Case Report

Asymptomatic Hereditary Xanthinuria: A Case Report

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A 22-year-old man with hereditary xanthinuria is reported. A biochemical study of the patient showed elevated serum levels of xanthine and hypoxanthine with concomitant increases in urinary excretion of xanthine and hypoxanthine. The xanthine oxidase activity in the duodenal mucosa of the patient was about 1.5% of normal value. Urinary excretion of xanthine and hypoxanthine of his parents and his eldest brother were significantly higher than the corresponding normal values, but the values were much less than those of the patient. The results suggested that the patient was homozygote, and his parents and his eldest brother were heterozygotes.

Key words: Hypouricemia, Xanthine, Hypoxanthine, Xanthine oxidase

Xanthinuria is a rare hereditary disorder of purine metabolism in which the enzyme xanthine oxidase is grossly deficient. This abnormality causes high concentrations of the oxypurine precursors of uric acid, xanthine and hypoxanthine, and a very low concentration of uric acid in plasma and urine. The first well characterized case described by Dent and Philpot (1) in 1954 was brought to medical attention by the formation of a urinary stone composed of xanthine. But many of the patients had no clinical symptoms or signs (2).

We report an asymptomatic patient with xanthinuria discovered incidentally by a periodic medical examination.

CASE REPORT

A 22-year-old man, a boiler man, was referred to Ehime University Hospital in March 1989 by the physician of the industrial company for investigation of hypouricemia. The hypouricemia was first recognized during the medical examination on entering the company in March 1985. The periodic medical examinations always showed low levels of

serum uric acid (ranging from 0.1 mg/dl to 2.5 mg/dl; 0.76 ± 0.83 (SD) mg/dl ($n = 7$)). He had no complaints when he was admitted to the hospital. He was a normally developed man (178 cm, 64 kg). He had no history of a renal stone and no neurologic abnormality. The findings on physical examination were entirely normal. Routine hematological examination, liver function test and blood chemistry revealed normal values except for an extremely low concentration of serum uric acid (Table 1). Daily urinary excretions of sodium, potassium, chloride, calcium and phosphorus were within normal limits. However, the daily urinary excretions of uric acid on the normal diet were very low (ranging from 1.8 to 6.2 mg/day; 4.03 ± 1.23 (SD) mg/day ($n = 10$)). No abnormal finding was observed by urinalysis. Amino acid analyses of plasma and urine were normal. Creatinine clearance was 101.1 ml/min. Renogram and phenolsulphophtalein test revealed no abnormality. Abdominal roentgenogram, intravenous pyelogram and echogram of the kidneys showed neither stone nor abnormality.

Oral administration of inosine (1.6 g/day) for

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Table 1. Laboratory examination data on admission.

Blood		γ -GTP	7 IU/l
WBC	4100/mm ³	ZTT	7 IU/l
RBC	479 × 10 ⁴ /mm ³	Uric-A	0.2–0.5 mg/dl
Hb.	15.3 g/dl	T.Chol.	165 mg/dl
Ht.	43.6%	Lactic acid	4 mg/dl
Urinalysis		Fe	133 μ g/dl
Protein (–), Sugar (–)		Cu	84 μ g/dl
Sediments		Renal function	
RBC: 0–1/HPF		BUN	17 mg/dl
WBC: 1–3/HPF		Creatinine	0.8 mg/dl
Cast: (–)		CCr	101.1 ml/min
ESR		PSP	
2 mm/h		15 min	37.1%
		120 min	79.8%
Electrolytes		Serology	
Na	144 mEq/l	CRP	(–)
K	3.6 mEq/l	RA	(–)
Cl	111 mEq/l	AFP	(–)
Ca	9.5 mg/dl	CEA	(–)
In.P	4.2 mg/dl	75 g OGTT	
Blood chemistry		before	92 mg/dl
T.Prot.	6.8 g/dl	30 min	146 mg/dl
Alb.	4.7 g/dl	60 min	120 mg/dl
T.Bil.	0.3 mg/dl	120 min	94 mg/dl
GOT	8 IU/l	Others	
GPT	14 IU/l	%TRP	87.1%
LDH	45 IU/l	Urinary uric acid	1.8–6.2 mg/day
ALP	76 IU/l		

three days increased serum and urinary oxypurines without an increase in uric acid excretion (Table 2). Furthermore, plasma levels of xanthine and hypoxanthine (3) and their urinary excretions were much higher than those of normal subjects (Table 3).

