Autosomal dominant transmission of gouty arthritis with renal disease in a large Japanese family

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Abstract

Six generations of a Japanese family had gouty arthritis and progressive nephropathy. Data on nine of 51 women (18%) and 15 of 66 men (23%) with either asymptomatic hyperuricaemia, gouty arthritis, or renal insufficiency were obtained. Renal function in four men and one woman with hyperuricaemia or gouty arthritis was also examined. Urinary excretion of uric acid was decreased in all subjects examined, including the young. Erythrocyte phosphoribosylpyrophosphate synthetase and hypoxanthine-guanine phosphoribosyltransferase activities determined in 10 patients were normal. Some patients had been treated with allopurinol to reduce serum uric acid concentrations, but the treatment did not prevent progression of renal impairment. Transmission of the disease in this large family is considered to be autosomal dominant. The data suggest that the disease in this family is the same entity as that described by other workers—that is, familial urate nephropathy. As far as is known this is the largest family with this disease so far reported.

Primary gout is a metabolic disease which may be closely linked to nephropathy. As a cause of severe renal impairment, however, it accounts for only a small proportion of all cases. According to a report by the Japanese Society for Dialysis Therapy in 1989, only 0.7% of 80 075

patients undergoing dialysis had gout as a primary disease.¹ Several articles have described families with gout and renal failure.²⁻¹³ Richmond *et al* described such a family with 'familial urate nephropathy',² while Duncan and Dixon reported a similar disease and termed it 'familial gouty nephropathy'.³ Members of these families had marked hyperuricaemia and gout even when young, and their renal function progressively deteriorated. In addition, women commonly had the disease, in sharp contrast with the rare occurrence of gout in women in the general population. In this article we describe the findings in a six generation Japanese family, many of whom had gout and progressive nephropathy; abnormal renal handling of uric acid was found in some members.

Methods

CLEARANCE STUDY

Amounts of uric acid excreted in urine and values of uric acid clearance were determined from 24 hour urine specimens obtained from subjects not receiving a purine restricted diet. The concentrations of serum and urinary uric acid or creatinine were measured by an automatic analyser (TBA-50S, Toshiba, Japan).

DETERMINATION OF ENZYME ACTIVITIES

Activities of hypoxanthine-guanine phosphoribosyltransferase and phosphoribosylpyrophosphate synthetase were determined in

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Figure 1 Pedigree of a six generation Japanese family with gouty arthritis and renal disease. Roman numerals in the left margin indicate generation; arabic numerals, members of each generation. Hyperuricaemia was defined as over 0.45 mmol/l of serum uric acid; renal dysfunction, over 133 μ mol/l of serum creatinine.

the erythrocyte lysate from patients and normal subjects according to the methods of Seegmiller *et al*¹⁴ and Wood *et al*¹⁵ respectively.

Results

PROPOSITUS

The propositus (a 53 year old man shown as V-5 in fig 1) attended the outpatient clinic of Miyazaki Medical College Hospital with acute arthritis in the knee. He had had a typical podagra on the right big toe at the age of 33, which was effectively controlled by colchicine treatment. After age 40 he had had recurrent attacks of gouty arthritis in the joints, including ankles, knees, and fingers. He had no history of haematuria, renal colic, or analgesic abuse.

On admission, blood pressure was 180/110 mmHg. There were no other remarkable physical findings. Urine analysis showed pH 5.0, gravity 1.010, protein 1+, two to three white blood cells per high power field, five to six red blood cells per high power field, and occasional granular casts. Laboratory findings showed serum creatinine 212 $\mu\text{mol/l}$, blood urea 6.7 mmol/l, and haemoglobin concentration 117 g/l. Serum uric acid was 0.4 mmol/l while he was receiving allopurinol 200 mg/day. Ultra-sound echography showed bilateral contracted kidneys. Allopurinol was prescribed to treat hyperuricaemia, with both propranolol and nifedipine for hypertension control. During a clinical course of over 26 months after the start of treatment gouty arthritis did not recur. Serum creatinine concentrations, however, gradually rose to 283 $\mu\text{mol/l}$, indicating progression of renal impairment.

FAMILY STUDY

Patients in this family first had attacks of gouty

arthritis between the ages of 21 and 35 (average 26.9 years), much younger than the usual onset of primary gout. Serum creatinine concentrations exceeded 177 $\mu\text{mol/l}$ in eight patients, and either peritoneal dialysis or haemodialysis was started for four of them. Eight subjects who died with severe renal failure were identified.

