□ Case Report □

A case of idiopathic renal hypouricemia

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Idiopathic renal hypouricemia is a disorder characterized by impaired urate handling in the renal tubules. This disease usually produces no symptoms, but hematuria, uric acid nephrolithiasis or acute renal failure may develop. A defect in the *SLC22A12* gene, which encodes the human urate transporter, is the known major cause of this disorder. We describe a 10-month-old boy with idiopathic renal hypouricemia. He was diagnosed with transient pseudohypoaldosteronism at admission, but hypouricemia was accidentally found through follow-up study. By gene analysis, his diagnosis was confirmed to idiopathic renal hypouricemia. In addition, we report a mutation in the human urate transporter 1 (hURAT1) gene identified in his family. **(Korean J Pediatr 2007;50:489-492)**

Key Words : Human urate transporter 1 (hURAT1) gene, Idiopathic renal hypouricemia, *SLC22A12* gene, Transient pseudohypoaldosteronism

Introduction

Hypouricemia, as defined by serum uric acid levels less than 2.0 mg/dl, is rare in U.S.A, but it is relative in common in Japan. Hypouricemia occurs in various pathological conditions, including Wilsons disease, Fanconi syndrome, primary biliary cirrhosis and Sjögrens syndrome as a result of renal tubular damage[1]. Idiopathic renal hypouricemia is a disorder characterized by impaired urate handling in the renal tubules. Most patients are clinically silent, but hematuria, urolithiasis or acute renal failure (ARF) may develop [2-6]. Recently, human urate transporter 1 (hURAT1), a urate anion exchanger that regulates blood uric acid levels, was identified in the human kidney and mutations in *SLC22A12* gene encoding hURAT1 cause renal hypouricemia[7, 8]. We describe a case of idiopathic renal hypouricemia, and we demonstrate a mutation in the responsible gene (*SLC22A12*).

Case Report

A 10-month-old male infant was referred to our hospital because of vomiting and poor oral intake for 2 days. When he was 5 months of age, he was treated for UTI and electrolyte imbalance. At that time he was also diagnosed having a moderate hydroureteronephrosis on the left kidney by ultrasonography. At admission, the infant was acute ill looking and severely dehydrated. Physical examination showed body temperature of 36.9℃, pulse rate of 138 beats per minute and arterial blood pressure of 60/40 mmHg. Laboratory data at admission showed hyponatremia, hyperkalemia and uremia. Serum uric acid level was normal despite of acute renal failure (Table 1). *E. coli* (10^6 CFU/mL) were cultured from urine. Abdomen and pelvis computed tomography revealed a severe hydroureteronephrosis on the left side (Fig. 1). Dimercaptosuccinic acid (DMSA) renal scan and voiding cystourethrogram (VCUG) appeared normal. Mercaptoacetyltriglycine (MAG3) renal scan revealed delayed excretion, but no significant obstruction. He was treated with glucose/saline infusions, antibiotics (ceftriaxone 100 mg/kg per day, amikacin 22.5 mg/kg per day). Electrolyte imbalance was corrected during four days. Endocrine test results revealed high levels of aldosterone and plasma renin activity (PRA) (Table 1). Considering the clinical and laboratory findings, he was diagnosed with transient pseudohypoaldosteronism (TPHA). On the 9th day of therapy for UTI, blood aldosterone and PRA returned to normal. On the 14th day of therapy, his uric acid level was

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found to be abnormally low (Table 1). But he was discharged with plan to recheck serum uric acid level at OPD follow-up.

At OPD follow-up, serum uric acid level was persistently low (0.6 mg/dL). We measured fractional excretion of uric acid, which is 184% (normal <10%). We also measured serum uric acid level and FEUA in other family members. Serum uric acid level of patients brother decreased to 0.6 mg/dL and the FEUA increased to 93.8% (Table 2). Serum uric acid levels of the parents were normal but fractional excretions of uric acid were mildly increased. Sequence analysis of *SLC22A12* gene was performed in all family members. In the patient and his brother, 90th amino acid of hURAT1, arginine (CGC) was substituted with histidine (CAC) by mutation of G269A [R90H] and 258th amino acid, tryptophan (TGG) was replaced with stop codon (TGA) by mutation of G2191A [W258X]. In the patients mother, 258th amino acid, tryptophan was replaced with stop codon. In the patients father, 90th amino acid of hURAT1, arginine was substituted with histidine. The genotypes of the *SLC22A12* gene in the patient and his family are described in Table 3. His parents were identified as having a different heterozygous mutation each, and the patient and his brother were identified as having compound heterozygous mutations in the *SLC22A12* gene.

