NOVEL MUTATION ON SLC5A2 GENE CAUSING FAMILIAL RENAL GLUCOSURIA IN A PATIENT WITH HYPOKALEMIC PERIODIC PARALYSIS TYPE 2

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ABSTRACT Introduction: Glucosuria is usually a red flag leading to diabetes mellitus screening in pediatric patients. Despite this correct approach, high levels of glucosuria without hyperglycemia should raise suspicion for other diagnoses, namely renal tubular disease, such as Familial Renal Glucosuria (FRG). A large number of mutations on the solute carrier family 5 member 2 (SLC5A2) gene, which encodes sodium-glucose cotransporter 2 (SGLT2), have been reported to be responsible for the increase in renal excretion of glucose. (1) **Case Report:** We report a case of a teenager, followed in our outpatient clinic for Hypokalemic Periodic Paralysis type 2 (HyPP2), in which persistent renal glucosuria was fortuitously found. Genetic testing for the SLC5A2 gene was conducted, leading to the identification of two mutations in the SGLT2 gene, both in heterozygosity, one in exon 14 (N654S), previously reported, and another in exon 2 (A94C), a novel mutation not yet described in population databases. **Discussion:** The fact that our patient had mutations in two genes from different chromosomes related to sodium channels and one of these not previously described makes this case interesting. The key point is that it is important to be aware of these diseases and assess the child as a whole. Despite the apparent benignity of these two diseases, clinical surveillance must be tight. We advise avoiding prolonged fasting, a carbohydrate-rich diet, and intense physical exercise. **Conclusion:** Without hyperglycemia, we should suspect Familial Renal Glucosuria in the presence of isolated glucosuria. Familial Renal Glucosuria is a rare disease caused by a mutation in the SGLT2 gene. Exon 2 (A94C) in heterozygosity is a novel mutation not yet described in population databases. This is the first description of a patient with both Familial Renal Glucosuria and Hipokalemic periodic paralysis type 2. The association of both these diseases had not yet been reported.

KEYWORDS Hypokalemic Periodic Paralysis type 2, renal glucosuria, Familial Renal Glucosuria, novel mutation

Introduction

Familial Renal Glucosuria (FRG) (PRG; OMIM #233100) occurs in about 0.29% of the general population, but its prevalence depends on the diagnostic criteria used. The revised criteria for diagnosis of this condition include a normal oral glucose tolerance test in regard to plasma glucose concentration, normal plasma levels of insulin, free fatty acids, glycosylated haemoglobin, and relatively stable urinary glucose levels (10 to 100 g/d, except during pregnancy, when it may increase) with glucose present in all urine samples. The urine should contain glucose as the only source of carbohydrates, and individuals should have normal carbohydrate storage and use. It is an inherited renal disease that affects males and females equally, impairing the kidney's ability

DOI:10.5455/IJMRCR.172-1683128127
First Received: May 3, 2023
Accepted: May 27, 2023
Associate Editor: Ivan Inkov (BG)
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to reabsorb excreted glucose, resulting in persistent glucosuria in the absence of hyperglycemia. (1,2) The glomerulus filters glucose and more than 99% reabsorbed within the proximal tubule through a sophisticated coupling of luminal secondary active glucose transporters, such as sodium-glucose cotransporter 1 (SGLT1) and sodium-glucose cotransporter 2 (SGLT2), with basolateral passive glucose transporters, such as GLUT2. All known cases of FRG are due to mutation on the SLC5A2 gene that encodes the SGLT2 cotransporter. These mutations cause an altered function of SGLT2, leading to isolated renal glucosuria, normal blood glucose levels and no other impaired tubular functions. Glucosuria in these patients can range from <1 to >150 g/1.73 m2 per d. (2) We report a case of a teenage boy that presents in the emergency department with muscle weakness, hypokalemia and glucosuria. After investigation, it is diagnosed with Hypokalemic Periodic Paralysis type 2 (HyPP2) and FRG. Besides genetic mutation on the SCN4A gene, he also has two mutations in the SGLT2 gene, both in heterozygosity, one in exon 14 (N654S), previously reported, and another in exon 2 (A94C), a novel mutation not yet described in population databases. To date, no association between these two diseases has been described. This uncommon association is the center of discussion in this case report.

