IJKD KIDNEY DISEASES

Recurrent Acute Kidney Injury Caused by Idiopathic Renal Hypouricemia: The First Report from Iran with A Novel Mutation

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Keywords. renal hypouricemia, acute kidney injury, mutation

Numerous factors have been involved in exercise-induced acute kidney injury (EIAKI), such as using non-steroidal anti-inflammatory drugs following exercise and idiopathic renal hypouricemia (IRHUC). IRHUC is an autosomal recessive inherited disorder characterized by impaired tubular uric acid transfer, impaired reabsorption, and accelerated uric acid secretion. Some IRHUC patients have been shown to have EIAKI.

A 27-year-old police officer was admitted to the hospital due to anorexia and a serum creatinine level of 18 mg/dL, after a "tug-of-war" game. After one dialysis sessions per day over five days, his creatinine dropped to 1.3 mg/dL. Six months later, he developed bilateral flank pain and red discoloration of urine, following a 300-meter chase of a convict, and his creatinine level increased to 2.3 mg/dL, which was corrected with proper hydration alone. Recurrent acute kidney injury can be due to hereditary renal hypouricemia, which should be considered among differential diagnoses for patients.

IJKD 2022;16:374-9
www.ijkd.org
DOI: 10.52547/ijkd.6992

Special Report

INTRODUCTION

Idiopathic renal hypouricemia (IRHUC) is an autosomal recessive inherited disorder characterized by impaired tubular uric acid transport, impaired reabsorption, and accelerated uric acid secretion.[1-4] It is usually divided into two subgroups, type 1 encodes reduced function of SCL22A9 urate transporter one gene, and most patients fall in this group. The recently identified type 2 is rarer and caused by SLC2A9 gene mutation.[5] The SLC22A9 gene that encodes the urate transporter 1is expressed on the apical membrane of human proximal tubules.[1-5] The SLC2A9 gene encodes the short and long GLUT9 isoforms. The long isoform is expressed in the proximal epithelial tubular cells, especially in the basolateral region. In contrast, the short isoform is expressed on the apical luminal surface of canine kidney cells.[2] The urate is filtered in proximal tubules and primarily reabsorbed through apical membrane URAT1 and GLUT9 through apical and basolateral membranes. Mutation in the SLC22A12 gene is responsible for most cases of hyperuricosuria. Over 100 patients have been identified with SLC22A12 mutation and merely a few with SLC2A9 mutation.[6] If the disease is not diagnosed, recurrence of acute episodes of acute kidney damage is evident and can result in end-stage kidney disease. Homozygous mutations in the SLC2A9 gene have been reported to worsen hypouricemia in patients with IRHUC compared with mutations in the SLC22A12 gene.[7] It has been noted that mutations in the SLC2A9 gene are associated with a high prevalence of kidney stones in patients with EIAKI.[8] In these patients, hyperuricosuria and hypercalciuria lead to kidney stones.[9] Diagnosis of the disease is based on serum

and urine biochemistry, including hypouricemia (< 119 µmol/L or 2.0 mg/dL) and increased fractional excretion of uric acid (FE-UA) to more than 10%.[10] Secondary causes of hypouricemia and hyperuricosuria should be excluded before the diagnosis IRHACK is made. Finally, the SCL22A12 and SLC2A9 genes must be analyzed for definitive diagnosis. Because these tests are expensive, they are recommended to be used in obscure and complex cases. Here we present a case of hypouricemia induced acute kidney injury referred to our hospital.

