Ophthalmic manifestations of primary oxalosis

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SUMMARY The clinical and pathological findings of a 6-month-old infant with primary oxalosis, who died in renal failure, are presented. The oxalate crystalline deposition in the retinal pigment epithelium corresponded to the flecked retinopathy observed ophthalmoscopically. The difficulties in establishing a precise biochemical diagnosis are discussed and the relevant ophthalmic literature is reviewed.

Oxalate is an end product of metabolism which can be removed from the body only by the kidney. Therefore, if the total body oxalate increases, whether from increased ingestion of oxalate (or a precursor), hyperabsorption, or increased synthesis of this substance, hyperoxaluria will result, and in certain circumstances insoluble calcium oxalate in the tissues will be deposited to create the condition known as oxalosis. Although oxalate crystals have been recognised in urine for over a century, it was not until the 1950s that the metabolic and hereditary significance of hyperoxaluria was appreciated, and at present 2 variants of primary hyperoxaluria are recognised, both of which are uncommon and inherited in an autosomal recessive mode.

Type I hyperoxaluria is due to a deficiency of the cytoplasmic enzyme α-ketoglutarate: glyoxylate carboligase. Normally, under the influence of this enzyme glyoxylic acid, derived in the first instance from the breakdown of glycine, combines with α-ketoglutarate to form α-hydroxy-β-ketoacidipate. In its absence, however, glyoxylic acid is diverted to form glycolic acid and oxalic acids, the latter being irreversible, with the accumulation and increased urinary excretion of oxalic, glycolic, and, at times, glyoxylic acids. Although Bourke and co-workers recently have described a patient with high urinary oxalate and glycolate levels, but normal α-ketoglutarate: glyoxylate carboligase activity, these workers used skeletal muscle, whereas Koch et al.’s study related to the activity of this enzyme in liver, kidney, and splenic homogenates (Fig. 1).

Type II hyperoxaluria is characterised by a urinary excess of both oxalic and L-glyceric acids.

Leucocyte D-glyceric dehydrogenase has been found to be deficient in 4 patients with this disorder, leading through the action of lactic dehydrogenase to increased production and urinary excretion of L-glycerate from the reduction of hydroxypyruvate. The increase in oxalate synthesis is considered to reflect a concomitant oxidation of glyoxylate in response to lactic dehydrogenase activity.

Most patients with primary hyperoxaluria present in the first few years of life. Renal tract involvement dominates the clinical picture, with nephrolithiasis usually progressing to renal failure and death from uraemia within 10 years. It is, however, unusual for this condition to become apparent within the first year of life, only 16 of 105 recorded cases reviewed by Hockaday et al. presenting at this early age, and many of these presenting atypically.

The patients with type II hyperoxaluria so far reported have run a relatively benign course, remaining alive and well for over 15 years.

Secondary hyperoxaluria may occur in many conditions, including ingestion of oxalic acid or a precursor such as ethylene glycol, hyperabsorption of oxalate following small bowel resection, renal failure, sarcoidosis, and cirrhosis of the liver. Both thiamine and pyridoxine deficiencies cause hyperoxaluria in the experimental animal, but their role in the production of this state in man has yet to be clarified. The anaesthetic agent methoxyflurane, which is also a precursor of oxalic acid may cause renal failure, hyperoxaluria, and even retinal oxalosis.

Case report

A caucasian male was born on 11 July 1978 with a birth weight of 7 lb 15 oz (3600 g) after an uneventful pregnancy. There was no family history of renal
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Fig. 1  Simplified diagram of oxalate metabolism.

Disease, and the other sib, a boy aged 3 years, was healthy. Development was normal until the age of 5 months, when he contracted an upper respiratory tract infection. Within a few days he began vomiting after every feed and was admitted to the Derbyshire Children’s Hospital 1 month later (4 January 1979) having been anuric for 48 hours. Over the ensuing 20 days peritoneal dialysis was undertaken in 3 periods for a total of approximately 150 hours.

