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The Case | A young man with acute kidney injury after exercise

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Table 1 | Laboratory data

	Units	Reference	Admission	3 Weeks later
Serum				
Na^+	mmol/l	135–145	135	142
K^+	mmol/l	3.5–5.0	3.6	4.2
Cl^-	mmol/l	96–108	102	108
HCO_3^-	mmol/l	22.0–26.0	21.2	23.6
Total Ca^{2+}	mg/dl	8.1–10.4	8.8	9.3
Phosphate	mg/dl	2.6–4.5	3.9	4.1
Uric acid	mg/dl	2.7–6.9	6.5	0.9
Urea nitrogen	mg/dl	7–20	69	15
Creatinine	mg/dl	0.6–1.6	8.9	1.0
CPK	IU/l	30–200	212	
WBC	$\times 10^3/\mu l$	4.0–10.0	10.5	
Hemoglobin	mg/dl	12.0–16.0	12.8	
Urine				
Na^+	mmol/l		35	
Uric acid	mg/dl		43.6	141.5
Creatinine	mg/dl		88.4	189.4
Osmolality	mOsm/kg		182	575
Fractional excretion (FE)				
FE_{Na}	%		2.6	
FE_{UA}	%		67.5	83.0

Abbreviations: CPK, creatine phosphakinase; UA, uric acid; WBC, white blood cell.

A 21-year-old man presented with nausea, bilateral groin pain, and progressive oliguria since 2 days after running a 400-m dash. He did not take medications and his medical and family histories were unremarkable. His pulse was 84 min, blood pressure was 142/76 mm Hg, and body temperature was 36.7 °C. His jugular vein was not flat or distended. The remainder of his physical examination was unrevealing. Urinalysis was normal, except for a red blood cell count of 8–10 HPF and protein of 1^+. A pertinent serum laboratory test revealed acute kidney injury (AKI, Table 1). Serological tests including complement, anti-nuclear antibody, anti-neutrophil cytoplasmic antibody, and anti-glomerular basement membrane antibody were all negative. Abdominal ultrasonography showed a normal kidney size without hydronephrosis. Renal biopsy on the second day showed acute tubular necrosis. After three sessions of hemodialysis, his renal function began to recover and normalized 3 weeks later (creatinine 0.7 mg/dl).

What is the cause of his acute kidney injury after strenuous exercise?

SEE NEXT PAGE FOR ANSWERS

The Diagnosis | Exercise-induced acute kidney injury in hereditary renal hypouricemia

Table 2 | Causes of exercise-induced acute renal failure

Rhabdomyolysis		Non-rhabdomyolysis
Acquired	Familial	
Direct muscle injury/excess activity	Glycogen storage disorders	NSAID
Medications (aspirin, anticholinergic agents)	Fatty acid oxidation disorders	Severe volume depletion
Metabolic (hypothyroidism/ hyperthyroidism, hypokalemia)	Mitochondrial disorders	HRH
Heat stroke	Sickle cell anemia	
Myositis: infection, autoimmune	Muscular dystrophy	
Toxins (snake venom, insects, alcohol, stimulants)		
Diet/herbal supplement (ephedra, synephrine)		
Environment (high altitude, humidity, temperature)		
PAOD		

Abbreviations: HRH, hereditary renal hypouricemia; NSAID, nonsteroidal anti-inflammatory drugs; PAOD, peripheral arterial occlusive disease.

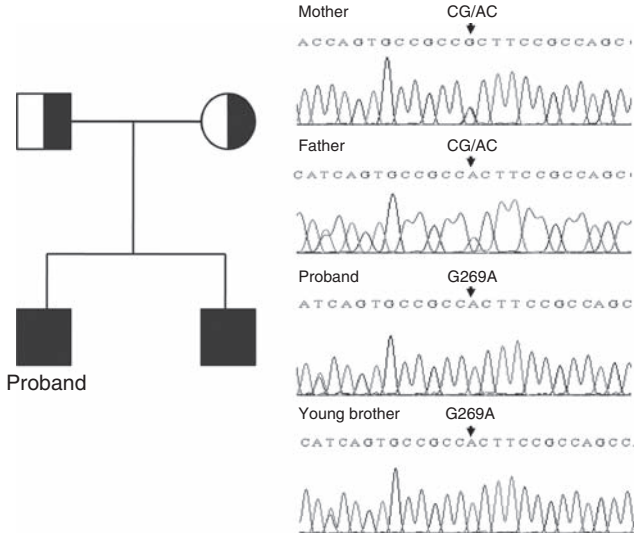

Figure 1 | Pedigree of the family and sequencing of PCR fragments of exon 1 for *URAT1* mutations in this family. Both male and female are indicated by squares and circles, respectively. Filled symbols represent affected individuals.

Although exercise-induced AKI usually reflects massive rhabdomyolysis and rarely severe hypovolemia or analgesic use, our patient did not have these identifiable causes (Table 2). His blood uric acid (UA) was unexpectedly normal during AKI. After renal function recovery, his profound hypouricemia with increased UA clearance indicated renal hypouricemia. HRH was considered on the basis of the absence of other causes of hyperuricosuric hypouricemia and evidence of renal hypouricemia in his younger brother (UA 0.7 mg/dl, FE_{UA} 62.4%). Genetic analysis of urate-anion exchanger (*URAT1*) and glucose transporter 9 (*GLUT9*) revealed a homozygous missense mutation (G269A:R90H) of *URAT1* in this patient and his brother, (Figure 1). By avoiding strenuous exercise, he has not experienced recurrent ARF.

HRH is an autosomal recessive disorder characterized by hypouricemia with high UA clearance. Filtered UA is reabsorbed in proximal tubules, primarily through *URAT1* in the apical membrane and through *GLUT9* in both apical and basolateral membranes.[1–3] Most patients with HRH have mutations in *URAT1* and *GLUT9*.[3]

Patients with HRH, face increased risk of urolithiasis due to hyperuricosuria and hypercalciuria, as well as the less-appreciated exercise-induced AKI during anaerobic conditions.[4] Although the pathogenesis remains unclear, two mechanisms have been proposed: (1) acute UA nephropathy from increased UA production during exercise-induced ATP degradation; and (2) oxidative stress from oxygen-free radicals produced during exercise. In addition, free radicals can cause renal vasoconstriction, ischemia, and subsequent reperfusion injury.[1,4]

Exercise-induced AKI associated with HRH occurs predominantly in young males and is characterized by nausea, vomiting, and groin pain after strenuous exercise. CPK may be normal or slightly elevated. UA levels are often 'inappropriately' normal. ~20% of patients require dialysis, and renal function usually recovers within 2–3 weeks.[1,4] The use of NSAID for groin pain may worsen AKI.[5] If HRH is not recognized, recurrence of exercise-induced ARF can cause irreversible renal damage.[4]

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