Case report

We present a case of a 14-year-old Caucasian boy, previously healthy, with past familial history of an uncle and a great-uncle with "weakness episodes", that showed up in the emergency department with a paralytic episode characterized of decrease muscle tone (flaccidity) and bilateral and symmetric ascending paralysis of both lower and upper limbs with concomitant hypokalemia (2.35 mEq/L) after intense physical exercise the day before. He denied other symptoms and similar previous episodes. Physical examination revealed decreased strength of the upper and lower limbs, especially in the arms and thighs and decreased deep tendon reflexes. The remaining physical examination, including blood pressure, were normal. Admission electrocardiogram showed sinus rhythm with flattened t-waves. Besides hypokalemia, the initial investigation revealed glucosuria in the urine dipstick analysis (glucose level 854 mg/dL with 1049 osmolarity, range 300-900 and protein-creatinine ratio 0,11) in the absence of other urine abnormalities or hyperglycemia. Several urine analyses were performed during hospitalization, all revealing glucosuria. No alterations in blood count, renal function, thyroid function, calcium, phosphorus, magnesium and venous blood gas were observed. The patient was treated with intravenous potassium, with a resolution of symptoms and serum potassium correction. After stabilization, further investigation was made, and a genetic test found a c.2015G>A (p.(Arg672His) exon 12 mutation on the SCN4A gene confirmed the diagnosis of Hypokalemic Periodic Paralysis Type 2 (HyPP2).

Towards a persistent isolated renal glucosuria and to exclude other tubulopathies, 24-hour urine was performed, revealing 3.015 g of glucose and normal levels of proteins, albumin, creatinine, urea, uric acid, calcium, phosphorus, magnesium, oxalate, citrate and amino acids. Laboratory analysis also revealed normal values of fasting glucose levels, glycated haemoglobin (HbA1C 5%), fasting insulin, oral glucose tolerance test and free fatty acids. Towards this persistent glucosuria with no other abnormalities, we suspected Familial Renal Glucosuria (FRG). A genetic test revealed two heterozygous mutations at the SGLT2 gene, both in heterozygosity, one in exon 14 (N654S) and another in exon 2 (A94C). Exon 14 (N65AS) is a rare but well-documented mutation that represents 0.6% of all the described alleles and is associated with renal glucosuria. On the other hand, exon 2 (A94C), on the second cytoplasmatic domain, is a novel mutation not previously described, affecting highly conserved residues in the orthologues (A94). The mother and brother were screened with a urine test that did not reveal glucosuria. Unfortunately, we were unable to study the father.

Four months after being discharged, the patient was hospitalized with a hypokalemic crisis after eating a high-carbohydrate meal. Since then, he has been followed for 4 years and maintains persistent glucosuria (from 40-100 mg/dL to >750 mg/dL) in urine samples. He had no more hospitalizations, and no treatment was needed. Because of HyPP2, he currently avoids heavy exercise, fasting and high-carbohydrate meals.

Discussion

FRG it's a challenging diagnosis since most patients have no symptoms, and the diagnosis is often made after detecting isolated glucosuria in an occasional urinalysis.

In this case, the patient presented to the emergency department with a paralytic episode and hypokalemia. A urine test was performed to exclude renal disease, and renal glucosuria was detected during the investigation. Glucosuria is an elevation of urinary glucose levels, and its mechanisms depend on renal glucose filtration and reabsorption. The most frequent cause of glucosuria is diabetes, so our first concern was to exclude hyperglycemia.

In normal conditions, the kidney contributes to glucose homeostasis by reabsorbing approximately 180 g of glucose from the glomerular filtrate daily. Because of the activity of glucose transporters in the renal proximal tubule, roughly 0.5 g/day (range 0.03 to 0.3 g/day) is excreted in the urine of healthy adults. (5) In diabetes mellitus, the high plasma glucose concentration exceeds the maximum renal reabsorption capacity, increasing urinary glucose excretion. In renal glucosuria, glucose reabsorption is impaired despite normal blood glucose and glomerular filtration rate. (6)

Renal glucosuria can occur by mutations in four members of two glucose transporter families, SGLT1, SGLT2, GLUT1 and GLUT2, which are expressed in the kidney, and three of them be necessary for normal glucose reabsorption from the glomerular filtrate. Mutations in SGLT1 are associated with glucose-galactose malabsorption, SGLT2 with familial renal glucosuria (FRG), and GLUT2 with Fanconi-Bickel syndrome. There are two forms of glucose transport: facilitative and secondary active. The concentration gradient across cellular membranes drives facilitative transport, occurs in essentially all cell types and is mediated by members of the GLUT transporter family. Secondary active transport is the first step in transcellular glucose transport in the intestine and kidneys and is mediated by members of the SGLT transporter family. The SLC2 genes encode GLUTs, whereas SGLTs are encoded by the SLC5 genes. In the early proximal tubule or S1 segment of the proximal tubule, the low affinity, high-capacity transporter SGLT2, with sodium-to-glucose coupling 1:1, reabsorbs the bulk of the filtered glucose. In the late proximal tubule or S2 segment of the proximal tubule, the high affinity, low-capacity transporter SGLT1, with the sodium-to-glucose coupling of 1:2, nearly completes the reabsorption of glucose, removing practically all of the glucose from the urine. (1,7) SGLT1 and SGLT2 are important in the kidney's apical membrane of proximal tubular cells (Figure 1). There are >220

