

Familial gout and renal failure

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SUMMARY Clinical gout and renal failure was seen in a 9-year-old girl. The family tree showed that 9 out of 11 young females in three generations suffered from hyperuricaemia and normal ($n=1$), or impaired ($n=8$), renal function. One set of twins occurred in each generation and there is only one living male subject. In members with renal failure there was no improvement in renal function after treatment of hyperuricaemia, and in 2 sisters oral contraceptives appeared to precipitate hypertension. This clinical picture may be more common than is generally realised because of failure to compare blood uric acid values with suitable age- and sex-matched controls. The evidence from this family suggests that hyperuricaemia preceded the development of renal failure.

Classical gout occurs most commonly in middle-aged men,¹ and is extremely rare in premenopausal women or children. In children a specific metabolic abnormality resulting in gross uric acid over-production—such as the Lesch-Nyhan syndrome—can often be identified.² Although at one time renal failure was common in gouty patients³ Berger and Yu⁴ could find no case in which death might be attributed to renal failure in 524 men with gout. Conversely, in renal failure from other causes, hyperuricaemia occurring as part of the general retention of nitrogenous waste is invariably mild even if there is severe reduction in glomerular filtration rate. Gout is rare as a primary cause of renal failure and accounts for only 0.8% in 69 400 European patients treated by dialysis (A J Wing, 1979, personal communication).

In this paper a family is described with the unusual combination of precocious gout and progressively fatal renal disease occurring in young women. There is strong evidence to suggest that raised uric acid levels preceded the onset of the renal disease.

Patients and methods

All biochemical results were obtained from routine analysis of blood samples in the hospital laboratory using SMA 12-60 colorimetric methods. Detailed investigations using a specific enzymatic method for uric acid are presented elsewhere.^{5,6}

Clinical features.

Case 1

This 9-year-old girl presented in 1961 with gout in the left big toe. Her blood urea concentration was 12.5 mmol/l (75.3 mg/100 ml) and blood uric acid

0.55 mmol/l (9.2 mg/100 ml), but the uric acid at another hospital had been found to be 0.78 mmol/l (13 mg/100 ml). She was treated with sulphinyprazone in varying dosages between 1961 and 1967 when allopurinol was started, and on which she remains. Poor patient compliance probably explains the pronounced variation in the blood uric acid level during treatment (Fig. 1), and two attacks of gout in the left

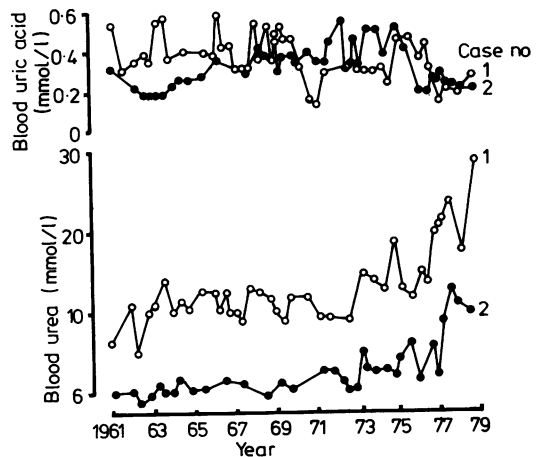


Fig. 1 Changes in blood urea and blood uric acid levels in the twin sisters Cases 1 and 2. During nearly the entire period both patients were treated with sulphinyprazone, and, latterly, with allopurinol. The rise in blood urea in each at a time when uric acid levels were under good control followed the development of high blood pressure after the introduction of combined oestrogen/progesterone oral contraceptives.

big toe occurred in 1962 when the uric acid level was 0.56 mmol/l (9.40 mg/100 ml). Despite fluctuations the blood urea did not change appreciably during the 13 years between 1963 and 1976, and throughout this period the blood pressure remained in the range 90–95/60–70 mmHg. The only symptom recorded was thirst in the evening, and nocturia.

