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CASE REPORT

Heterozygous mutation in *SLC36A2* gene causing hyperglycinuria and nephrolithiasis

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ABSTRACT

Background: Childhood nephrolithiasis cases reported worldwide has been increasing over the last decade. The majority of the cases reported are related to calcium oxalate formation which results in impairment of glycine transport in the renal tubule leading to hyperglycinuria and impaired urinary oxalate excretion with resultant nephrolithiasis.

Case Presentation: A 4-year-old boy was presented with oxalate nephrolithiasis and hyperglycinuria. Molecular testing confirmed a c.448G > A p. (Val150Met) mutation of heterozygous status in *SLC36A2* gene.

Conclusion: The likelihood of cases being reported with renal hyperglycinuria along with oxalate nephrolithiasis is very rare. The present study reports a patient presented with oxalate nephrolithiasis, hyperglycinuria, and a molecular confirmation for a heterozygous c.448G > A p. (Val150Met) mutation in *SLC36A2* gene.

Keywords: Children, case report, hyperglycinuria, nephrolithiasis, oxalate stone, *SLC36A2*.

Introduction

Nephrolithiasis in children is quite rare. However, understanding its underlying causes is critically important for effective management and identification of risk factors associated with its recurrence (1). In children, 40%–50% of cases reported are associated with an identifiable metabolic abnormality (2). Calcium oxalate represents the common form of nephrolithiasis (40%–65%), while 14%–30% of the cases are associated with calcium phosphate, in addition to other existing rare forms (2,3). Oxalate is a metabolic end product of glycine, ascorbic acid, and few other amino acids. It is primarily excreted by the kidneys (1). The relationship between oxalate renal stones and hyperglycinuria were well discussed previously (4,5). Hyperglycinuria (HG) (OMIM# 138500) is a rare amino acid transport defect that occurs due to impairment of glycine transport in the renal tubules. HG is usually considered as a normal finding in neonates and infants <6 months (6). HG is generally presented in two forms either isolated or associated with proline and hydroxyproline excretion [Iminoglycinuria (IG)] as they share the same renal tubular reabsorption mechanism (7). Despite the benign nature of inborn errors observed in amino acid transport, the presentation of IG and HG has wide features associated with nephrolithiasis (4). Familial IG and HG phenotypes are characterized by genetic complexity as previously reported cases were linked to mutations in many genes encoding amino acid transporters, including *SLC36A2*, *SLC6A20*, *SLC6A18*, *SLC6A19*, and *SLC36A1* (8,9). When the cases reported with *SLC36A2* mutation are considered (the common high-capacity proline and glycine transporter), the homozygous patients are found to show IG. Interestingly, few heterozygote patients show HG only, whereas some other cases neither showed HG, not IG (9).

The incidence of renal hyperglycinuria with oxalate nephrolithiasis is exceptionally rare (4). In this study, we report two patients from the same family with oxalate nephrolithiasis with variable age presentation that was associated with a variable degree of HG due to a heterozygous mutation in *SLC36A2* gene in both cases. To best of our knowledge, this is the first time, a heterozygous mutation in SLC36A2 is being associated with oxalate nephrolithiasis.

Case Report

A 4-year-old boy (Saudi) was presented with renal stones and hyperglycinuria. Born of a consanguineous marriage

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the patient had a remarkable family history of renal stones among paternal side family members (Figure 1). His medical history showed the development of dysuria at 2 years of age and urine retention. Even though proper care and treatment were provided, the symptoms recurred after 10 months, and he further developed bilateral renal stones. He underwent cystoscopy and ureteroscopy twice. At the time of assessment, his development milestones were appropriate to his age. He was not taking any medication and blood pressure was normal. On examination, his growth parameters, height, weight, and head circumference were at 50th Percentile for age and sex. There were no apparent dysmorphic features and had normal findings for systemic examination. Abdominal X-ray showed two radiopaque densities projecting over the left renal silhouette. Renal ultrasound scan showed the left kidney of normal size measuring 7.6 cm in long axis with multiple echogenic stones noted in mid and lower calyces of the left kidney. The largest stone measured 6 mm, with no evidence of hydronephrosis, and a normal right kidney. Further biochemical investigations showed normal calcium, 25-OH Vitamin D, and Parathyroid hormone levels. The 24 hours urine collection were normal, including oxalate 0.06 (0.14–0.42 mmol/day in children). The stone analysis revealed 60% calcium oxalate monohydrate, 20% calcium oxalate dihydrate, and 20% triglycerides. Urine amino acid showed increased glycine 511 (91–264 µM/mM creatinine) and decreased cysteine 3 (4–11 µM/mM creatinine), with normal levels for proline 0 (<9 µM/mM creatinine) and hydroxyproline 10 (<13 µM/mM creatinine). The patient's father was 33-year old, diagnosed with renal stones 2 years ago. His renal functions remain stable, where the urine analysis was normal, and random urine amino acid showed glycine in upper normal range 137 (43–173 µM/mM creatinine), and normal levels for another amino acid.

