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RENAL TUBULAR HYPOURICEMIA AND CALCIUM UROLITHIASIS

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Abstract

The information concerning the relationship of hypouricemia with urinary tract stones is limited. We investigated the incidence and types of hypouricemia, and also studied its relationship to urinary tract stones. Hypouricemia was detected in 3 out of 1520 outpatients (0.20%). The loading tests using pyrazinamide, probenecid and benzbromarone showed that uric acid absorption was impaired before tubular secretion in two cases and incomplete postsecretory reabsorption in one case. Complication of urinary tract stone was found in two cases. The composition of the stones was mixed calcium oxalate and uric acid. Hypouricemia should be recognized as one of the causes of kidney stone formation.

Key Words: Renal tubular hypouricemia, incidence, calcium urolithiasis, pyrazinamide loading test, probenecid loading test, benzbromarone loading test, hyperuricosuria, diet.

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Introduction

While hyperuricemia is well known to be associated with calcium nephrolithiasis (Smith *et al.*, 1969), only limited information is available on the relationship of hypouricemia with urinary tract stones (Kawabe *et al.*, 1976). Hypouricemia provides important clues for explaining the mechanism of renal urate handling. We investigated the incidence and types of hypouricemia, and also studied its relationship to urinary tract stones.

Subjects and Methods

The subjects studied were three hypouricemic patients screened from 1520 outpatients who received blood biochemistry tests between May, 1986 and April, 1990 at the Urology Department of Teikyo University Hospital in Ichihara. Hypouricemia was defined as serum uric acid concentration of 2mg/dl or less. Two of these patients had urinary tract stones. Informed consents were obtained from these patients.

Throughout the study, the patients were maintained on a regular hospital diet. Uric acid in serum and urine was determined by automated colorimetric procedure with use of a uricase-peroxidase system. Pyrazinamide suppression test was performed, using previously described procedure (Shichiri *et al.*, 1982, 1985). Briefly, renal clearance of urate and creatinine prior to and following oral administration of 3.0 g pyrazinamide were measured. Probenecid test and benzbromarone test were done using the same procedure, with the exception that 1.5 g probenecid and 200 mg benzbromarone were given orally instead of pyrazinamide, respectively. These tests were undertaken on the morning following an overnight fast. Bladder catheterization was avoided by oral hydration with 500 ml water before study. Normal control data were obtained from two healthy male volunteers. A 14-day period was allowed between tests to avoid pharmacologic interference. The various parameters of urate handling were calculated according to Steele and Rieselbach (1967). Other measurements involved 24-hour urine chemistry, copper metabolism and urinary amino acids.

Table 1. Clinical features and uric acid metabolism.

	Case 1	Case 2	Case 3	Controls	
Age (years)	47	62	36	36	30
Sex	male	male	female	male	male
Occupation	truck driver	farmer	house-wife		
Sur (mg/dl)	0.9	0.8	1.5	6.5	6.3
Cur (mg/min)	60	61	19	6.3	5.8
Ccr (mg/min)	118	97	99	95	102
FEurate (%)	56	60	19	6.1	5.7
Urine pH	5.5-7.0	5.5-7.0	5.5-7.0	5.0-6.5	5.0-7.0
Stone formation	(+)	(-)	(+)	(-)	(-)

Values are mean of 3 determinations.

Abbreviations used are: Sur: serum uric acid level; Cur: uric acid clearance; FEurate: Cur/Ccr x 100.

Table 2. Urine chemistry in patients with hypouricemia

		Case 1	Case 2	Case 3	Control values*
Cre	(mg/24 hr)	1430	980	1050	1820±710
Ca	(mg/24 hr)	221	226	88	189± 59
P	(mg/24 hr)	750	900	575	1020±270
Mg	(mg/24 hr)	83	187	67	88± 22
UA	(mg/24 hr)	640	830	440	750±290
Na	(mEq/24 hr)	185	150	135	254± 90
K	(mEq/24 hr)	46	53	39	62± 17
Cl	(mEq/24 hr)	198	145	125	268± 86

Values are mean of two determinations; *Data obtained from 13 male volunteers (mean ± standard deviation).
Abbreviations used: Cre: creatine, UA: uric acid

Results

Incidence of hypouricemia

Hypouricemia was detected in 3 out of 1520 ambulatory patients (0.20%).