Blood creatinine concentration was first measured in 1968 when it was 0.31 mmol/l (3.41 mg/100 ml); it remained unchanged, as did the blood urea, until June 1976 when the blood pressure was found to be 170/120 mmHg after she had been taking oral contraceptives for 9 months. Oral contraceptives were stopped in June 1976 but blood pressure remained high and treatment was required to control it. There has been pronounced deterioration in renal function for the 3 years since treatment started for high blood pressure in 1976 (Fig. 1), despite good control of blood uric acid levels. Microscopical examination of urine samples was normal in 1976 and there was less than 30 mg/100 ml proteinuria. This patient is now being treated by intermittent haemodialysis.

Case 2

This non-identical twin sister of Case 1 was found to be hyperuricaemic in January 1961 when her sister presented with gout. Her blood uric acid concentration was 0.33 mmol/l (5.54 mg/100 ml) and the blood urea 6.45 mmol/l (39.4 mg/100 ml) (Fig. 1), but the uric acid level at another hospital had been previously reported as 0.45 mmol/l (7.5 mg/100 ml). She has never suffered from gout. Her blood pressure was 92/60 mmHg at presentation. She was treated with sulphinyprazole until 1964 with good control of blood uric acid, and allopurinol was started in 1968 when the blood uric acid was 0.47 mmol/l (7.9 mg/100 ml). She has subsequently remained on allopurinol in varying dosages. Blood creatinine concentration was first measured in 1969 and remained between 0.12 and 0.17 mmol/l (1.32 and 1.87 mg/100 ml) until 1976. Blood pressure was first found to be high (165/90 mmHg) after she started taking oral contraceptives in 1976 and blood urea, which had previously varied between 5.7 and 12.6 mmol/l (34.3 and 75.8 mg/100 ml), rose to a maximum of 19.4 mmol/l (116.8 mg/100 ml) and the creatinine had risen to 0.19 mmol/l (2.09 mg/100 ml) by May 1977. Although she stopped taking oral contraceptives within 6 months, the blood pressure remained high (as in her twin) and has required treatment. Renal function appears to have deteriorated greatly since hypertension was noted, despite good control of serum uric acid (Fig. 1). Albuminuria has at no time been noted, and

microscopical examination of the urine was normal in 1977.

Case 3

This 39-year-old woman and cousin of the twins (Cases 1 and 2) first came to attention in 1968 when admitted for investigation of menopausal symptoms after hysterectomy. Two previous pregnancies had resulted in miscarriages and the elder daughter had had a twin brother who had died with a collapsed lung at 2 months. In 1969 her blood pressure was 132/88 mmHg at which time she was investigated for urinary tract infection. An intravenous pyelogram showed possible renal scarring and two small kidneys, 6–7 cm in length. An open renal biopsy was carried out. The blood uric acid was first measured in 1971, after the family history of gout and renal failure had been recognised, and was found to be raised (0.42 mmol/l; 7.1 mg/100 ml). This was treated successfully with allopurinol and the blood pressure was treated with methyldopa in 1972, diuretics being avoided because of the family history of uric acid disorders. Initially the blood urea level was 21 mmol/l (126.4 mg/100 ml) and the creatinine level 0.27 mmol/l (2.97 mg/100 ml) but both of these subsequently fluctuated between 21 and 29 mmol/l (126.4 and 174.6 mg/100 ml) and between 0.27 and 0.35 mmol/l (2.97 and 3.85 mg/100 ml) respectively until 1977. Pyuria was noted in 1969 but subsequent urine analysis has been normal.

Case 4

This girl, born in 1962 and the elder daughter of Case 3, has been investigated repeatedly since 1968 because of her mother's anxiety and the family history. At that time epithelial cells, leucocytes, and some uric acid crystals were reported in a centrifuged deposit. In 1969 an intravenous pyelogram, a micturating cystogram, and urine culture were normal. The blood pressure was 100/65 mmHg and the child remains normotensive. The blood urea, creatinine, and uric acid concentrations were normal when first measured. During the period from 1971 to 1977 the blood urea rose slowly to 12.4 mmol/l (74.6 mg/100 ml), plasma creatinine to 0.17 mmol/l (1.87 mg/100 ml), and uric acid to 0.43 mmol/l (7.2 mg/100 ml) (Fig. 2), all high for a slender 15-year-old girl. The hyperuricaemia was successfully treated with allopurinol. It is of interest to compare the slow progressive rise in both serum creatinine and uric acid concentrations in Case 4 with that in her 2nd-cousin Case 2 (Fig. 3).