Discussion

Uric acid, which provides a beneficial antioxidant defense, seems to be one of the most important antioxidants in human plasma. In contrast, uric acid may also have harmful biological functions. Although it is controversial whether hyperuricemia is an independent risk factor for cardiovascular diseases, several recent studies suggest a pathogenic role of uric acid in the development of hypertension, vascular diseases, and renal diseases[8]. Renal regulation of uric acid excretion occurs in the following sequence: 1) filtration of uric acid in the glomerulus 2) extensive reabsorption in the proximal tubule 3) massive secretion and 4) post-secretory reabsorption of secreted uric acid[9, 10]. Based on the four-compartment hypothesis, renal hypouricemia can be classified into five types: 1) total transport defect (no reabsorption and no secretion), 2) total reabsorption defect, 3) pre-secretory reabsorption defect, 4) post-secretory reabsorption defect, and 5) increased secretion[2]. Recently, a urate anion exchanger that regulates blood uric acid levels was identified in the human kidney (hURAT1) by Enomoto et al[11, 12]. A defect in the *SLC22A12* gene, which encodes hURAT1, is the known major cause of idiopathic renal hypouricemia. Most patients with idiopathic renal hypouricemia have loss-of-function mutations in *SLC22A12*. So far, 16

Table 1. Laboratory Data on Admission and Follow up

	At admission	During treatment	At discharge	Normal ranges
Sodium (mEq/L)	113	143	142	139-146
Potassium (mEq/L)	7.0	3.8	3.7	3.5-6.0
Chloride (mEq/L)	89	108	108	58-106
Total CO_2 (mEq/L)	7	25	22	10-28
BUN (mg/dL)	98.2	5	2.1	5-18
Creatinine (mg/dL)	1.1	0.4	0.7	0.3-0.7
Calcium (mg/dL)	7.7	8.7	9.7	8.8-10.8
Phosphorus (mg/dL)	2.6	4.6	4.2	3.8-6.5
Uric acid (mg/dL)	5.2	-	0.7	1.7-5.8
Aldosterone (ng/dL)	> 600	-	6.20	5-90
Plasma rennin activity (ng/mL/hr)	> 31.62	-	8.78	<16.6

Table 2. Laboratory Findings about Hypouricemia in the Family Members

	Serum Creatinine (mg/dL)	Urine Creatinine (mg/dL)	Serum uric acid (mg/dL)	Urine uric acid (mg/dL)	Fractional excretion of uric acid (%)
Patient	0.5	17.4	0.6	38.6	184
Brother	0.6	98.0	0.6	91.9	93.8
Mother	0.9	117.3	2.9	91.7	24
Father	1.2	111.9	3.9	66.6	18.3

different mutations have been reported in *SLC22A12*; 11 missense mutations (R90H, V138M, G164S, T217M, A226V, R228E, E298D, Q312L, Q382L, M430T, R477H), two nonsense mutations (W258X, Q297X), two short deletions (1639-1643delGTCCT, del313D-333P), and one splicing mutation (IVS2+1G>A). W258X and R90H are the common mutations in the URAT1 gene (*SLC22A12*) in our country. Allele frequencies of G2191A (W258X) and G269A (R90H) in general population are 1.7% and 0.9%, respectively, and those in subjects with hypouricemia (serum uric acid<3.0 mg/dL) are 22.6% and 12.9%, respectively[2]. In this case, the father of patient, who is heterozygous for R90H, and the mother of patient, who is heterozygous for W258X, had an increased FEUA without hypouricemia. In contrast, the patient and his brother, who are compound heterozygous for W258X, R90H, had much more severe hypouricemia with much higher FEUA than their parents.

The incidence of renal hypouricemia has been reported to be 0.12-0.72%, and clinical manifestations are expressed in silence, hematuria, urolithiasis, or ARF[3]. Especially, a number of patients with renal hypouricemia who developed exercise-induced ARF might have been overlooked due to the fact that the serum uric acid levels in these patients increase to the normal to high-normal range, during an exercise-induced ARF[7].

