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A patient with renal hypouricemia and acute renal failure after exercise in whom *URAT1* gene mutation was demonstrated

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Abstract

Patients with the disease entity termed acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE) manifests non-oliguric renal failure, usually accompanied by few urinary abnormalities such as hematuria and proteinuria. This condition, diagnosed by the demonstration of hypouricemia in addition to these features, usually responds well to conservative treatment. However, differentiation from other renal disorders occasionally proves difficult, which can lead to unnecessary steroid administration and renal biopsy. In the patient reported here, acute glomerulonephritis (AGN) was initially suspected based on his course and urinalysis findings, although typical AGN symptoms such as oliguria, edema, and hypertension were absent. After the detection of hypouricemia, renal hypouricemia was added to the clinical picture. *URAT1* gene mutation (W258X, homozygote) was demonstrated by gene analysis. The patient's mother was heterozygous for mutation at the same site.

Key words: renal hypouricemia, acute renal failure, exercise, *URAT1*, *GLUT9*

Introduction

Acute renal failure with severe loin pain and patchy renal ischemia after anaerobic exercise (ALPE) was proposed in 1982 as a disease entity differing from typical myoglobinuric renal failure.[1] Subsequent investigation disclosed that renal hypouricemia is caused by mutation of a gene encoding a transporter involved in uric acid reabsorption in the proximal convoluted tubule. The *URAT1* gene, which codes for a such uric acid transporter, was cloned by Enomoto et al. and identified as a gene whose mutation causes renal hypouricemia.[2] Recently, mutation involving *GLUT9*, which encodes another uric acid transporter, was reported as a cause of the disorder in some patients.[3]

Renal hypouricemia is complicated by ALPE or urolithiasis in about 10% of patients.[4] ALPE, most frequent in young men, is associated with a relatively favorable prognosis: the renal function often improves following conservative treatment such as rest and transfusion, but dialysis is sometimes required.[5] ALPE may also recur. Here, we report a patient in whom acute glomerulonephritis was initially suspected. However, the clinical features and finding of hypouricemia suggested ALPE. A definitive diagnosis was established by demonstrating *URAT1* gene mutation.

Case presentation

A 20-year-old man was referred to our hospital with a chief complaint of hypouricemia. When he was 13 years old, he had developed nausea,

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vomiting, and macroscopic hematuria after baseball practice and was brought to a local physician. Because of elevations of blood urea nitrogen (BUN, 23.7 mg/dL) and creatinine (Cr, 1.7 mg/dL), acute glomerulonephritis (AGN) was suspected. However, the symptoms were relieved with conservative treatment consisting of rest and dietary therapy. When the patient later presented with fever, hypouricemia was detected and he was referred to our hospital for diagnostic evaluation.

The patient's past medical history was unremarkable, but his mother had experienced 2 episodes of acute nephritis. On admission, his height was 177 cm and body weight was 72 kg. His blood pressure was 112/70 mmHg and heart rate was 70 bpm. No abnormality was evident on general physical examination. On laboratory data, uric acid (Ua) was low, fractional excretion of Ua was determined, which was found to be elevated (55.0%; normally, 7-12%) (Table 1). Ultrasonography showed no enlargement of the kidneys, dilation of the renal pelvis, or intrarenal calcification. As these findings suggested ALPE, informed consent was obtained from the patient and his parents for *URAT1* gene analysis, which was performed by direct sequencing. A nonsense mutation (W258X, homozygote) was detected in which a stop codon was substituted for tryptophan due to the replacement of guanine as the 774th base in exon 4 with adenine. Accordingly, the patient was definitively diagnosed with ALPE (Figure 1). Hypouricemia (1.2 mg/dL) was also present in his mother, and she was heterozygous for URAT1 mutation at the same site (Figure 1). The patient has been instructed regarding the necessity of sufficient warm-up before exercise, urged to maintain frequent fluid

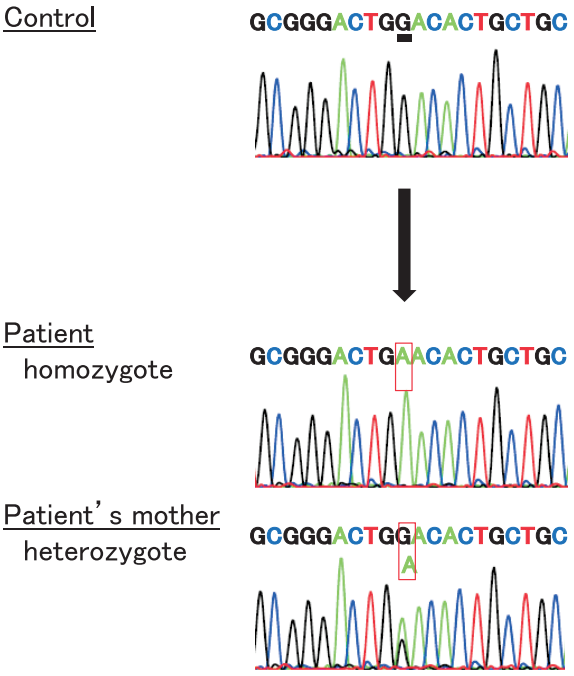

Fig. 1 *URAT1* gene analysis of the patient and his mother. The *URAT1* gene shows a nonsense mutation in which tryptophan (TGG), the 258th amino acid, becomes a stop codon (TGA) due to the replacement of G, the 774th base of exon 4, with A. Heterozygous mutation is present at the same site in the patient's mother.