Case 5

This girl, the younger sister of Case 4, was born in 1964 and had also been investigated annually

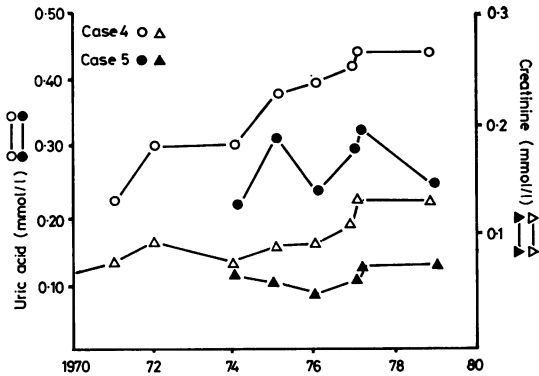


Fig. 2 Changes in blood uric acid and creatinine levels in the sisters Cases 4 and 5. The plasma creatinine appears to have stabilised since allopurinol treatment was started in each in 1977.

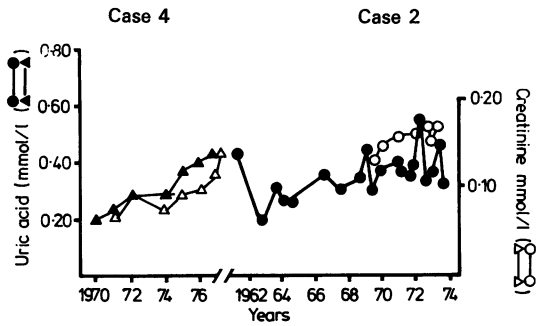


Fig. 3 Comparison of blood uric acid and creatinine levels in Case 4 and her second cousin showing marked similarity in the rate of change of both renal function and blood uric acid levels in two female members of the same family.

since 1971 when she was 7-years old (Fig. 2). She has had no symptoms apart from traces of proteinuria in 1975 and 1976. Blood levels for creatinine and uric acid were considered normal from 1971 to 1977 as were uric acid and creatinine clearances. The blood pressure was initially 90/65 mmHg and has remained constant. However, as with Case 4 blood creatinine and uric acid levels rose slowly from 1971 to 1976 (Fig. 2). An intravenous pyelogram in 1977 showed normal kidneys and normal urinary tract. Severe bleeding associated with grossly abnormal renal vasculature followed needle biopsy of the kidney and led to nephrectomy. However, creatinine clearance in 1978 was 104 ml/min. Allopurinol treatment was started after the renal biopsy and has continued.

Family study. The study extended over five generations and included detailed histories of relatives of both the maternal and paternal grandfathers. Information after 1837 was obtained from local registry offices and before that date from St Catherine's house. Facts were checked with parish records or county archivists whenever possible. Many living descendants agreed to be interviewed. Detailed case histories of the immediate family members were obtained from family doctors and hospital records for periods up to 18 years.

The affected members of the family were traced back to I, 2 (Fig. 4) who was born in 1861 and married I, 1 (Fig. 4) and died in 1932. She is reported to have suffered from Bright's disease. Nine of 11 females in the kindred had gout, hyperuricaemia, or renal failure, or a combination of the three. Renal failure without coexisting hyperuricaemia did not occur but hyperuricaemia without renal failure was found in one young girl (Case 5, V, 3). All were normotensive at the time of the original diagnosis. At the time of presentation with gout in Case 1 at age 9 years, three of these women—the child's mother, her own twin, and a third sister—were all being treated for renal failure. Only when the child's gout was diagnosed was the coexisting hyperuricaemia and gout identified.