CASE PRESENTATION

A 31-year-old male patient presented with symptoms of nausea and vomiting, abdominal pain (epigastric region), severe back pain, and lethargy following heavy physical activity (participating in a tug-of-war game) about five days before admission. He has been prescribed a non-steroidal analgesic (diclofenac) and a muscle relaxant (baclofen) in another center for abdominal pain, flank pain, and muscle stiffness. Due to worsening of symptoms and the occurrence of anuria, laboratory tests were requested. The patient had a history of kidney stones and renal colic attacks. The patient was referred to our medical center due to anuria and a serum creatinine level of 18 mg/dL. The vital signs were including blood pressure and heart rate were normal. The most important laboratory findings were metabolic acidosis with an elevated anion gap, urinary red blood cells 35 to 40 / HPF, and white blood cells 10 to 15 /HPF. In addition, hepatitis B antigen and hepatitis C and HIV antibodies were negative. No coagulation disorders were observed. Markers of autoimmune diseases such as anti-nuclear antibody, anti-double strand antibody and anti-neutrophil cytoplasmic and perinuclear antibodies (c and p ANCA) were negative (Table 1).

The ultrasound report showed a simple 17 mm cyst and a 5.2 mm stone in the right kidney, without any obstruction. The sizes of the right kidney and left kidneys were 113 and 117 mm, respectively. Color Doppler sonography of the renal arteries and veins were reported normal. The patient underwent

Table 1. Tests at Admission and During Hospitalization

Variables	Admission	1th Day	2th Day	3th Day	4th Day
WBC	8100	8100	7500	8300	9100
Hb, mg/dL	14.8	14.1	14,1	13.3	
PLT, mm^+	151000	137000	140000	167000	17100
FBS, mg/dL	91	100			92
Urea, mg/dL	171	112	76	110	87
Cr (mg/dL	17.9	12.6	11.9	9.6	7.6
Na, meql/dL	130	129	136	135	144
K, meq/L	4.3	37	3.5	4.4	3.8
AST, IU/L	13	18			
ALT, IU/L	11	20			
ALP, IU/L	160				
LDH, IU/L	490	600	560		
CPK, IU/L	800	750		187	
Ca, meq/L	9.1	9	8.5	8.8	
P, meq/L	3.9	4	3.8	4.1	
Uric Acid, mg/dL	9	8.9	8.6		
ESR, 1 hours	20				7
CRP, mg/L	7.5				
Chol, mg/dL	201				
TG, mg/dL	225				
pH	7.33				
pCo_2, mmHg	34.1				
HCo^{3-}	16.9				
PTT	38				
PT	18	13.3			
INR	1.8	1.1			

dialysis due to anuria and serum creatinine of 17.9 mg/dL. Supportive care was initiated for the possibility of rhabdomyolysis and acute interstitial nephritis due to five days prescription NSAIDs. Urine volume increased to 2.1 L in 24 hours, after 48 hours anuria, and serum creatinine decreased to 7.8 mg/dL. The patient was transferred to another hospital on his own request. Further follow-up disclosed decreased creatinine level from 7.8 to 5.6 mg/dL. The patient was discharged from referred hospital with a diagnosis of tubular necrosis (ATN) induced by rhabdomyolysis.

During outpatient follow-up, serum creatinine was reduced to 1.3 mg/dL, and no more problems were reported. Six months later, after a 300-meter pursuit of a convict, the patients developed a creatinine increase to 2.3 mg/dL. On re-examination after six months of recovery, the patient's uric acid was measured between 1.7 to 2.1 mg/dL with a 24-hour urine uric acid of 900 mg/dL. Based on the recurrence of AKI, low serum uric acid level and high urine uric acid, the diagnosis of idiopathic renal hypouricemia was made. Sequence analysis of the SLC22A12 gene was carried out. The patient's DNA was assessed using the "Whole Exome Sequencing" method (Figure 1, 2), and two probable pathogenic variants were identified (Table 2). The first-degree relatives of the patient were recommended be examined for the same variant. The patient's mother was not alive, so these variants were examined in his father and his only child. The position and variant of NM_144585: exon3: e.568G > C: P. A190P Chr11: 64360938: G > C: were confirmed in the patient, his father, and his son and the variant NM144585: exon8: e.1301G > C: P. R4341H Chr11: 64367854: G > C: was found only in the patient. As far as this variant was not identified in his father and son, who were normal in terms of changes in exon3: e.568G > C: P. A190P (Figure 1), it seems that the mutation maybe inherited from the mother (Figure 3). These mutations were novel. IRHUC was diagnosed based on low serum uric acid level and increased fractional excretion of uric acid (FE-UA) of more than 10%, and genetic findings after exclusion of other causes of AKI.