Table 1 Laboratory data at the time on the first visit

Urinalysis		Blood Chemistry		Hematology	
比重	1.034	CRP	0.008 mg/dl	WBC	4,900/μl
pH	6.0	Na	141 mEq/l	Neutro	48.9%
Protein	(−)	K	4.7 mEq/l	Lymph	37.6%
Occult Blood	(−)	Cl	105 mEq/l	Eosino	0.7%
WBC	<1/HPF	Ca	9.6 mg/dl	RBC	465×10⁴/μl
RBC	<1/HPF	BUN	19 mg/dl	Hb	14.5 g/dl
β2-MG	111 μg/day	Crn	0.82 mg/dl	Ht	45.5%
24h Ccr	117.2 ml/min/1.73 m²	UA	0.7 mg/dl	Plt	14.1×10⁴/μl
FEUA	55.0%(7-12%)	TP	6.8 g/dl		
		Alb	4.7 g/dl	Serology	
		GOT	25 U/l	C3	80 mg/dl
		GPT	17 U/l	C4	14 mg/dl
		LDH	194 U/l	CH50	29.1 U/ml
		CPK	72 U/l	IgA	80 mg/dl
		TC	164 mg/dl		
		Trig	93 mg/dl		

intake, and warned about possible adverse effects of using non-steroidal anti-inflammatory drugs (NSAIDs).

Discussion

Ishikawa et al. first proposed ALPE as a disease entity distinct from myoglobinuric renal failure.[1] Then, a lot of patients with renal hypouricemia affected with ALPE have been reported.[5] ALPE has come to be noted along with the cloning of the URAT1 gene, which coded a uric acid transporter. Renal hypouricemia arises from the increased renal excretion of uric acid, resulting from the abnormality of a gene encoding a uric acid transporter involved in uric acid reabsorption in the proximal convoluted tubules. The incidence of hypouricemia has been only about 0.15% in Japan,[6] and about 10% of the patients have developed ALPE. About half of the patients develop renal hypouricemia due to underlying diseases.[7] While diagnostic criteria have not been established for renal hypouricemia, this condition is characterized by the absence of other diseases compromising uric acid transport, an increase in the fractional excretion of uric acid (FEUA) to 25% or higher (normal, 7 to 12%), and the presence of hypouricemia (a serum uric acid concentration of 2 mg/dL or less).[1] Additionally, ALPE is diagnosed when it meet the following three events. 1 : Acute renal failure that occurs after strenuous exercise in a short time. 2 : Increase in CK as high as 9 times of the normal value, and in serum myoglobin that can reach 7 times the normal value. 3 : Severe loin pain.[1,5,8] Two hypothesis have been proposed as the mechanisms of ALPE. First, acute urate nephropathy may be related, which resultes from the increase of urate production by exercise.[9] Second, the increase of oxygen free radical may be related, which results from ischemic disorders of the kidney. In the condition oxygen free radicals increase during ewercise with the lack of urate free radical scavengers.[10] In Japan, abnormality of the *URAT1* gene accounts for 80% or more of cases of renal hypouricemia, and mutations implicated include W258X, R90X, V138M, and Q297X.[4] In our patient, a homozygous nonsense mutation was detected in which tryptophan (TGG), the 258th amino acid, became a stop codon (TGA) due to replacement of guanine by adenine as the 774th base of exon 4. This has been reported to be the most frequent mutation,[4] with an allele frequency of 2.30 to 2.37%.[11] In patients lacking abnormalities of the *URAT1* gene, the *GLUT9* gene has been implicated.[3,12] Because the defect of the GLUT9, which was expressed on the vascular side in the proximal tubule, resulted in renal hypouricemia, it was involved in urate reabsorption in the proximal tubule. There were still few reports of renal hypouricemia cases by the deficiency of this GLUT9, therefore clinical comparison between the deficiency of URAT1 and GLUT9 was difficult.[3,12] The renal hypouricemia may also present in another gene abnormalities, which don't belong to URAT1 and GLUT9, so the elucidation of the molecular mechanisms and identification of new genes pathogenesis are needed.

In our patient, AGN was initially suspected. However, there was no preceding hemolytic streptococcal infection or disease-precipitating medication. Furthermore, nausea, vomiting, and gross hematuria occurred after exercise, while no typical AGN symptoms were noted such as oliguria, edema, or hypertension. ALPE was therefore suggested to be highly likely. The patient's mother was proved to be heterozygous for mutation at the same site. As gross hematuria and acute impairment of the renal function have been reported in such heterozygous individuals,[13] her episode of acute nephritis probably represented ALPE.

ALPE shows a high recurrence rate, and the long-term prognosis after repeated recurrences is unclear. To prevent recurrence, limitation of exercise intensity, prevention of dehydration, and avoidance of NSAIDs in managing loin pain are important.

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Conflicts of Interest

We have no conflicting interest regarding the present study.

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