Clinical data

Clinical features, uric acid metabolism and the type of renal tubular defects are summarized in Table 1. All patients had no urinary tract infection and did not take any medicine. Urine chemistries of the 3 patients are listed in Table 2. The amount of uric acid excreted in urine was not reduced. Urinary amino acids excretion was within normal limits. Serum copper and lead levels were also normal. There was no evidence that these patients had malignancies (such as lung cancer, multiple myeloma and Hodgkin's disease) by radiographical and hematological examinations.

Loading tests to identify the site of disturbance

(a) **Pyrazinamide loading test**: FEurate (the ratio of uric acid clearance to creatinine clearance) failed to respond to pyrazinamide in Cases 1 and 2, while it approached 0 in Case 3 as in the healthy control (Fig. 1).

(b) **Probenecid loading test**: Initial rate of FEurate increase was identical in patients as well as controls, but plateau was reached early on in patients compared to controls (Fig. 2).

(c) **Benzbromarone loading test**: As in the probenecid test, FEurate slowly increased (Fig. 3).

It was inferred from the above results that uric acid absorption was impaired before tubular secretion in Cases 1 and 2, while incomplete postsecretory reabsorption occurred in Case 3.

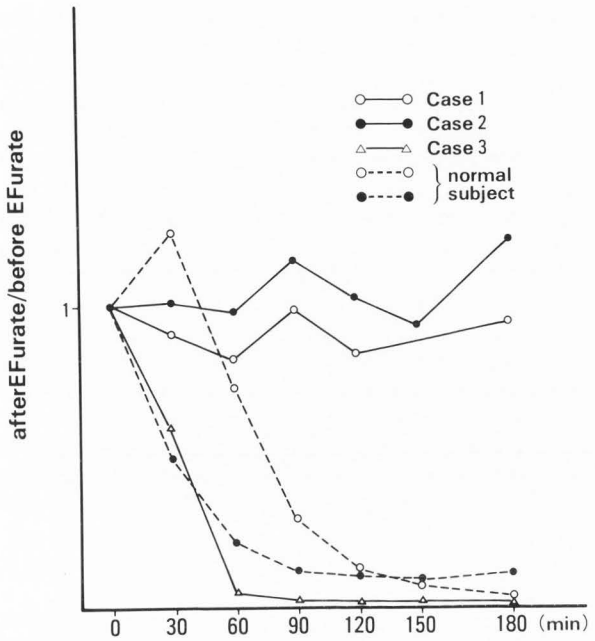

Figure 1. Results of the pyrazinamide suppression test.

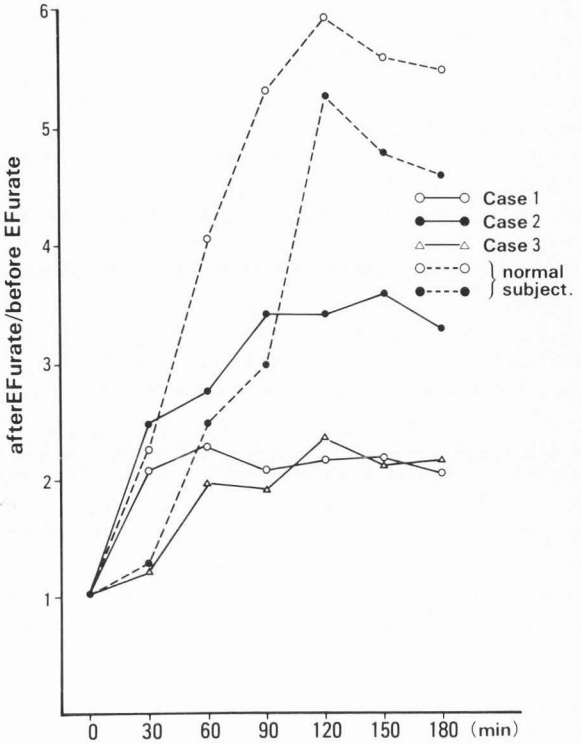

Figure 2. Results of the probenecid test.

