Idiopathic renal hypouricemia: A case report and literature review

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Abstract. Idiopathic renal hypouricemia is a rare hereditary condition. Type 2 renal hyperuricemia (RHUC2) is caused by a mutation in the SLC2A9 gene, which encodes a high-capacity glucose and urate transporter, glucose transporter (GLUT)9. RHUC2 predisposes to exercise-induced acute renal failure (EIARF) and nephrolithiasis, which is caused by a defect in renal tubular urate transport and is characterized by increased clearance of renal uric acid. In the present study a case of a 35-year-old Chinese man with EIARF is reported. The patient had isolated renal hypouricemia, with a serum uric acid level of 21 μmol/l and a fractional excretion of uric acid of 200%. The mutational analysis revealed a homozygous mutation (c.857G>A in exon 8) in the SLC2A9 gene. The patient's family members carried the same mutation, but were heterozygous and clinically asymptomatic. In conclusion, to the best of our knowledge, this is the first report of a RHUC2 patient with a GLUT9 mutation, p.W286X, which may be a pathogenic mutation of RHUC2. Further investigation into the functional role of GLUT9 in this novel SLC2A9 mutation is required.

Introduction

Hypouricemia is defined as a serum urate concentration of <119 μmol/l (2 mg/dl). Hypouricemia may be due to decreased uric acid production, defective renal tubular reabsorption caused by inherited or acquired disorders, or uric acid oxidation caused by treatment with uricase (1). The kidney is an important regulator of uric acid homeostasis, as urinary uric acid excretion normally accounts for 2/3 of the daily uric acid clearance. The uric metabolism is consistent with a four-step model for renal urate handling, comprising glomerular filtration, pre-secretion reabsorption, secretion and post-secretion reabsorption (2), with the latter three steps occurring in the proximal tubules, where urate is bidirectionally transported. As a result, ~10% of the filtered load of urate is excreted in the urine (3).

Idiopathic renal hypouricemia (iRHUC) is a rare hereditary disease caused by impaired uric acid transport, reabsorption insufficiency and/or secretion acceleration (4,5). There are two types of RHUC: Type 1 (RHUC1), which is caused by a mutation in the SLC22A12 gene that encodes a renal urate-anion exchanger, URAT1 (4,5); whereas type 2 (RHUC2) was previously found to be caused by a defect in the SLC2A9 gene, which encodes a high-capacity glucose and urate transporter, named glucose transporter (GLUT)9 (6). The majority of patients with iRHUC are clinically asymptomatic. However, patients with homozygous SLC2A9 mutations may present with nephrolithiasis, hematuria or exercise-induced acute kidney injury (EIAKI) (7), accompanied by homozygous loss-of-function mutations of GLUT9 and a resultant total defect of uric acid absorption.

The diagnosis of iRHUC is based on hypouricemia (<119 μmol/l or 2.0 mg/dl) and increased fractional excretion of uric acid (FE-UA) of >10%, without evidence of secondary causes of hypouricemia. The diagnosis can be confirmed by molecular analysis of the mutations in the SCL22A12 and/or SLC2A9 genes.

Over 100 cases with SLC22A12 mutations and ~20 cases with SLC2A9 defects, summarized in a Chinese literature review (8), have been reported to date worldwide. These patients exhibited common characteristics, including affected family members with inherited renal tubular defects resulting in hypouricemia, increased urinary excretion of urate, susceptibility to EIAKI and chronic renal dysfunction (9). The present study describes the case of a patient with iRHUC who presented with EIAKI and had a homozygous mutation c.857G>A in exon 8 of the SLC2A9 gene.

