Renal failure associated with crystal-induced nephropathy and gout in a baby boy

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There has been much controversy 1 over the relative roles of crystal deposition, vascular disease, and age in the genesis of the renal lesion in gout, where nephropathy was formerly common but is now extremely rare. 2 Considerable debate as to whether the origin of the lesion was interstitial 3 or stemmed from intratubular deposition.
of uric acid has also occurred. We have argued for the primacy of intratubular crystal deposition in the past based on studies using an animal model, as well as patients with inherited disorders resulting in gout and/or nephropathy. We present data on severe renal damage associated with tubulo-interstitial deposition of uric acid/urate in an infant with hypoxanthine-guanine phosphoribosyltransferase deficiency (HGPRT: EC 2.3.2.8), in the absence of hypertension or vascular pathology.

CASE HISTORY

A 5 week old boy was the first child of healthy unrelated parents. From 3 weeks he throve poorly, had feeding difficulties, and was extremely irritable. On admission the thumb and first two fingers of the right hand were red, swollen, and painful. Neurologically, he was slightly hypotonic. Plasma creatinine was 350 μmol/l (3·9 mg/100 ml) and plasma urate disproportionately high at 1·13 mmol/l (9 mg/100 ml). However, ratio of urine uric acid to creatinine (mmol/mmol) was 1·71, which is within the normal range for a child of this age.

Plain abdominal x-ray film showed no radio-opaque calculi, but renal ultrasound showed both kidneys were bright, suggesting a crystal nephropathy. A renal biopsy showed crystals in both tubules and interstitium in a cryostat section under polarised light. There was much tubular atrophy with extensive tubular epithelial giant cell transformation in the cortex and medulla. All crystals dissolved on fixing in formalin.

HGPRT activity was <0·01 nmol/mg Hb/h in lysed red cells, <0·9 nmol/mg protein/h in fibroblasts and <0·2% of normal in intact red cells. Incorporation of labelled hypoxanthine into nucleotides by intact fibroblasts was 6% of control, which is low on the criteria of Page et al. These results confirm severe HGPRT deficiency.

Treatment has consisted of allopurinol 5–10 mg/kg/24 h and sodium bicarbonate. Plasma uric acid on discharge had fallen to 0·5 mmol/l (8 mg/100 ml), plasma creatinine to 90 μmol/l (1·0 mg/100 ml). The allopurinol dose has subsequently required careful monitoring.

COMMENT

The onset of clinical gout at 5 weeks of age must be unique. The association of gout and renal failure due to crystal-induced nephropathy is also rarely seen today. The histological lesion is generally a non-specific interstitial nephritis considered to be due to age, hypertension, or both. Others have defined two specific nephropathies—acute nephropathy due to intratubular uric acid deposition (essentially reversible) as distinct from the slow insidious interstitial deposition of sodium urate from supersaturated body fluids (essentially irreversible).

The lesion in this young child supports our contention from animal studies, as well as a case of 2,8-dihydroxyadenine nephropathy, that the initial insult is intratubular, the natural sequelae of which, through basement membrane rupture, is the migration of crystals into the interstitium with subsequent inflammatory response (Fig. 1b) proceeding to fibrosis and permanent renal damage.

This hypothesis is supported by the fact that infants maintain a low plasma uric acid through a high urate clearance. Gross uric acid overproduction in HGPRT deficiency would result in high urinary urate which would provide the initial insult; the raised plasma uric acid must have been secondary to the subsequent renal damage. Plasma urate concentrations (after the immediate neonatal period) are extremely low; to those accustomed to adult values, the raised concentrations in children may thus not appear abnormal. In this child the concentrations were disproportionately high for the degree of renal damage, even for an adult. This provided the only clue to the possibility of uric acid overproduction in this infant, since the usual hallmark, high uric acid excretion on a creatinine basis, was obscured because of the renal damage.

Adequate control of uric acid concentrations by allopurinol has also presented a problem because of the renal damage, particularly in such a young child. Too high a dose has resulted in retention of oxipurinol, which could potentiate bone marrow depression, it has also resulted in the excretion of excessive amounts of xanthine, which is more insoluble than uric acid.

This case is important for several reasons. Firstly, it indicates the problems of diagnosis and treatment in HGPRT deficiency when renal function is impaired. The presence of crystals within the tubules as well as the interstitium in cryostat section only—but not formalin-fixed tissue—underlines the difficulty of identification of uric acid-induced crystal nephropathy histologically, unless special precautions are taken. The histological picture indicates that crystals can reach the interstitium in the 'gouty kidney', after disintegration of the tubules.

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References

Lean, dry gout patients

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Hypertriglyceridaemia is common in gout.1 2 Obesity may increase triglyceride concentrations, as may alcohol,3 but it remains uncertain whether obesity and alcohol, alone or in combination, are sufficient to explain the hyperlipidaemia in all cases. We looked for abnormal lipid concentrations in non-obese patients with gout who drank little or no alcohol to determine whether the hyperlipidaemia associated with gout occurred in such a lean and abstemious group.

All patients were of desirable weight or less for their age and frame4 and no patient drank more than one pint of beer per day or its equivalent. Such patients are rare, and only seven were found in four years from a busy clinic.

Fasting concentrations of lipid and lipoprotein were measured in serum at a laboratory with its own control population.5 Serum uric acid concentrations were determined for the patients with gout but unfortunately data for the control population were not available.

Readings for serum cholesterol, triglyceride, β-lipoprotein and prebeta lipoprotein concentrations in the patients with gout lay within 2 standard deviations of the corresponding mean for controls. This means that they were within the 95% confidence limits for the control population and it is therefore unlikely that there is any real difference between the patients with gout and control populations.

In spite of the small numbers of these, ‘lean, dry’ patients, the results revealed no intrinsic hyperlipidaemia in subjects with gout when obesity and an excess of alcohol were removed as causes of hypertriglyceridaemia.

References


Cardiovascular disease and gout: a function of sex and age?

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Hypertriglyceridaemia is common in patients with gout and hyperuricaemia but it is still not known whether this results from a link between purine and lipoprotein metabolism or whether they occur together due to other associated facts, particularly obesity and high alcohol intake, both of which are commonly found in patients with hyperuricaemia.1 Nor is it firmly established whether patients with gout are, in fact, predisposed to premature cardiovascular disease, and, if so, whether the raised serum uric acid concentration operates as an independent risk factor, or only via its association with hypertriglyceridaemia and hypertension, which are established as cardiovascular risk factors in their own right.2 Another possibility—namely, that a raised serum uric acid concentration causes platelet hyperaggregatability and hence thrombosis—has recently been investigated in our unit with negative results.3

Over a period of two and half years
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