Renal hypouricaemia in a patient with 48,XXYY syndrome

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Summary: Studies on hypouricaemia observed in a patient with 48,XXYY syndrome revealed an abnormality in renal urate handling. His renal urate clearance was abnormally increased. Inosine administration and provocative tests using probenecid and pyrazinamide identified an isolated renal tubular abnormality with increased urate secretion. Since the serum urate in his brother with a normal sex chromosome constitution was also low, the association of renal hypouricaemia and 48,XXYY syndrome in this patient is probably coincidental. Although the brother was not investigated, these siblings may be a previously unreported case of familial hypouricaemia due to isolated renal hypersecretion.

Introduction

The 48,XXYY syndrome, first reported by Muldal & Ockey (1960), is a rare sex chromosome number disorder. Compared to 47,XXY Klinefelter's syndrome, the incidence is very low (Bloomgarden *et al.*, 1980).

Renal hypouricaemia, first reported by Praetorius & Kirk (1950), is a unique condition characterized by low levels of serum urate with increased renal urate clearance. Harkness *et al.* (1983) reported the incidence of renal hypouricaemia in their hospital in UK as 1 in 23710. According to de Vries & Sperling (1979), there are three mechanisms responsible for renal hypouricaemia, namely pre-secretory, post-secretory and combined defects of renal tubular urate reabsorption. More recently, renal hypouricaemia with increased renal tubular urate secretion was reported by Shichiri *et al.* (1982). Similar findings were also reported by Dumont & Decaux (1983) and Sanz *et al.* (1983). Thus, four mechanisms should be considered in the study of renal hypouricaemia. We report a patient with 48,XXYY syndrome and renal hypouricaemia possibly due to the fourth mechanism, renal tubular urate hypersecretion.

Materials and methods

Case report

The patient was a 34 year old Japanese male, the first child born to a 32 year old father and a 27 year old mother. He had enjoyed good health, except that he had hypogonadism (Tanner stage II), recurrent foot ulcers and varicose veins of the legs. On examination, he was found to be eunuchoid. His height was 171 cm, weight 63 kg, arm span 157 cm and the upper to lower body segment ratio 1.04. Skeletal abnormalities were observed including cleft palate, genu varus, cubitus varus, clinodactylia and shortened fifth interphalangeal bones (Figure 1). His dermatoglyphics was abnormal in decreased total finger ridge counts (TFRC 47) and a-b ridges (right 25, left 30). Loop patterns were predominant (nine out of ten fingers). Simian creases were present. His I.Q. was 60 (Wechsler Adult Intelligence Scale). He did not show aggressive behaviour. Laboratory examinations were normal except for hypouricaemia (0.102–0.156 mmol/l, normal range, 0.162–0.360 mmol/l) and hypercalcuria (4.31–8.87 mmol/day, normal range, less than 3.80 mmol/day). Urinary urate concentrations and percentage tubular reabsorption of phosphate were within normal ranges. Basal gonadotrophins as measured by radioimmunoassays were elevated (LH, 71.0 U/l, normal range, 3–15 U/l; FSH, 51.2 U/l, normal range, 1.0–10 U/l). Gonadotrophin releasing hormone (LH–RH, 100 µg) administration resulted in

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Accepted: 1 August 1985

Figure 1 Photograph of the patient representing a cunuchoid body habitus with hypogonadism.

the hyperresponses of gonadotrophins (peak values, LH, 275.8 U/l; FSH, 89.5 U/l). Marked hyalinization of seminiferous tubules, interstitial fibrosis and lack of spermatogenesis were found in testicular biopsy. Chromosome analysis revealed that he had non-mosaic 48,XXYY karyotype without translocations (Figure 2). His younger brother (32 years old) and mother had normal chromosome constitutions. His father died before this study was performed. Hypouricaemia was also present in his younger brother (0.150 mmol/l). (Conversion of S.I. units to metric units: serum urate 1 mmol/l = 16.67 mg/dl, urinary urate 1 mmol/day = 166.7 mg/day, urinary calcium 1 mmol/day = 39.5 mg/day).

Studies on urate metabolism

Oral inosine administrations were performed for 6 days, 400 mg (1.5 mmol) every 6 hours, and serum and urinary urate were examined. Probenecid 1 g (3.5 mmol) or pyrazinamide 3 g (24.4 mmol) were administered orally after an overnight fast and a one hour control period. Clearance studies were performed with an interval of one hour. Serum and urinary urate were measured by an enzymatic assay (uricase-catalase method). Normal subject data of the probenecid and pyrazinamide tests were obtained from three healthy male volunteers of the same age. Informed consent was obtained from all the subjects and the patient.

Results

Serum urate concentrations of the patient ranged from 0.102 to 0.156 mmol/l (0.126 ± 0.016 mmol/l; mean $\pm$ s.d., $n = 10$). Percent of urate clearance to creatinine clearance (%Cur/Ccr) was high (24–32%, controls, 4–13%) with a normal creatinine clearance. Inosine administrations resulted in increases of both serum (from 0.120 to 0.276 mmol/l) and urinary (from 5.38 to 10.26 mmol/day) urate concentrations, but %Cur/Ccr remained unchanged. Probenecid administration caused an increase in %Cur/Ccr reaching

Figure 2 Chromosome analysis of the patient showing non-mosaic, 48,XXYY constitution without translocations. G-banding patterns of sex chromosomes are also shown.

