Oxalosis in infancy

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SUMMARY We describe 3 infants with nephrocalcinosis and terminal renal failure. In all 3 there was widespread oxalate deposition: biochemical evidence of primary hyperoxaluria was sought but the presence of severe renal failure and the lack of established normal values for urinary and plasma oxalate and glycollate in infants made this diagnosis difficult to establish.

Oxalosis is the widespread deposition of calcium oxalate crystals throughout the body.¹ In primary oxalosis a recessively inherited enzyme defect in organic acid metabolism causes oxalate accumulation; at least two types have been described in children and young adults but there have been few reports of the condition in infancy.^{2–7} The clinical consequences of primary oxalosis are mainly renal with nephrocalcinosis, stone formation, and progressive renal insufficiency. Secondary oxalosis occasionally results from excessive intake of oxalate or its precursors (for example ethylene glycol antifreeze), but more commonly it results from decreased oxalate excretion in chronic renal failure from any cause. We describe the investigations and clinical course of 3 infants with oxalosis and discuss the difficulties in establishing whether it was primary or secondary.

Case reports

Case 1. An 11-month-old boy was admitted to Guy's Hospital with a short history of pallor and breathlessness; unusual thirst had been noted from age 1 month. He had been born in Kuwait of healthy unrelated Jordanian parents, and had 4 healthy siblings. His birthweight had been 3.75 kg. On admission his weight was 7.36 kg and blood pressure 160 mmHg systolic. There was no peripheral oedema. A 'pepper and salt' retinopathy was noted. Details of plasma biochemistry are shown in Tables 1 and 2. Abdominal x-ray film showed bilateral nephrocalcinosis; an intravenous urogram (IVU) showed no excretion of contrast, and a voiding cystogram was normal. A bone marrow aspiration from the left anterior iliac crest showed no oxalate crystals but a trephine biopsy from the same site

showed typical birefringent crystals in the zone of endochondral ossification. Because of deteriorating renal function he required peritoneal dialysis. He was started on pyridoxine 150 mg daily. No improvement in his clinical or biochemical status occurred during the next 10 days and after a second short period of dialysis he was discharged.

Case 2. A 3½-month-old girl was admitted to The Hospital for Sick Children after a convulsion with renal failure. She was the first child of healthy, unrelated parents and had been born at term after a normal pregnancy. Birthweight had been 3.2 kg and the neonatal period was uneventful. She had failed to thrive since age 7 weeks with poor weight gain and increasing pallor, and then developed vomiting and diarrhoea 2 days before admission. By this time she was moribund, being pale, grossly oedematous, and in heart failure with a blood pressure of 150/80 mmHg. Her weight was 5.4 kg. Optic fundi were normal and there were no other abnormal findings. Biochemical results are shown in Tables 1 and 2. An IVU showed no excretion of contrast, and a voiding cystogram showed a normal bladder and urethra, with bilateral vesicoureteric reflux into both pelvicalyceal systems and a normal calyceal pattern. Her 24-hour urine volume was only 20 ml; this did not increase after repeated doses of frusemide 5 mg/kg, so peritoneal dialysis was begun. When her condition had improved an open renal biopsy was performed; at operation the kidney was large, pale, firm, and did not bleed on incision. Histology showed normal glomeruli but there was markedly disturbed architecture of the renal parenchyma particularly in the cortex. Under partially polarised light there were numerous birefringent crystals with the classical fan-shaped pattern of calcium oxalate.

These were situated in the tubular lumina and the interstitial tissue. Silver rubeanate staining for oxalate was also positive. A 24-hour urine volume of 40 ml examined for organic acids by gas chromatography and mass spectrometry showed no evidence of glycolic acid excess, no glyoxylic acid or glyceric acid; oxalate concentrations are shown in Table 2. The other organic acids were in the normal range except for raised lactic acid and high glucose metabolites (3-deoxyhexonic acid and the tetrionic acids), presumably because of peritoneal dialysis. She was started on pyridoxine 80 mg daily in divided doses. However, her urine output remained scanty, dialysis was stopped, and she died a few days

later. At necropsy the right kidney weighed 21 g and the left kidney 24 g (normal for age). Heavy oxalate deposition was confirmed in the renal cortex, in the bone marrow immediately adjacent to the costochondral junction, in the myocardium, and the obliterated ductus arteriosus. Other organs, including the brain, were normal.