The father of the family (II, 3 in Fig. 4) is thought to have suffered from gout; he died at age 40 after tuberculosis. His brothers and sisters and their descendants do not have a record of gout, renal failure, twins, or early death.

The mother of the kindred lived to a healthy 80 years and there is no suggestion of gout or renal failure in her kindred. The family history thus

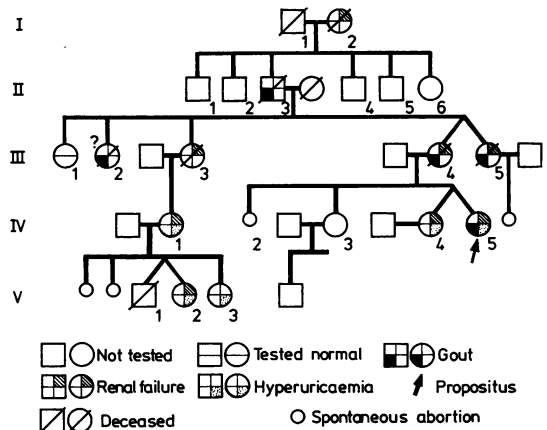


Fig. 4 Family tree to show the incidence of gout and renal failure.

suggests a spontaneous mutation manifest in her husband (II, 3 in Fig. 4) born in 1884.

Histological investigation. Renal biopsy, performed in Case 3 (IV 1) when she was 30 years old and before the family history of gout had been recognised, showed intracapsular fibrosis in 5 out of 50 glomeruli, with foci of chronic cell infiltration and fibrosis in the interstitium. Mild chronic pyelonephritis was considered possible but the appearances were non-specific. Tubular basement membrane thickening with patchy mild interstitial fibrosis were also seen in the biopsy in her daughter (Case 4; V, 2). The biopsies have now been re-examined in detail and will be reported elsewhere.⁷

Discussion

The single fact which initially distinguished this kindred was gout in the big toe in a young girl of 9. An aunt had already died 10 years earlier of 'nephritis', and the child's mother and the mother's identical twin sister were both being treated for gout and progressive renal disease which developed in their late twenties. The fact that the little girl's own non-identical twin was also hyperuricaemic, and that renal function was varyingly reduced in both, served to focus attention on the coexisting abnormality of uric acid metabolism which had hitherto escaped notice. Alport's syndrome had been diagnosed in the family but clinical features in recently affected members do not support this. Failure to recognise the severity of the hyperuricaemia in these young women was partly due to comparing their blood uric acid levels with a range for normal adults issued by the hospital laboratory. Thus laboratory results should be compared with appropriate control values.

These investigations confirm a repetitive abnormality of uric acid metabolism associated with a high incidence of renal disease of varying degree. The family study suggests an autosomal dominant disease which has, by chance, affected only females in a family with few males. Alternatively, II 3 (Fig. 4) could have been a mosaic for an X-linked somatic mutation, and this would explain the absence of the disease in one of his daughters.

The high incidence of twins in affected family members is remarkable and was noted by us in another study of families with a similar history of precocious gout and progressive renal disease.⁶ There is evidence to support the possibility that these young, gouty patients may form a distinct subgroup or groups within the gouty population which is almost certainly more common than currently

realised. For instance, several recent surveys of large gouty populations have confirmed the rarity of gouty women as well as confirming the fairly good renal function in most of today's gouty subjects—a group predominantly middle aged and male.^{1,4} Within each survey however, a few subjects have been identified in whom gout developed before age 40 and in whom it was associated with severe renal disease, and such surveys have shown a high incidence of females.

The nature and origin of the defect in this present kindred remains unknown. The close similarity in the development of the disease (around puberty) in one generation and between generations suggests a process common to all affected members of the family. Although urinary tract infection was noted early in the cousin of Case 1, the disease was by then well established and urinary tract infection has not been a recurrent clinical problem, nor was it present in family members who were equally badly affected. Primary renal disease—such as in Bartter's syndrome, Alport's syndrome, medullary cystic disease, saturnine gout, and analgesic abuse—may occur in childhood but there was no clinical evidence of such a disorder in any member of the family. The incidence over several generations, the exclusive occurrence in females, and the distribution of the patients over a wide area of southern England excludes the possibility of saturnine gout. Glycogen storage disease type I can also be excluded on clinical grounds.