Figure 1 shows the family pedigree. Clearly, the disease causing gout/hyperuricaemia and renal insufficiency is genetic, inherited dominantly through six generations. As far as we know this is the largest family with urate nephropathy to be reported. Among the 117 members in this pedigree, 23 (20%) had gouty arthritis or asymptomatic hyperuricaemia and 17 (15%) had renal insufficiency. The occurrence of gout/hyperuricaemia and renal disease tended to coincide. Thus a subject with renal insufficiency almost always had gout or hyperuricaemia. Furthermore, all descendants of subjects with neither gout/hyperuricaemia nor renal insufficiency were free from related diseases. Table 1 summarises the clinical course and outcome of disease.

Renal function was evaluated by clearance studies in 10 subjects (table 2). Five of these patients had histories of gouty arthritis, while the other five had neither gout nor hyperuricaemia. Daily excretion of uric acid and fractional clearance of uric acid (C_{UA}/C_{Cr}) were decreased in all the subjects with gout. It should be emphasised that even in a 20 year old patient with gout (VI-10 in fig 1) urinary excretion of uric acid was low. It seems that reduced excretion of uric acid is the primary cause of hyperuricaemia in this family.

To exclude the possibility of other causes of genetic hyperuricaemia and gout the activities of hypoxanthine-guanine phosphoribosyltransferase and phosphoribosylpyrophosphate syn-

Table 1 Clinical course and outcome in family members with renal disease or gout, or both

Patient	Sex	Blood pressure mmHg (age)	Age at presentation with gout	Serum creatinine $\mu\text{mol/l}$ (age)	Allopurinol treatment	Outcome (age)
I-1	M	NA*	NA	NA	No	Died of uraemia (73)
III-2	F	140/90 (39)	29	NA	No	Died of uraemia (48)
III-4	M	NA	23	NA	No	Died of uraemia (45)
III-6	M	NA	25	NA	No	Died of uraemia (53)
IV-4	F	190/110 (67)	29	PD* (67)	No	Died of uraemia (67)
IV-6	F	200/100 (65)	35	248 (65), 398 (77)	Continuous from age 65 to 76	Alive (77)
IV-19	M	NA	26	NA	No	Died of uraemia (45)
IV-21	M	NA	24	NA	No	Died of uraemia (45)
V-3	M	210/120 (46)	31	787 (46), HD* (46)	No	Died of cerebral bleeding (54)
V-5	M	180/110 (53)	33	212 (53), 283 (55)	Continuous from age 53	Alive (55)
V-9	M	160/100 (49)	25	239 (49), 380 (53)	Intermittent only from age 30	Alive (53)
V-15	M	184/114 (40)	—	HD (42)	No	Alive (55)
V-21	M	176/112 (38)	22	HD (40)	No	Alive (45)
VI-6	M	132/70 (22)	21	88 (22), 186 (30)	Continuous from age 21	Alive (30)

*NA=not available; PD=peritoneal dialysis; HD=haemodialysis.

Table 2 Clearance studies in 10 family members

Patient	Age	Sex	History of gout	Serum uric acid (mmol/l)	UV_{UA} * (mmol/24 h)	C_{UA} * (ml/min)	C_{Cr} * (ml/min)	C_{UA}/C_{Cr} * (%)
IV-6	72	F	Yes	0.52	1.3	0.4	10.3	3.88
V-5	55	M	Yes	0.42†	0.8	1.24	23.0	5.39
V-9	53	M	Yes	0.52	1.4	1.43	38.2	3.74
VI-6	30	M	Yes	0.38†	1.2	3.9	61.2	6.37
VI-10	20	M	Yes	0.41	2.6	5.97	108.0	5.53
V-2	62	F	No	0.27	3.7	6.67	78.7	8.48
VI-1	42	M	No	0.39	4.8	16.65	90.2	18.46
VI-4	31	F	No	0.32	7.3	13.10	96.4	13.59
VI-5	24	M	No	0.37	6.1	17.88	92.3	19.37
VI-23	32	M	No	0.4	3.1	8.62	80.3	10.73

* UV_{UA} =urinary uric acid excretion; C_{UA} =uric acid clearance; C_{Cr} =creatinine clearance; C_{UA}/C_{Cr} =fractional clearance of uric acid.
†Receiving allopurinol 200–300 mg/day.