Case 3. A 6-month-old boy was admitted to Derbyshire Children's Hospital with a 4-week history of vomiting, intermittently at first and then persistently, and 48 hours of anuria. He was the second child of healthy, unrelated parents, and had been born at term after a normal pregnancy. Birthweight had been 3.6 kg. On admission he was tachypnoeic and irritable. His weight was 7.22 kg and blood pressure 110/60 mmHg. His fundi showed a flecked retinopathy. Bladder catheterisation yielded 5 ml of cloudy urine; a plain abdominal x-ray film showed bilateral nephrocalcinosis and an IVU with tomograms showed a normal pelvicalyceal pattern. Peritoneal dialysis was begun and the condition of the infant improved. Renal biopsy was performed and widespread oxalate deposition could be seen; fluorescent staining showed no deposition of immunoglobulins, fibrin, or complement. He was begun on pyridoxine, 200 mg/day, but there was no further clinical improvement despite repeated dialysis during the next 2 weeks. Treatment was therefore stopped and he died a few days later. At necropsy the kidneys were of normal size (right 40 g, left 35 g) and were pale yellow on cut sections with poor corticomedullary demarcation. Histology showed normal glomeruli and vessels. There were oxalate crystals in the tubules and interstitium where there was a chronic inflammatory infiltrate. Deposits of calcium oxalate crystals were also found in the heart, lung, thymus, brain stem, adrenals, epididymis, and pancreas. His eyes were enucleated shortly after

Table 1 Initial investigation results in 3 infants with oxalosis

Plasma	Case 1	Case 2	Case 3
Sodium (mmol/l) (normal 135-143)	135	141	125
Potassium (mmol/l) (normal 4.1-5.6)	6.4	4.9	7.1
Bicarbonate (mmol/l) (normal 18-22)	18	18	6.5
Urea (mmol/l) (normal 3.3-7.5)	32	28	67
Creatinine (μ mol/l) (normal 28-53)	488	172	1384
Calcium (mmol/l) (normal 2.13-2.62)	1.75	1.9	1.26
Phosphate (mmol/l) (normal 1.29-1.78)	3.75	ND	ND
Haemoglobin (g/dl) (normal 10-15)	9.0	4.6	8.9
Urinary protein	+++	0	+++
White blood cells ($\times 10^9$ /l)	22	0	100
Red blood cells ($\times 10^9$ /l)	8	0	0
Culture	No growth	No growth	No growth

Conversion: SI to traditional units—plasma urea: 1 mmol/l $\approx$ 6.02 mg/100 ml; creatinine: 1 μ mol/l $\approx$ 0.0113 mg/100 ml; calcium: 1 mmol/l $\approx$ 4 mg/100 ml; phosphate: 1 mmol/l $\approx$ 3.1 mg/100 ml. ND = not done.

Table 2 Organic acid and creatinine analysis in 3 patients with oxalosis

	Case 1	Case 2	Case 3
24-hour urinary oxalate excretion, mmol/1.73 m ² (mg/1.73 m ²) (normal <0.46 mmol/1.73 m ²)	0.54 (49)	0.01 (0.9)	ND
24-hour urinary glycollate excretion, mmol/1.73 m ² (mg/1.73 m ²) (normal <0.34 mmol/1.73 m ²)	0.67 (51)	ND	ND
Urinary oxalate/creatinine ratio (normal <0.086)	0.3	0.079	ND
Plasma creatinine, μ mol/l (mg/100 ml) (normal 28-53 μ mol/l)	540 (5)	ND	750 (8.5)
Plasma oxalate, μ mol/l (mg/100 ml) (normal 0.74-1.4 μ mol/l (7-13 mg/100 ml))*	51 (459)*	ND	33 (297)+†
Plasma glycollate, μ mol/l (mg/100 ml) (normal 31 μ mol/l (<2.4 mg/100 ml))*	36 (2.7)*	ND	26 (2.0)+†
Plasma glycerate, μ mol/l (mg/100 ml)†	ND	ND	6.6 (0.62)+

*Enzymatic method + gas chromatography method.
ND = Not done.

†Normal range not established in children.

death, and the histological findings have been reported elsewhere.⁸ The elder brother was investigated and his serum creatinine concentration, plain abdominal x-ray film, and urinary oxalate excretion were normal.

Discussion

Primary oxalosis is an inherited disorder characterised by the excretion of excessive amounts of oxalate in the urine. Two distinct types have been described;⁹ in type 1, a deficiency of the soluble thiamine pyrophosphate-dependent carboxylase enzyme, which converts glyoxylate to α -hydroxy- β -ketoadipate (Figure) and causes excessive excretion of glycollate and glyoxylate as well as oxalate in the urine. In the rarer type 2 disorder, there is increased urinary excretion of oxalate and L-glycerate, but diminished excretion of glycollate and glyoxylate. Secondary oxalosis may be associated with pyridoxine deficiency, ingestion of large amounts of oxalate or its metabolic precursors, or with certain intestinal disorders—such as ileal resection, where there is increased absorption of the normal dietary oxalate.⁹ The condition will also occur if renal clearance of oxalate is diminished, as in patients with chronic renal failure. Widespread tissue deposition of calcium oxalate crystals occurs in type 1 oxalosis (but not type 2), enteric hyperoxaluria, poisoning with ethylene glycol, xylitol, or methoxyflurane, and in renal failure.¹⁰ The main clinical effect is in the kidney with the development of nephrocalcinosis and stones leading to parenchymal destruction and renal insufficiency. Myocardial deposits of oxalate sometimes cause conduction defects, cardiac arrhythmias, or sudden death.