DISCUSSION

Hypouricemia refers to a serum uric acid level of less than 2 mg /dL. Low serum uric acid results from either decreased production or increased excretion. IRHUC is an autosomal recessive inherited disorder, characterized by increased urinary excretion of uric acid, due to a particular inherited defect in urate

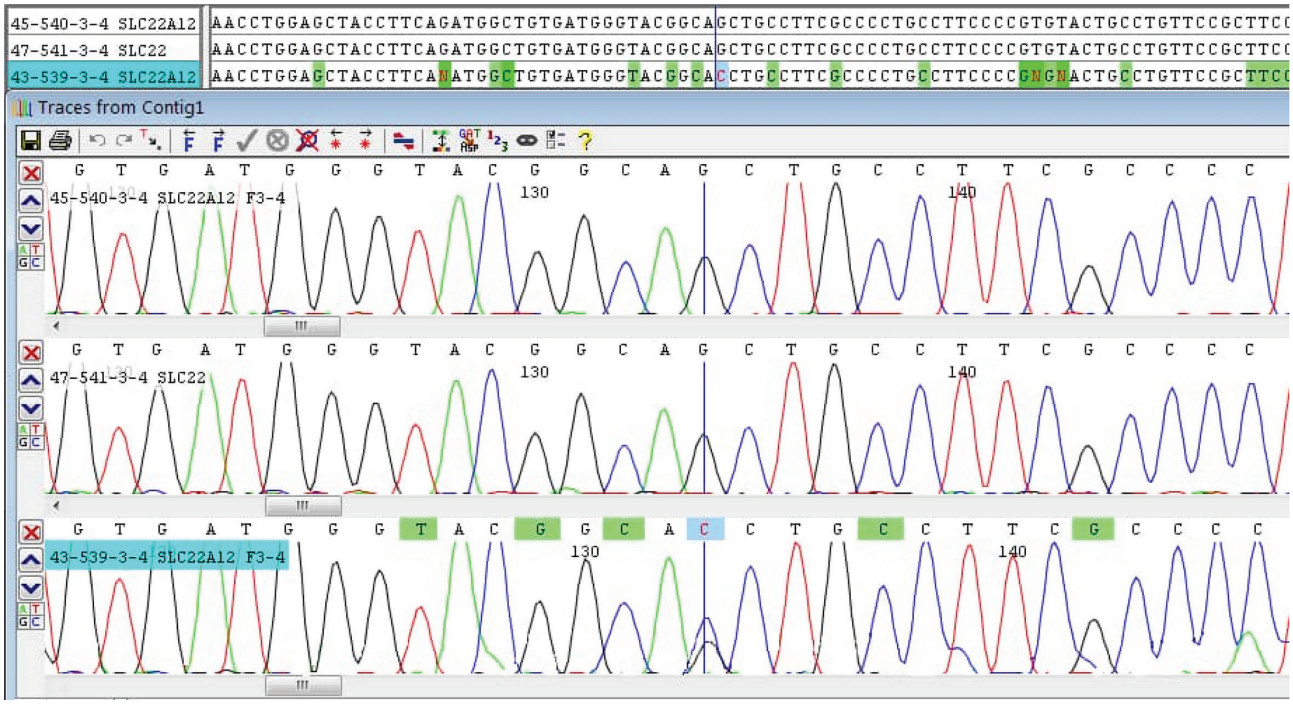

Figure 1. Patient Test (NGS-Whole Exome Sequencing)