Case report

A 35-year-old young man with unremarkable medical history was admitted to the Nephrology Department of Shenzhen Hospital, Southern Medical University on May 23, 2018. The patient complained of nausea, vomiting and abdominal pain for 3 days after strenuous exercise, but without oliguria, hematuria or myalgia. The physical examination was performed and vital signs were normal. The laboratory tests revealed increased

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levels of urea (67.76 mg/dl) and creatinine (11.86 mg/dl), but a normal uric acid level at 265 µmol/l (1 mg=59.5 µmol/l; Table I). Therefore, the patient was diagnosed with AKI and was started on hemodialysis.

A total of two family members of the patient had uremia (Fig. 1) and required long-term renal replacement therapy, but without any evident causes of renal insufficiency. The patient’s family history included consanguineous parents (cousins), whereas both parents had nephrolithiasis; the proband had one healthy brother. On serum UA level screening, the proband’s parents, younger brother and son all had normal serum urate levels.

FE-UA was 200% of the normal reference range of 8.3 (5.5-11.1)%). Renal ultrasound revealed hyperechogenic kidneys, without detection of stones (Fig. 2). Due to the deterioration of renal function, the patient received hemodialysis treatment for 2 weeks, starting on the 2nd day after hospitalization; subsequently, a renal biopsy was performed.

Histological analysis (Fig. 3) revealed normal glomeruli and arterioles, patchy or diffuse denudation and vacuolar degeneration in the renal tubular cells with loss of the brush border, accompanied by interstitial edema. Immunofluorescence showed traces of C3; however, C4, immunoglobulin (Ig)A, IgG, IgM and fibrinogen (Fib) were all negative.

The patient was advised to avoid physical exertion and increase his fluid intake. One month after his discharge from the hospital, his uric acid level was 18 µmol/l, with improved renal function (blood urea nitrogen level: 12.3 mg/dl and serum creatinine: 1.2 mg/dl; Table I), suggesting recovery of the kidneys from acute tubular necrosis (ATN).

A SLC2A9 homozygous mutation was identified (Figs. 4 and 5), namely 857G>A (p.W286X; nucleotide number 857 in the coding region is mutated from guanine to adenine), resulting in amino acid changes. The variation in the normal population database frequency is 0.00020. It was verified that the patient’s family (his father, mother, younger brother and son) were heterozygous for this site, which is a suspected pathogenic mutation (Table II).

Sequence analysis of the SLC22A12 and SLC2A9 genes was performed in the patient and his family members (his father, mother, brother, son and nephew) by Beijing MyGenostics, Co., Ltd. Briefly, the detection process was as follows: i) DNA extraction and next generation sequencing library preparation: Genomic DNA was extracted from whole blood using the QIAamp DNA Mini kit (180134; Qiagen, Inc.) following the manufacturer’s protocol. ii) Targeted gene capture: Next, genes associated with renal hypouricemia and other hereditary nephropathy-related diseases were selected by a gene capture strategy, using the GenCap custom enrichment kit (MyGenostics Inc.) following the manufacturer’s protocol. iii) Sequencing: The enriched libraries were sequenced on an Illumina HiSeq 2000 sequencer (Illumina, Inc.) for paired-end reads of 150 bp. iv) Data analysis and determination of gene pathogenicity.

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Table I. Laboratory results of the proband.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 5.23</th>
<th>Day 5.31</th>
<th>Day 6.02</th>
<th>Day 6.15</th>
<th>Day 7.16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>67.76</td>
<td>40.6</td>
<td>37.52</td>
<td>21.8</td>
<td>12.3</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>11.86</td>
<td>8.59</td>
<td>6.40</td>
<td>2.22</td>
<td>1.20</td>
</tr>
<tr>
<td>Uric acid (umol/l)</td>
<td>265</td>
<td>105</td>
<td>44.5</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Sodium (mmol/l)</td>
<td>138.2</td>
<td>139.6</td>
<td>142.2</td>
<td>141.5</td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/l)</td>
<td>3.84</td>
<td>4.39</td>
<td>4.19</td>
<td>3.92</td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>1.98</td>
<td>2.18</td>
<td>2.4</td>
<td>2.42</td>
<td></td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>2.24</td>
<td></td>
<td>1.15</td>
<td>1.10</td>
<td></td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>41.2</td>
<td></td>
<td>45.6</td>
<td>48.7</td>
<td></td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>36</td>
<td></td>
<td>35</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>26</td>
<td></td>
<td>24</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>310.1</td>
<td></td>
<td>87.49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serum urate levels (1 mg/dl is equivalent to 59.5 µmol/l); Serum urate levels normal range: Man: 149-416 µmol/l (2.5-7.0 mg/dl); woman: 89-357 µmol/l (1.5-6.0 mg/dl). aInitiation of dialysis. bDay of renal biopsy. ALT, alanine aminotransferase; AST, aspartate aminotransferase; PTH, parathyroid hormone.
v) Validation by Sanger Sequencing: All mutations identified by HiSeq 2000 sequencing were confirmed by Sanger sequencing.