Molecular analysis performed using whole exome sequencing detected the *SLC36A2* variant c.448G > A p.(Val150Met), which was further confirmed using Sanger sequencing. The variant found has not been previously reported in any of the large-scale exome sequencing databases, including dbSNP/1000 genome or Exome Sequencing Project. Moreover, this variant is absent in 1,500 ethnically matched controls accessed in the local database and was predicted to be deleterious by major online prediction tools (PolyPhen, SIFT, and Mutation Taster). Segregation analysis for mutation among the parents revealed the presence of the same variant in the father who had a history of renal stone, and negative in the mother.

Discussion

Glycine and other amino acid concentrations levels in the body are maintained through reabsorption and absorption process carried out by the proximal tubule and intestinal brush border epithelium, respectively. This process is controlled by cellular transport mechanism also known as IMINO system (10,11). The genetic causes of IG/

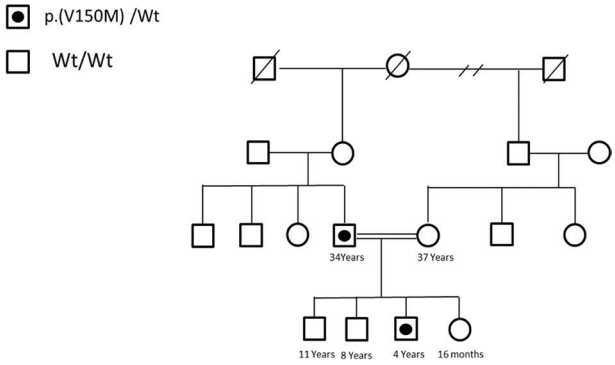

Figure 1. *Family pedigree.*

HG have remained obscure since its first description 50 years ago (5). However, in the previous decade, the reabsorption of the imino acids, proline, hydroxyproline, and glycine, from the glomerular filtrate was linked to at least two common tubular transporter agency, namely, Proton-coupled amino acid transporter 1 (PAT1) and Proton-coupled amino acid transporter 2 (PAT2) which are encoded by *SLC36A1* and *SLC36A2* genes, respectively (12,13). These two transporters are different in their substrate affinity. The *SLC36A1* has low-affinity transporter, while *SLC36A2* has a high-affinity transporter (14). *SLC36A2* is a member of the solute carrier (SLC) 36 family, that are involved in trans membrane movement of amino acids, and their derivatives remain expressed at the apical surface of the human renal proximal tubule. Specifically, within the S1 segment of the most proximal part of the convoluted tubule adjacent to the glomerulus. It is majorly involved in the reabsorption of glycine, proline, and hydroxyproline (15). In the previous cases reporting genetic complexity in pedigrees, the IG was observed only in the presence of mutations in both *SLC36A2* and *SLC6A20*. Partial inactivation of *SLC36A2* alone did not cause IG. HG was observed in some previous cases reported with heterozygote genotype (9). This could be explained by the fact that mutations in *SLC36A2* are not sufficient to cause HG alone and result in causing IG only in combination with more severe mutations or gene modifiers (9,12). This might be a reason for the absence of HG in the father of the case studied.

Conclusion

In conclusion, renal stones of calcium oxalate in the patients with HG developed were reported with a variable time of onset from childhood to adulthood. Although no genetic association was provided among similar cases reported previously, herein, we report a rare case of a young child who was presented with oxalate nephrolithiasis and HG. The molecular testing confirmed a genetic variant in the *SLC36A2* gene running through the family in an autosomal dominant inheritance pattern which could be attributed as a possible causative factor for HG presented by the individual.

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The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript**.**

Consent for publication
Informed consent was obtained from the parents.

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