Table I Effects of oral probenecid and pyrazinamide administration on serum urate (s-UA), urate clearance (Cur), creatinine clearance (Ccr) and %Cur/Ccr.

Time (hours)	s-UA (mmol/l)	Cur (ml/min)	Ccr (ml/min)	%Cur/Ccr
Probenecid				
- 1 to 0	0.132 (0.281 $\pm$ 0.055)	31.2 (16.1 $\pm$ 5.0)	97.8 (149 $\pm$ 29.9)	31.9 (10.4 $\pm$ 1.1)
0 to 1	0.114 (0.248 $\pm$ 0.062)	54.9 (13.3 $\pm$ 3.0)	98.7 (97 $\pm$ 6.3)	55.6 (25.9 $\pm$ 9.0)
1 to 2	0.102 (0.220 $\pm$ 0.054)	72.8 (32.0 $\pm$ 5.8)	88.9 (96 $\pm$ 15.9)	81.9 (38.5 $\pm$ 10.1)
Pyrazinamide				
- 1 to 0	0.156 (0.362 $\pm$ 0.061)	20.7 (11.4 $\pm$ 3.9)	80.3 (131 $\pm$ 6.6)	25.8 (8.6 $\pm$ 2.9)
0 to 1	0.168 (0.376 $\pm$ 0.070)	12.9 (6.7 $\pm$ 1.0)	110.0 (132 $\pm$ 3.0)	11.7 (5.0 $\pm$ 0.7)
1 to 2	0.174 (0.382 $\pm$ 0.065)	7.6 (2.2 $\pm$ 0.4)	106.0 (107 $\pm$ 6.6)	7.2 (2.0 $\pm$ 0.3)

Data from age and sex match controls ($n = 3$) are in parentheses (mean $\pm$ s.d.).

81.9%, much greater than in the control subjects (Table I). After pyrazinamide administration, final %Cur/Ccr in the patient and the control subjects decreased. The decrements were 72.2% and $70.5 \pm 15.7\%$ ($n = 3$) from the basal values respectively. The patient's tubular secretion of urate as estimated through a pyrazinamide suppression test was 27.6 nmol/ml at a final serum urate level of 0.174 mmol/l.

Discussion

During a thorough examination on a patient with the 48,XXYY syndrome, we noticed that he had hypouricaemia uncomplicated with other systemic disorders known to cause hypouricaemia. Since urate synthesis from inosine was not disturbed in the patient, the presence of any defects in purine metabolism was excluded (Kondo *et al.*, 1977). The increased %Cur/Ccr suggested that hypouricaemia observed in the patient was a result of abnormal renal urate handling. According to de Vries & Sperling (1979) and Shichiri *et al.* (1982), renal hypouricaemia can be classified into four types of tubular dysfunction, hypersecretion and pre-secretory, post-secretory and combined defects of reabsorption, using probenecid and pyrazinamide tests. Inhibition of tubular urate reabsorption by probenecid increases %Cur/Ccr in normal subjects as well as in patients with pre-secretory defect or increased secretion. Pyrazinamide suppresses %Cur/Ccr through inhibition of tubular urate secretion in normal subjects as well as in patients with post-secretory defect or increased secretion. In this patient, basally elevated %Cur/Ccr further increased after probenecid administration. Pyrazinamide administration resulted in almost normal decrease of %Cur/Ccr. These findings suggested that

hypouricaemia in this patient was due to urate hypersecretion. His tubular secretion of urate exceeded the 95% confidence range obtained for normal subjects by Steele & Rieselbach (1967). This finding further supports the possibility that urate hypersecretion existed in the patient.

Since the serum urate level of his younger brother was also low, hypouricaemia observed in this patient may be familial. To our knowledge, familial cases of renal hypouricaemia due to hypersecretion have not been previously reported. As his brother had normal chromosome constitution, it appears that the combination of the two rare syndromes observed in this patient may be coincidental.

This report indicates that detailed investigation including family studies is needed in characterizing renal hypouricaemia. Serum urate estimations in chromosomal abnormalities are also warranted.

Acknowledgements

This study was supported, in part, by Grant-in-Aids for Scientific Research (Nos. 59480214, 59480255, 59570484 and 59870040) from the Ministry of Education, Science and Culture of Japan and Basic Research Grant from the Muscular Dystrophy Association of the United States.

We wish to thank Mr Shigeaki Kobayashi, M.T., and Mr Shigemoto, M.T., of the Central Laboratory for Clinical Investigation, Osaka University Hospital, for their skilful technical assistance in the chromosome analyses. We are also grateful for the helpful advice received from Dr Noriyuki Suehara, M.D., of the Department of Obstetrics and Gynecology and Dr Kiyoshi Miyai, M.D., professor of the Department of Laboratory Medicine, Osaka University Medical School. Finally, we also wish to thank Dr Masayoshi Shichiri, M.D., of the Second Department of Medicine, Tokyo Medical and Dental University, School of Medicine, for useful discussions.

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