threshold for glucose and, therefore, exceptional glucosuria [17].

This characterization of renal hypouricaemia as an incompletely penetrant feature of FRG needs confirmation by similar observations in other patients with severe forms of FRG. If replicated, this will argue for glucosuria being directly responsible for the disruption of urate transport in the proximal tubule and renal hypouricaemia in FRG as well with pharmacological inhibition of SGLT2.

Conflict of interest statement. None declared.

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