Complication of stone and its components

Two of 3 hypouricemic patients had urinary tract stones. The composition of the stones was mixed calcium oxalate and uric acid, the latter predominating (55% in Case 1, 89% in Case 3).

Discussion

Hypouricemia is generally considered to be present if the serum uric acid level is continuously 2.0 mg/dl (Kelley, 1975) or less, although 1.5 mg/dl is thought to be more appropriate as the lower limit for the Japanese (Sasaki, 1980). Its incidence among the Japanese population is estimated at 0.15-0.56% (Hisatome *et al.*, 1989; Sasaki, 1982). Consistent with this rate, 3 out of 1520 patients (0.20%) were found to have hypouricemia in our survey. The incidence is said to be higher in Japanese than in Caucasians. Idiopathic hypouricemia is frequently congenital, with no sex difference in its incidence. It is considered an autosomal recessive inherited disease (Frank *et al.*, 1979; Weitz *et al.*, 1980), although some authors reported it as dominantly inherited (Suzuki *et al.*, 1981). Familial occurrence was not noted in our cases. Hypouricemia occurring in diminished production of uric acid is best known in a congenital defect of xanthine oxidase. In idiopathic hypouricemia, the transport of uric acid in the kidney is impaired. Hypouricemia may be secondary to such diseases as severe liver damage, Wilson's disease, Fanconi syndrome, abnormality in antidiuretic hormone (ADH) secretion, heavy metal intoxication, and malignant

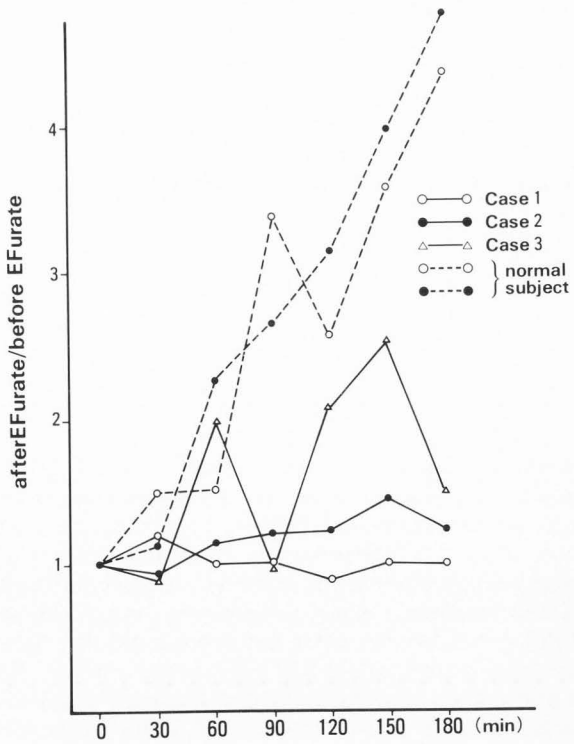

Figure 3. Results of the benzbromarone test.

tumors such as liver cancer, lung cancer, Hodgkin's disease and multiple myeloma (Weinstein *et al.*, 1965; Tykarski, 1988; Mitnick and Beck, 1979). All our patients showed a normal urinary excretion of amino acids. Serum ADH, copper, ceruloplasmin and lead were also normal. As chest X-ray, abdominal CT and fluoroscopy of the stomach were all negative, it seemed unlikely that a malignant tumor was present. In one patient who had a superficial bladder tumor, hypouricemia remained unchanged two years after complete excision of the tumor by transurethral resection. Tumor recurrence was denied by endoscopic examinations. Since they all had been healthy and had not received the drug in the past, hypouricemia associated with the drug was ruled out. Alcohol consumption was 180 ml/day of Japanese Sake in Case 2, and almost nothing in Cases 1 and 3. Moreover, the findings suggestive of renal tubular disturbance were not obtained, such as glycosuria, proteinuria and persistent acidosis. From these findings, all 3 patients were considered to have idiopathic hypouricemia. This may be partly explained by the fact that our cases were detected by the screening of outpatients, not by testing of inpatients.