Discussion

Increased urinary excretion of uric acid may be observed in patients with familial hypouricemia (an inherited disorder) and in association with a variety of acquired conditions. Hereditary hypouricemia may be complicated by nephrolithiasis and E1ARF. A total of two types of uric acid transport proteins, uric acid transporter 1 (URAT1) and GLUT9, expressed in the gut as well as the kidney, regulate serum urate levels (4‑6). Previous studies have reported cases of patients with hypouricemia due to loss‑of‑function mutations of the URAT1 gene (4,9). Furthermore, several studies also reported that loss‑of‑function mutations in the SLC2A9 gene (encoding GLUT9) also cause hypouricemia (6‑8,10).

Familial hypouricemia, also referred to as iRHU, is caused by a defect in renal tubular urate transport. The majority of iRHU cases are caused by a mutation in the SLC22A12 gene that encodes URAT1, among which ~half are homozygotes, one‑third compound heterozygotes and the remaining cases are heterozygotes (11). In Japanese and Koreans, the W258X mutation is reported as the predominant genetic cause of iRHU (3,11). URAT1 is highly urate‑specific and it is expressed in the luminal membrane of the proximal tubular cells, but is absent from the distal tubular cells or elsewhere in the body; it is largely responsible for proximal urate reabsorption (Fig. 6).

The residual apical uptake of urate is likely mediated by the OAT4 (SLC22A11) and OAT10 (SLC22A13) urate‑anion exchangers (12,13). Mutations in the SLC2A9 gene have also been found to be associated with familial renal hypouricemia. This gene encodes the high‑capacity urate transporter GLUT9. GLUT9 has two subtypes, one short (GLUT9S) and one long (GLUT9L) (6,7,10). Urate reabsorption from the tubular lumen into the cell is mediated by URAT1 and other anion exchangers, as mentioned above. Uric acid efflux from the cell across the basal membrane appears to be mediated only by basolateral GLUT9a (14) (Fig. 6). There have been several reports of SLC2A9 gene mutations leading to iRHU. One study (7) reported that the impact of GLUT9 deficiency on renal excretion of uric acid and serum uric acid levels exceeds that of URAT1 deficiency. In the present study, the result of the genetic test revealed homozygosity for a SLC2A9 mutation, the source of which were the parents. The uric acid excretion rate was as high as 200%. The result is consistent with the report (7), of a girl with severe iRHUC (serum urate 2.97 µmol/l, fractional excretion of uric acid 295.99%).