Figure 2 Clinical course of patients with gouty arthritis and renal disease. Concentrations of serum uric acid (●—●) and serum creatinine (○—○) were determined serially in these patients, all of whom had been receiving allopurinol to control hyperuricaemia.

thetase were assayed in the erythrocytes from 10 subjects in this family. There are two major purine metabolising enzymes, genetic abnormalities of which may result in overproduction of uric acid. These enzyme activities were normal, however. These results exclude the possibility of partial deficiency in hypoxanthine-guanine phosphoribosyltransferase and hyperactivity of phosphoribosylpyrophosphate synthetase as the cause of hyperuricaemia.

At least four patients were treated with allopurinol 200–300 mg/day. Figure 2 shows the effect of this treatment on serum uric acid and creatinine concentrations. Despite control of serum uric acid concentrations with allopurinol, serum creatinine concentrations gradually increased in all patients, indicating progressive deterioration of renal function.

Discussion

In most chronic diseases serum uric acid concentrations are not greatly increased before renal function is severely impaired because reduction in the amount of uric acid filtered through the glomerulus is well compensated for by increasing tubular excretion of uric acid.¹⁶ Therefore chronic renal insufficiency from primary renal disease is a rare cause of severe hyperuricaemia or gout. On the other hand, impairment of renal function usually develops only at a later stage of primary gout unless hypertension or renal calculi occur.^{17,18} It is also rare, therefore, that young subjects develop severe renal impairment because of primary gout.

The cause of the familial disease described here could be explained neither by renal insuff-

iciency secondary to usual primary gout, nor by gout/hyperuricaemia secondary to the usual renal disease. Early onset of hyperuricaemia and gout followed by rapid development of renal impairment is a characteristic feature of this familial disease. Strict control of hyperuricaemia with allopurinol in some family members prevented gouty arthritis, but not the progression of renal impairment, indicating that hyperuricaemia is not the primary cause of this renal disease. The mechanism causing hyperuricaemia seems to be a marked reduction in urinary excretion of uric acid.

Another characteristic of this familial disease is a high rate of association with hypertension, even in those without marked renal insufficiency. Thus seven out of 14 patients with this renal disease or gouty arthritis (or both) had hypertension. One member (V-3 in fig 1) had malignant hypertension and died of cerebral bleeding at the age of 54. Although the mechanism of hypertension in this family is not clear,^{19,20} it apparently modified the clinical course of the disease.

Occurrence of the disease in every generation is evidence of transmission from father to son, and approximate equivalence between sexes among affected subjects strongly suggests dominant transmission. Hypoxanthine-guanine phosphoribosyltransferase deficiency (complete or incomplete) and phosphoribosylpyrophosphate synthetase superactivity, two known causes of familial hyperuricaemia, were excluded as possible causes of the disease in this family because no supporting evidence indicated that such enzyme activities played a part in disease transmission.

The clinical and laboratory features of the

familial renal disease described here are consistent with those reported by Richmond *et al* as 'familial urate nephropathy' in a white family with gout and renal disease.² Similar conditions have been reported in families elsewhere.^{2-5 7-13} In most of these reports renal biopsy specimens showed non-specific tubulointerstitial nephropathy. Uric acid crystals were not identified, except for a case described by Farebrother *et al*.¹¹ Richmond *et al* described an 8 year old boy with hyperuricaemia and a normal serum creatinine concentration.² A renal biopsy specimen showed advanced interstitial fibrosis and tubular atrophy. Thus kidney lesions may occur before the appearance of gouty arthritis.

Dominant inheritance of the disease indicates that a single locus has an aetiological role. Among various loci related to genetic renal diseases, the locus for adult polycystic kidney disease may possibly be identical to the locus for this disease. A recent report by Mejias *et al* stated that hyperuricaemia and gout were common complications of adult polycystic disease.²¹ A marked underexcretion of uric acid was seen in the patients in this family, however, whereas most patients with adult polycystic kidney disease and hyperuricaemia excrete a normal amount of uric acid into the urine. Thus our conditions were genetically different from those of most cases. Linkage analysis using DNA probes for genetic loci and restriction fragment length polymorphism might provide further evidence on the origin and transmission of this disease.

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