Table 3. Human Urate Transporter 1 Mutations in the Family Members

	hURAT1 genotype	
	Nucleotide	Amino acid
Patient	G269A/G2191A	R90H/W258X
Brother	G269A/G2191A	R90H/W258X
Mother	G2191A (heterozygous)	W258X (heterozygous)
Father	G269A (heterozygous)	R90H (heterozygous)

ARF can be divided into three categories: prerenal ARF, intrinsic ARF, postrenal ARF. Prerenal ARF is characterized by diminished renal blood blow. Prerenal causes of ARF are common, with intravascular volume depletion being the most common cause. Fever, vomiting, and diarrhea can lead to decreased kidney perfusion. Dehydration from any cause, including diuretics, can precipitate ARF. Prerenal azotemia occurs in diseases that lead to a decrease in the effective arterial blood volume. These diseases include heart failure, liver failure, and nephrotic syndrome. Nonsteroidal anti-inflammatory drugs (NSAIDs) and angiotensin-converting enzyme (ACE) inhibitors are known to cause prerenal azotemia. Large-vessel diseases, such as thrombosis, embolus, and dissection, also can reduce renal perfusion[13].

In this case, initial serum uric acid level of the patient was within the normal range because of prerenal ARF. The initial diagnosis of this case at admission was TPHA with hydroureteronephrosis. Up until now, there is no study of the relationship between TPHA and idiopathic renal hypouricemia. But idiopathic renal hypouricemia might have been overlooked during dehydration state in TPHA.

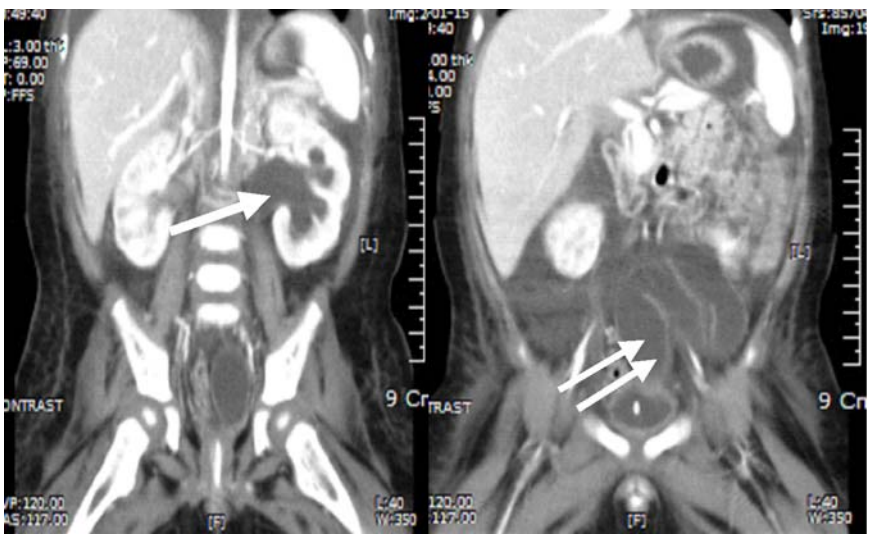

Fig. 1. Abdomen and pelvis computed tomography showed severe hydronephrosis in the left kidney (arrow). The left ureter was dilated up to the ureterovesical junction level (double arrow).

Aldosterone, the principal mineralocorticoid hormone in human, has a major role in the maintenance of water and salt homeostasis[14]. Pseudohypoaldosteronism due to renal tubular unresponsiveness to aldosterone is manifested by hyperkalemia, hyponatremia, metabolic acidosis and marked increase in plasma aldosterone concentration[15, 16]. In TPHA, aldosterone resistance arises from urinary tract malformations with or without UTI[17]. UTI affects renal tubular function, possibly through a bacterial endotoxin, such as *E. coli* lipopolysaccharide, and interstitial inflammation, and leads to increased sodium excretion and elevated aldosterone. The results of this nephrotoxic effect of UTI include renal tubular resistance to aldosterone and a state of pseudohypoaldosteronism that may include hyperkalemia. Hyperreninemia results from decreased blood volume[18, 19]. In this case, the patient had a hydroureteronephrosis on the left kidney. And at that point of having TPHA, *E. coli* (106 CFU/mL) were cultured from his urine.

We report a case of idiopathic renal hypouricemia, with definite demonstration of a mutation in the *SLC22A12* gene.

한 글 요 약

신성 저요산혈증 1례

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신성 저요산혈증은 신장에서 요산의 배설이 증가하는 것으로 무증상이거나 이차적으로 혈뇨, 요로결석, 신부전 등을 일으킬 수 있다. 저자들은 가성저알도스테론혈증으로 진단된 환아의 추적검사에서 추가적으로 신성 저요산혈증을 진단하고 환아 및 가족의 유전자검사를 통해 hURAT1 유전자의 R90H, W258X 이형접합자 변이를 확인하였기에 문헌고찰과 함께 보고하는 바이다.

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