The SLC2A9 gene is located on human chromosome 4p15.3‑16, including 14 exons (1 non‑coding and 13 coding), and is 195‑Kb long, encoding 540 amino acids. There have been a number of studies on SLC2A9 mutations leading to
low uric acid nephropathy, but the gene mutation sites are different. Several Japanese studies have investigated hypouricemic acid nephropathy and reported a number of cases, among which two families were found to have RHUC2 due to GLUT9 missense mutations R198C or R380W (10,15). A total of two Chinese studies reported a homozygous mutation (g.68G>A in exon 3) in the SLC2A9 gene (8) and a homozygous splice-site mutation (c.1215+1G>A) in
GLUT9L (16), corresponding to c.1128+1G>A in GLUT9S. In Spanish patients (17), the SLC2A9 mutation site was reported to be p.T125M. A young Pakistani patient (18) was reported to have severe renal hypouricemia, with compound heterozygosity for SLC2A9 p.Arg380Trp and p.Gly216Arg mutations. A total of two British pediatric patients (19) with AKI were found to have the missense transitions p.G216R and p.N333S in the SLC2A9 gene. The majority of reported pathogenic SLC2A9 gene mutations are homozygous, but heterogeneous mutations of the SLC2A9 gene may also lead to RHUC2 (13,15).

In the present case, a novel homozygous mutation, c.857G>A (p.W286X), was identified in exon 8 of SLC2A9 (Figs. 4 and 5). This mutation leads to amino acid changes. Whether these specific amino acid changes compromised the uric acid transport by GLUT9 remains elusive. To the best of our knowledge, mutations at this site have not been reported in previous genetic studies on hypouricemic acid nephropathy. The prediction results of protein function prediction software SIFT (http://sift.jcvi.org/), PolyPhen_2 (http://genetics.bwh.harvard.edu/pph2/) and REVEL (https://sites.google.com/site/revelgenomics/downloads) all showed ‘unknown’. Therefore, the significance of the amino acid substitution in the novel SLC2A9 mutation needs be determined.

EIARF has been reported in patients with familial renal hypouricemia (9,20). It was first reported in 1989 by Erley et al (21). The largest study to date was a review of 54 patients with renal hypouricemia, of whom ~90% were male (20). AKI most often occurs after strenuous exercise, such as a short-distance race. The presenting symptoms are always severe abdominal pain and nausea, usually occurring within 6-12 h after exercise. At the time of presentation, the mean serum creatinine level of the patients was 5.5 mg/dl (486 mmol/l) and the mean serum uric acid level was normal (262 µmol/l), which was at least partly indicative of be renal failure. After recovery, serum uric acid was reduced to 42 µmol/l. Renal function was restored in all patients, whereas some patients required hemodialysis. During follow-up, 13 patients (24%) developed recurrent AKI; repeated AKI episodes may lead to chronic kidney disease in some patients (20).

The mechanisms underlying renal hypouricemia-induced EIARF remain unclear. Two possible pathogenetic mechanisms have been proposed: i) During exercise, increased oxidative stress may lead to renal vasoconstriction, ischemia and oxidative damage (22), possibly leading to reduced glomerular filtration rate and acute tubular injury (also referred to as ATN). ii) During exercise, increased uric acid production leads to uric acid excretion stress and deposition in the renal tubules, as occurs in uric acid nephropathy.

For patients with renal hypouricemia-related AKI, most of the reported renal biopsy results showed ATN, without renal uric acid crystallization and intratubular deposition (20,23). Plasma uric acid is a powerful antioxidant, which appears to play a protective role in the kidney; renal hypouricemia may be associated with decreased antioxidant capacity and potential kidney injury caused by reactive oxygen species (24). It is hypothesized that a decrease in circulating uric acid, a known antioxidant (25), impairs the ability of the kidney to respond to increased oxidative stress associated with strenuous

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**Table II. DNA variation information.**