Upper gastrointestinal series and gastrofiberscope showed no abnormality. Xanthine oxidase activity in the duodenal mucosa measured by a previously reported method (4) was 0.3 mU/g tissue, which was extremely low compared to that in normal duodenal mucosa (20.6 ± 6.5 (SD) mU/g tissue ($n=3$)). Diagnosis of xanthinuria in this patient was established. Biochemical analysis of his family (Fig. 1) is shown in Table 3. The serum uric acid concentrations of his parents, his eldest brother and his second brother were within normal limits. The level of serum uric acid of his grandfather, who was being

Fig. 1. Pedegree of family with xanthinuria. □: Male, ○: Female, +: Dead, ■: Homozygote (patient), ▨: Heterozygote. The numbers indicate the age of the subject.

treated for gastric cancer and chronic lymphocytic leukemia in another hospital, was slightly lower (2.1–4.2 mg/dl) than that of normal subjects. Plasma xanthine and hypoxanthine were normal in his family members. However, urinary xanthine and

Table 2. Effect of oral administration of inosine (1.6 g/day).

	Before administration			After administration			
	2 days	1 day	mean	1st day	2nd day	3rd day	mean
Plasma oxypurine (ug/ml)	4.1	3.5	3.8	4.8	4.8	4.4	4.7
Serum uric acid (mg/dl)	0.4	0.3	0.4	0.5	0.3	0.4	0.4
Serum creatinine (mg/dl)	0.7	0.6	0.7	0.8	0.7	0.6	0.7
Urinary oxypurine (mg/day)	365	317	341	841	918	641	800
Urinary uric acid (mg/day)	3.6	3.1	3.3	6.1	4.1	1.8	4.0
Oxypurine clearance (ml/min)	57	63	60	122	133	101	119
Uric acid clearance (ml/min)	0.6	0.7	0.7	0.9	0.9	0.3	0.7
Oxypurine clearance/ Creatinine clearance (%)	52	58	55	83	124	70	92
Uric acid clearance/ Creatinine clearance (%)	0.5	0.5	0.5	0.5	0.7	0.2	0.5
Urinary oxypurine/ Creatinine clearance (μ g/ml)	2.29	2.01	2.15	3.99	5.93	3.08	4.33
Urinary uric acid/ Creatinine clearance (μ g/ml)	0.02	0.02	0.02	0.03	0.02	0.01	0.02

Table 3. Plasma concentrations and urinary excretions of xanthine, hypoxanthine, and uric acid in the patient and his family members.

	Normal*	Patient	Father	Mother	Eldest brother	Second brother	Grand-father
Serum uric acid (mg/dl)	M:4.3-8.6 F: 2.7-5.8	0.2-0.5	6.1	3.3	6.2	7.8	2.1-4.2
Plasma xanthine (mg/dl)	0.01 $\pm$ 0.01	0.37	0.01	0.01	0.01	0.01	0.01
Plasma hypoxanthine (mg/dl)	0.02 $\pm$ 0.01	0.07	0.03	0.02	0.02	0.01	0.02
Urine							
Uric acid (mg/dl)	30-100	0.3	53	30	59	67	12
(mg/g creatinine)	400-1000	2.7	482	500	786	475	400
Xanthine (mg/dl)	—	30.0	1.5	1.1	1.1	1.3	0.3
(mg/g creatinine)	8.3 $\pm$ 3.0	229.0	14.0	18.7	15.1	9.0	9.0
Hypoxanthine (mg/dl)	—	14.9	1.0	0.7	0.9	1.1	0.2
(mg/g creatinine)	6.6 $\pm$ 2.9	113.7	8.8	11.0	11.7	7.9	7.3

* mean $\pm$ 2SD (n = 15)

hypoxanthine excretions of his mother and his eldest brother were significantly higher than those of normal subjects. His father showed an increased excretion of urinary xanthine and normal hypoxanthine excretion.