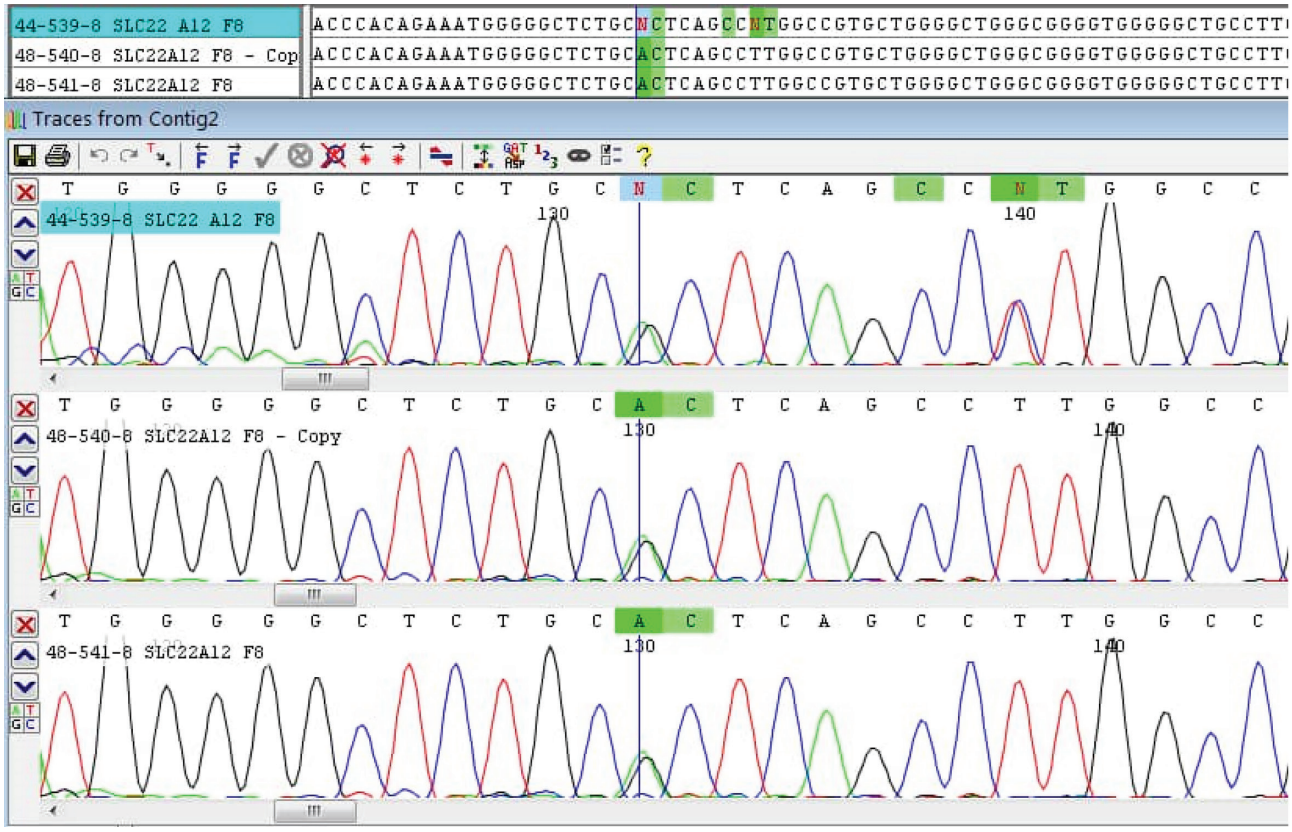

Figure 2. Test Mutation Confirmation (Family)

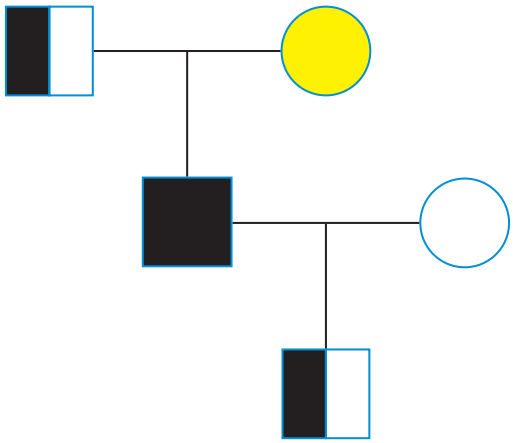

Figure 3. Patient's deceased mother could be homozygous or heterozygous for NM, and NM_144585: exon3:e.568G > C: P.A190P. Chr11:64360938:G > C: gene was confirmed in the patient's father and son, but NM144585:exon8:e.1301G > C:P. R4341H Chr11:64367854:G > C: variant was only confirmed in the patient.