<table>
<thead>
<tr>
<th>Chromosome position</th>
<th>Transcript Exon</th>
<th>Gene</th>
<th>Variation source</th>
<th>Pathogenicity analysis</th>
<th>Disease/phenotype</th>
<th>Genetic variation</th>
<th>Homozygous/heterozygous mutation</th>
<th>Frequency</th>
<th>Medium pathogenic</th>
<th>Disease/phenotype source</th>
</tr>
</thead>
<tbody>
<tr>
<td>chr4:4927267</td>
<td>NM_001001290 (exon8)</td>
<td>SLC2A9</td>
<td>Homozygous mutation was found</td>
<td>Pathogenic indicates pathogenic variation; likely pathogenic indicates suspected pathogenic variation.</td>
<td>Renal oliguria</td>
<td>Hom 0.00020</td>
<td>Likely pathogenic</td>
<td>medium frequency</td>
<td>0.00020</td>
<td>Hom</td>
</tr>
<tr>
<td>chr4:9922067</td>
<td>NM_001001290 (exon8)</td>
<td>SLC2A9</td>
<td>homozygous mutation was found</td>
<td>Pathogenic indicates pathogenic variation; likely pathogenic indicates suspected pathogenic variation.</td>
<td>Renal oliguria</td>
<td>Hom</td>
<td>Likely pathogenic</td>
<td>medium frequency</td>
<td>0.00020</td>
<td>Hom</td>
</tr>
<tr>
<td>chr4:9922067</td>
<td>NM_001001290 (exon8)</td>
<td>SLC2A9</td>
<td>homozygous mutation was found</td>
<td>Pathogenic indicates pathogenic variation; likely pathogenic indicates suspected pathogenic variation.</td>
<td>Renal oliguria</td>
<td>Hom</td>
<td>Likely pathogenic</td>
<td>medium frequency</td>
<td>0.00020</td>
<td>Hom</td>
</tr>
</tbody>
</table>

Pathogenicity analysis: Pathogenic indicates pathogenic variation; likely pathogenic indicates suspected pathogenic variation. Hom/het, homozygous/heterozygous mutation; AR, autosomal recessive; AD, autosomal dominant.
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...exercise (26). The pathological examination of renal biopsy samples supports this hypothesis.

The following conditions support the theory of uric acid deposition: In a case report (21) on EIAKI, a renal biopsy revealed blockage of the renal tubules by uric acid crystals; in addition, an increased prevalence of uric acid kidney stones has been reported in patients with renal hypouricemia (7,27,28). A total of 19 patients with familial renal hypouricemia were enrolled in two case series studies, of whom 5 (26%) had a history of kidney stones (27,28). The majority of these reports describe uric acid stones (7). However, the pathological examination of renal biopsy samples does not support this view. Further evidence comes from patients with recurrent EIAKI that may be preventable by allopurinol therapy. Bhasin et al (29) reported that an 18-year-old male patient repeatedly developed AKI after a 400-m race and was eventually diagnosed with iRHUC. The patient was prescribed oral allopurinol tablets 300 mg/day x 3 days and AKI did not develop again after the race. However, allopurinol is also an antioxidant, which may partly explain its protective effect against AKI (22). Therefore, the mechanism of EIARF remains unclear and requires further research.

In conclusion, this is the first report of a patient with RHUC2 due to the mutation of SLC2A9, which encodes GLUT9. p.W286X may be a pathogenic mutation of RHUC2; however, further investigations into the functional properties of GLUT9 in this novel SLC2A9 mutation are required. In clinical practice, the diagnosis of EIAKI should be considered in patients manifesting symptoms of AKI and moderately elevated or normal serum concentrations of uric acid, particularly after strenuous exercise.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors’ contributions

XHG designed the study and guided the writing of the manuscript. CYW drafted the manuscript and oversaw the figures. JW helped in drawing Fig. 1, analyzing and discussing the results of Figs. 4 and 5, and describing the pathogenic SLC22A9 mutation in detail. SL contributed to the collection of important background information and editing the language (translating Chinese into English). XHL and YFS performed the histological examination and completed the manuscript review. LF and LXZ provided and collated medical records.
Clinical and molecular analysis of the W258X mutations in glucose transporter 9 gene - URAT1 mutations cause renal hypouricemia

SLC2A9 is

The authors declare that they have no competing interests.

Patient consent for publication

Informed consent was obtained from the patient regarding the publication of the case details.

Competing interests

The authors declare that they have no competing interests.

References


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