Oxalosis in infancy has been described at least 6 times.²⁻⁷ The infants presented at about 3-4 months old, with failure to thrive and poor appetite; 3 had convulsions before admission, one had nephrocalcinosis, and all died soon after admission. Oxalate excretion was increased in one infant,⁷ although no information was available on the normal

Figure *The glyoxylate, glycine, and ethanolamine cycle.*

plasma oxalate was disproportionately high in Case 1. In Case 2, the biochemical diagnosis of hyperoxaluria was not established. The urinary oxalate excretion was normal. However, her urinary volume was greatly diminished, and the diagnosis of hyperoxaluria is complicated by the presence of renal failure, as urinary oxalate excretion may decrease and even fall within the normal range as renal failure becomes more advanced. In Case 3, urinary studies could not be undertaken as the patient was anuric. The plasma oxalate, measured by gas chromatography, was $33 \mu\text{mol/l}$ (326 mg/100 ml) with a simultaneous plasma creatinine of $750 \mu\text{mol/l}$ (8.48 mg/100 ml). The normal range for plasma oxalate using this method had not been established, but the elder brother of Case 3, who had no clinical or biochemical evidence of primary hyperoxaluria had a plasma oxalate level of $5.6 \mu\text{mol/l}$ (53 mg/100 ml). Thus although the plasma oxalate in Case 3 was high it did not seem disproportionately so compared with his plasma creatinine level. Plasma glycerate measured by gas chromatography was $6.6 \mu\text{mol/l}$ (0.62 mg/100 ml) in the patient and $22 \mu\text{mol/l}$ (2.1 mg/100 ml) in his brother and plasma glycollate $26 \mu\text{mol/l}$ (2 mg/100 ml) compared with $68 \mu\text{mol/l}$ (5.2 mg/100 ml): normal ranges by this method have not been established in children.

We are confident that these children had primary oxalosis. We then tried to determine which type; this is generally done by measuring urinary glycollate and glycerate but in renal failure their clearances may be reduced and the effect of peritoneal dialysis on plasma levels is unknown. Plasma glycollate was slightly raised in Case 1 and was normal in Case 3 when compared with the normal adult range. Plasma glycollate is raised in adults with type 1 primary hyperoxaluria both before and after onset of renal failure, whereas it is normal in adults with renal failure from other causes (G P Kasidas and G A Rose, 1980, unpublished data). Thus plasma glycollate is a useful differential diagnostic test for the type 1 disorder in adults. The high plasma concentration and increased urinary excretion of glycollate in Case 1 are consistent with the type 1 disorder. In Case 2 the lack of excess glycollate and the absence of glyoxylate and glycerate in the urine (although oxalate was present) might suggest that some variant of the type 1 defect, or even a different enzymatic defect, may have been present but again the severity of renal failure makes interpretation difficult. The results in Case 3 are difficult to interpret because of lack of information about normal values in infants and the effects of renal failure and dialysis: they are not consistent with any known form of oxalosis.

Our most important conclusion is that the

diagnosis of primary hyperoxaluria is difficult to establish in infants, especially in the presence of advanced renal failure. From the clinical course and the widespread tissue deposition of oxalate, primary hyperoxaluria remains the most likely cause of renal failure in all 3 infants; there was no evidence of other primary renal disorders nor was there exposure to oxalate precursors. The disorder is inherited as an autosomal recessive trait so it is particularly important to try to establish the diagnosis so that appropriate genetic counselling can be given to the family. From our experience, and that of others, the prognosis of primary hyperoxaluria with oxalosis when it presents in infancy is very poor. Dialysis and transplantation have been offered to older children with oxalosis but they may develop disabling bone disease which is resistant to treatment and the disease can recur in the grafted kidney.¹⁴ Such treatment would be hard to justify in infantile oxalosis and renal failure. We were unable to show any improvement in our patients' condition with pyridoxine, but this could not reasonably have been expected as their disease was advanced. Pyridoxine therapy is of clinical and biochemical benefit in adults with type 1 primary oxalosis^{15 16} and if the diagnosis is made early in infants pyridoxine may be equally effective in them.

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