membrane transport in proximal tubules of the kidneys. Although most patients with IRHUC have no clinical sign or symptoms, the most common reported complications are kidney stones and EIAKI.[11] Here we present a similar case EIAKI, presented in earlier studies.[6,12-14]

The most common causes of AKI following exercise are dehydration, rhabdomyolysis, hemolysis, and/or medications used to reduce pain. However, IRHU was diagnosed, according to the blood levels of uric acid, phosphorus, calcium, CPK, and LDH, disproportionate to the aforementioned conditions. The most important clinical finding in these patients is an exercise-induced recurrence of acute kidney injury, which was observed in both the previous reports and the current investigation. Serum uric acid is considered a strong antioxidant.[1,6,10-16] However according to clinical and experimental findings, uric acid is

Table 2. The Patient Genetic Analysis

Gene	Position / Variant	Zygosity	Diseases	Inheritance	Pathogen
Chr11:64360938:G>C:	NM_144585:exon3: e.568G>C:P.A190P	HET	RHUC	AR	+/–
Chr11:64367854:G>C:	NM_144585:exon8: e.1301G>C:P.R4341H	HET	RHUC	AR	+

thought to have a dual role of pro-oxidant and antioxidant activity in the body.[15] Intracellular uric acid has been shown to have oxidant effects, and cells with organic anion inhibitory effects prevent its entry.[17] Although the pathogenesis of acute kidney injury is unknown, increased production of uric acid as a result of ATP degradation during exercise may lead to acute uric acid nephropathy.[1-3] In addition, uric acid supersaturation in renal tubules due to exercise-induced dehydration, as well as increased uric acid excretion, leads to intra-renal tubules crystallization and occlusion.[11] In addition, possible environmental factors can influence the pathogenesis of the disease, including ambient temperature, dehydration, changes in urinary PH, concomitant use of different painkillers or nephrotoxins, intensity and duration of exercise, fever, rhabdomyolysis, and hyperthyroidism.

Plasma uric acid level increases during exercise, which is protective against the antioxidant effects of iron. On the other hand, the increase in oxygen free radicals during anaerobic exercise leads to renal artery constriction, which further reduces glomerular filtration rate. Accordingly, low uric acid levels in patients with IRHUC cause to reduce the antioxidant potential and expose the kidneys to damage caused by ROS.[11] Ischemia/reperfusion and ROS activation are probably risk factors for kidney disease.[3,7,18,19] Severe hypouricemia possibly reduces renal function by reducing its antioxidant effects.[15-17]

However, the results that link the role of decreased uric acid levels to the development of acute kidney injury are inconsistent. Basin *et al*.[20] reported an 18-year-old Caucasian man with recurrent AKI due to IRHUC He was prescribed with 300 mg of allopurinol daily for three days, and the race ended uneventfully. Allopurinol is the drug of choice for inhibiting the production of uric acid and administration of 300 mg of allopurinol has been shown to prevent EIAKI and increase exercise-induced uric acid excretion.[1,21] Allopurinol prevents EIAKI in these patients by decreasing the production and excretion of uric acid. Therefore, the more intense or prolonged exercise, the greater risk and severity of kidney injury. The question is whether patients benefit from chronic administration of allopurinol and the prevention of CKD these patients.

Renal hypouricemia should be considered as one of the differential diagnoses of AKI cases that occur following exercise. Genetic analysis can make a definite diagnosis, despite the need for high expenses and time-consuming tests. Following the recovery of the kidneys and after exclusion of other causes of AKI, low serum uric acid, high urine excretion fraction of uric acid, and Urinary uric acid level > 750 mg/dL could be suggestive of existence of idiopathic renal hypouricemia.

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Received July 2022
Revised September 2022
Accepted October 2022