members in the SLC5 family, also known as the sodium substrate symporter gene family (SSSF). Of these, 12 have been identified in the human genome. For example, the SGLT2 gene is mapped to chromosome 16p11.2. The first report of such a gene mutation was in 2000. The mode of inheritance that best fits FRG has been suggested to be co-dominance with incomplete penetrance. Some authors defend that the type of mutation determines the severity of glucosuria. Santer et al. (2) found that all patients with SGLT2 mutations in both alleles showed severe glucosuria ($\geq$10 g/1.73 m2 per day), whereas patients with single heterozygous mutations showed mild glucosuria (<10 g/1.73 m2 per day). Lee et al. (8) found that patients with two mutations showed larger amounts of glucosuria than those with one mutation. In addition, they confirmed that although the FRG inheritance pattern appeared variable, it can be explained as a codominant trait with variable penetrance as a whole. In our case, the patient presented two mutations in heterozygosity and mild glucosuria.

Unfortunately, we could not complete the family study to confirm heritability in this case report. Nevertheless, we emphasize that several cases are described in the literature, but until now, none have evidenced this novel mutation in exon 2 (A94C). We also highlight that for the correct diagnosis of FRG, glucosuria should be quantified by a 24-hour urine collection and confirmed by genetic testing after excluding other causes of glucosuria, such as diabetes mellitus and other tubulopathies. FRG is considered a benign condition that is not a disease but a phenotype. Some authors speculate that carrying SGLT2 mutations is potentially beneficial in that persistent renal loss of glucose and sodium may result in a blood pressure lowering and weight control (calorie loss) effect. (8) In recent years, SGLT2 has been studied as a therapeutic target for type 2 diabetes mellitus. (2)

Our patient had the particularity of also having HyPP2. HyPP2 is a muscle channelopathy with an estimated prevalence of 1 in 100,000 individuals, with an onset in the first or second decade of life. It is characterized by painless muscle weakness episodes with normal to decreased deep tendon reflexes and with concomitant hypokalemia (serum potassium <3.5 mmol/L), which may be precipitated by heavy exercise, fasting, or high carbohydrate meals. Additional triggers include cold, stress/excitement/fear, salt intake, prolonged immobility, use of neurosteroids or alcohol, and anaesthetic procedures. The episodes develop over minutes to hours, lasting several minutes to several days with spontaneous recovery. The disorder is three to four times more commonly clinically expressed in men. (3,5)

HyPP2 can be divided into two forms, which are familial and sporadic. Most cases of HyPP2 are hereditary, usually with an autosomal dominant inheritance pattern. Approximately one-third of cases represent new mutations. The two genes associated with hyPP2 are CACNA1S and SCN4A. SCN4A is located on chromosome 17q23–25 and encodes the skeletal muscle sodium channel protein type 4 subunit alpha activated by membrane depolarization and is responsible for the upstroke of the action potential. It, therefore, plays a crucial role in muscle contraction, allowing a proper propagation of the action potential along the muscle membrane. Pathogenic variants in SCN4A cause HyPP2 within the voltage-sensitive segment S4 of domain II of the sodium channel alpha subunit. Disease-causing variants change positively charged arginine to non-charged amino acid residues enhancing fast and/or slow inactivation and reducing current density. (4)

The treatment of HyPP2 depends on the level of potassium deficit and the severity of the weakness; however, crisis prevention relies on a diet low in sodium and carbohydrate and rich in potassium and recognising symptoms. (4) The c.2015G>A (p.(Arg672His) exon 12 mutation at the SCN4A gene is benign and does not need treatment. The fact that our patient had mutations in two genes from different chromosomes, both related to sodium channels and one of these not previously described, makes this case interesting. The key point is that it is important to be aware of these diseases and assess the child. Despite the apparent benignity of these two diseases, clinical surveillance must be tight. We advise avoiding prolonged fasting, a carbohydrate-rich diet, and intense physical exercise.

Conclusion

Without hyperglycemia, we should suspect Familial Renal Glucosuria in the presence of isolated glucosuria. Familial Renal Glucosuria is a rare disease caused by a mutation in the SGLT2 gene. Exon 2 (A94C) in heterozygosity is a novel mutation not yet described in population databases. This is the first description of a patient with both Familial Renal Glucosuria and Hipokalemic periodic paralysis type 2. The association of both these diseases had not yet been reported.

Author's contribution:

Joana Moscoso, Joana Gonçalves: original draft conceptualization and design, manuscript writing. Paula Nunes and Sara Marcos: manuscript editing and review. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict or competing interests.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

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