DISCUSSION

Classic xanthinuria, or isolated deficiency of xanthine oxidase, has been recognized since 1954 (1). Outside Japan, there have been 53 patients with well-

documented xanthinuria (2). In Japan, fifteen patients have been reported (Table 4) (4, 5-15). Many patients with xanthinuria were asymptomatic and were usually discovered by the finding of a very low concentration of serum uric acid during investigation of a presumably unrelated medical problem or during screening tests. In 30 percent of the patients, xanthine calculi of the urinary tract developed. Myopathy was present in 6.9 percent of the patients, and 5.1 percent of the patients were

Table 4. Summary of clinical and chemical features of reported cases of xanthinuria in Japan.

Author	Date	No.	Age and sex	Uric acid		Oxypurine		Xanthine oxidase activity		Stone of urinary tract
				Serum (mg/dl)	Urine (mg/day)	Plasma (mg/dl)	Urine (mg/day)	Xanthine (U/mg protein)	Hypo-xanthine (U/mg protein)	
Kitamura T.(5)	1976	1	5,M	0.33	81.2	0.48(Total)	220.8(Total)	—	—	(+)
Yokoyama M.(6)	1977	2	9,M	0.59	0.48**	0.137	0.175	25.9**	5.68**	(+)
Katsuki T.(7)	1981	3	50,F	0.2	9	0.23(Total)	19.6*	5.3*	trace	(-)
& Kojima T.(8,9)	1982	4	67,M	0.1	160	—	11.3*	1.3*	—	(+)
		5	39,M	0.3	82	—	12.8*	1.9*	trace	(-)
		6	31,M	0.2	160	—	26.1*	5.4*	trace	(-)
Kono H. (10)	1984	7	37,M	0.1	6.0	0.585	0.022	35.68	11.48	0
		8	30,M	0.2	1.7	0.075	0.028	110.5	73.1	0
Hada T.(11)	1984	9	31,F	0.9	17	0.18	0.44	205.7	87.0	—
		10	34,F	1.5	11	0.38	0.31	270.9	64.0	—
		11	29,F	1.7	12	0.31	0.51	278.4	56.4	—
Miyazaki T.(12)	1985	12	29,M	0.1	4.9*	0.44	0.14	51.2*	15.5*	0***
& Kawachi M.(4, 13)		13	35,M	0.1	2.4*	0.40	0.10	29.0*	9.9*	0.2***
		14	48,F	0.1	0.1*	0.27	0.28	20.7*	0.87*	0
Takei H.(14)	1987	14	48,F	0.1	0.1*	0.27	0.28	20.7*	0.87*	0
Sato T.(15)	1988	15	81,F	0.015	0.035*	0.21	0.17	23.3*	3.81*	0.007

* mg/dl, ** mg/2 h, *** mU/g tissue

noted to have recurrent polyarthritis (2). Several investigators reported the xanthinuria to be associated with peptic ulcer (13, 16–18). The patient in our report had no clinical symptoms or signs.

All available data on genetic factors of xanthinuria are consistent with an autosomal recessive pattern of inheritance. Familial analysis of our patient showed that plasma xanthine and hypo-xanthine concentrations of family members examined were normal, while urinary xanthine excretion was significantly higher in his parents and his eldest brother than that of normal subjects. The criteria of the heterozygotes have not been established. It has been reported that the amount of urinary excretion of oxypurine, the plasma level of oxypurine and the activity of xanthine oxidase are varied among heterozygote subjects (1, 4, 19, 20). Although xanthine oxidase activity was not measured in the family members, urinary oxypurine excretions of his parents and his eldest brother were increased, indicating that a metabolic blockade exists at the step of xanthine oxidase in these three family members. The three family members are suggested to be probable heterozygotes.

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