The fact that affected family members were initially normotensive, despite coexisting renal disease of considerable severity, excludes any primary role for hypertension in the origin of the metabolic defect or the renal lesion. The subsequent development of hypertension associated with the introduction of oestrogen therapy in 2 cases is noteworthy. Hypertension is a well-documented consequence of the use of oral contraceptives⁸ and other methods of contraception should be recommended if such a family history is apparent. This deleterious effect of hypertension on renal function was noted in a study of middle-aged gouty men in which only those in whom the renal function was abnormal for age were also hypertensive.⁹

Similar families have been reported.^{10–14} Of these the present family most closely resembles that of Leuman and Wegmann.¹³ That family included a mother and 2 young daughters all of whom were normotensive. As in the present kindred the mother also developed hypertension after taking contraceptives and she too had suffered from gout and renal disease since childhood. All family members are now in renal failure, and 2 are being treated by

regular haemodialysis (E P Leuman, 1979, personal communication).

The central role for uric acid in the defect seems certain. The unusual combination of gout and hyperuricaemia in adolescence, together with the renal failure seen here, has been noted in at least some members of every family reported to date.¹⁰⁻¹⁴ Moreover, unlike primary renal disease, the hyperuricaemia has been disproportionate to the mild reduction in renal function. For example, a uric acid of 0.57 mmol/l (9.5 mg/100 ml) was found with a creatinine concentration of only 0.15 mmol/l (1.65 mg/100 ml) on more than one occasion in the less affected twin of the propositus in this family. Such uric acid levels are rare in primary renal disease even with less than 10% of renal function.¹⁵ This fact, together with the observation that hyperuricaemia without any evidence of renal disease was found in the youngest girl, while renal failure without coexisting hyperuricaemia was not noted, argues against a primary renal lesion in this kindred.

When Case 1 was identified at age 9 years, renal function was already less than 30% of normal while that of her non-identical twin was in excess of 70%, and remained little changed for the next 15 years. This long attenuation in development of renal failure is in sharp contrast with the earlier progression into terminal renal failure during a similar period in the mother and 2 aunts of Case 1. Whether the lack of recognition and treatment of the hyperuricaemia was associated with the early morbidity in the mother's kindred is a question which must remain unanswered at present. However, support for this hypothesis comes from the stability in renal function with effective treatment of hyperuricaemia during the last 2 years in the most recent case to be identified. Complicating hypertension after taking oral contraceptives has clouded the issue in Case 1 as well as in her sister and cousin. Thus continuing studies in the 2 youngest girls will be important.

Tradition still favours a primary renal disease in this defect. Nevertheless, gout is rare in women, even in those with the severest form of renal failure. A comparative study in which renal disease was considered the primary event and precipitated gout, the age was greater, and there was a gap of 10 years (mean) from the onset of renal disease to the appearance of gout.⁹ The difference in the clinical features between our patients and adult gout, whether primary or secondary, does appear so great that there are no grounds on which to draw a close analogy.

The existence of a specific lesion due to sodium urate deposition is still open to doubt. On clinical grounds there is no conclusive evidence that adult

gouty patients are susceptible to chronic renal failure.⁴ In addition, interpretation of the lesion is complicated by interstitial nephritis which may occur with advancing age, hypertension, nephrosclerosis, or urinary tract infection.^{16 17} The present family provides evidence that in one subgroup of gouty patients hyperuricaemia may antedate any deterioration in renal function as measured by blood urea levels (Case 5, V 2 and Case 2, IV 4) and in Case 5 by creatinine clearance.

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Annual meetings

1982	20-24 April	Aviemore Centre, Scotland
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1984	10-14 April	York University
1985	16-20 April	York University