For the mechanism of uric acid excretion from the kidney, the theory of a 4-component system (Rieselbach and Steele, 1974) is most widely supported. The 4 components refer to a complete filtration through the glomeruli, reabsorption before secretion, secretion at the renal tubules, and reabsorption after secretion. Finally, 6-10% of the filtrate is excreted in urine. The sites of disturbance at renal tubules can be classified into several types by the loading tests using pyrazinamide, which blocks uric acid secretion at renal tubules (Gutman *et al.*, 1969), probenecid (De Vries and Sperling, 1979) and benzbromarone, which block reabsorption after secretion. The loading tests revealed that hypouricemia in our patients was caused by a disturbance of reabsorption before secretion in two, and incomplete postreabsorption in the other. Since renal stones developed in both types, the formation of stones seemed not to be related to the site of disturbance of uric acid transport.

Hypouricemia produces few symptoms, and is usually discovered by chance. The only complication is urinary tract stones. The frequency of urinary stones in hypouricemia was reported to be 16% (Sasaki *et al.*, 1986), but it was present in as many as 2 of our 3 cases. In our 2 cases with stones, urinary uric acid and FEurate were lower than in the stone-free case. When hypouricemic patients take purine-rich diet, they will temporarily excrete excessive uric acid with the resulting considerable elevation of the urinary uric acid level even if the 24-hour uric acid excretion is normal. Urinary uric acid is said to increase roughly in proportion to the oral intake of purine. In our cases, urinary uric acid measurement after a high purine diet was not performed. We are going to do this type of study. It might be possible that the patients who had stones took more purine-rich food temporarily than the stone-free patient. Purine binges might be risky in the case of hypouricemia. The formation of calcium stones may also be affected by the oxalate (Ito *et al.*, 1992) and crystal growth inhibitors (Ito and Coe, 1977) in urine.

It is generally considered that no treatment is needed for hypouricemia. However, since idiopathic hypouricemia patients are said to be susceptible to acute renal failure (Ishikawa *et al.*, 1990, Numabe *et al.*, 1992) it is necessary to warn these patients of the possible danger of exercise and dehydration, and to follow them up. Acute renal failure in such a case seems to result from the obstruction of renal tubules by uric acid crystals, as exercise accelerates uric acid formation (Sutton *et al.*, 1980) and the crystals of uric acid are accumulated within renal tubules if dehydration follows exercise. If urinary tract stones are present, dietary measures or the use of allopurinol will become necessary to reduce temporary hyperuricosuria which will increase the risk of stone formation.

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Discussion with Reviewers

Reviewer II: Would the authors explain the double paradox of urate stone formation in the absence of hyperuricosuria and the absence of stones in the patients with the highest uric acid excretion? Do the authors assume that purine binges are a necessary and sufficient condition to account for urate stone formation? What is the relationship with calcium oxalate? Would the authors speculate on the specificity and nature of the tubular biochemical defect?

Authors: We do not think that purine binges are a necessary and sufficient condition to account for urate stone formation, but they may be very important. The theory of hyperuricosuric calcium oxalate stone formation is already established.

Reviewer IV: Unfortunately, uric acid levels were lower in 2 of the 3 cases studied than in stone-free cases. This observation strongly opposes the authors' view that intake of purine rich diet will result in hyperuricosuria in such patients and needs to be justified by results of urinary uric acid measurement after a high purine diet.

Authors: As a next step we will measure the urinary urate levels after a purine load. It will be important to see the magnitude of the temporary hyperuricosuria.