Despite his poor general condition and age he was visually alert on examination and responded to an optokinetic stimulus. The anterior segments of the eyes appeared normal. The posterior poles of both retiæae contained numerous minute round white flecks, which did not extend either to the optic disc or beyond the main vascular arcade. These areas were situated in the deeper retinal layers and appeared as pigment epithelial defects (Fig. 2).

Pyridoxine was administered, on an empirical basis, 50 mg intravenously 6 hourly for 3 days, but unfortunately no clinical improvement was obtained, and the infant, who had by this time been essentially anuric for 3 weeks, died on 24 January 1979.

Investigations

Blood. Before dialysis: Na 125 mmol/l, K 7.13 mmol/l, Cl 89 mmol/l, Ca 1.26 mmol/l, urea 67 mmol/l, creatinine 1384 μmol/l. During dialysis: glycolate 23 μmol/l (normal), oxalate 33 μmol/l (raised), L-glycerate 6.6 μmol/l (normal values as yet undetermined but probably normal).

Urine. Persistent anuria, no analysis possible. Plain abdominal x-ray showed diffuse nephrocalcinosis.

Renal biopsy. Glomeruli essentially normal for age. Almost all proximal tubules were packed with large crystalline aggregates, and the associated epithelial cells were either unidentifiable or degenerate. Some crystals had broken through the interstitium and stimulated a fibrotic and chronic inflammatory cellular infiltrate. Under partly polarised light the crystals showed the birefringent pattern of oxalate. The findings were confirmed by electron microscopy.

Bone marrow. A specimen obtained from the

Fig. 2 White flecks in the posterior fundus of the right eye.
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Fig. 3 Crystalline deposits of calcium oxalate in the pigment epithelium of the posterior retina. (Haematoxylin and eosin, ×180).

Fig. 4 Calcium oxalate crystals viewed through partially crossed polarising screens. (Haematoxylin and eosin, ×180).

Fig. 5 The calcium oxalate crystals are stained black by Yasue's silver-rubeanic acid technique (×180).

The anterior iliac crest did not contain any crystalline deposition.

Post-mortem pathology. The kidneys were of normal size (right 40 g, left 35 g) but the tubules were found to be packed with crystals. Crystals were also found in the heart, lung, thymus, thyroid, brain stem, adrenals, pancreas, and testis.

**Ocular histopathology**

The eyes were removed 5 hours after death. There was no discernible external abnormality of either globe.

The cornea, iris, ciliary body, and lens were normal and showed no evidence of crystal deposition. The posterior segment tissues were well formed and the retina was in situ. Towards the posterior pole, however, the retinal pigment epithelium showed several isolated crystalline deposits, which were colourless and birefringent (Figs. 3 and 4). The deposits consisted of sheaths of acicular crystals, and Yasue's stain for calcium oxalate was positive (Fig. 5). The smaller crystalline deposits were intracellular, whereas larger accumulations were associated with disruption and degeneration of the pigment epithelium (Fig. 6). Very occasionally crystals were seen within the neuroretina and were presumed to have migrated from their original location. Some penetration of Bruch's membrane with encroachment on the choroid was also observed in relation to the larger crystals.

Discussion

By definition the diagnosis of primary hyperoxaluria rests on the presence, in excess, of urinary oxalic and either glycolic or glyceric acids, and in
most instances such measurements can readily be made. In the present case, however, the persistent anuria precluded such estimations. The use of plasma oxalate levels has proved to be of limited value, as levels may rise in renal failure unrelated to oxalosis, though patients with primary hyperoxaluria tend to have higher concentrations than other patients with comparable blood urea or creatinine levels. Serum oxalic acid in our patient was estimated after peritoneal dialysis had started, and although the effect of this treatment on the plasma levels of this substance is not known with certainty it has been shown that peritoneal dialysis is not an efficient method of oxalate removal.

Other diagnostic possibilities which should be considered in this case are ingestion of oxalic acid (or precursor) or oxalosis secondary to renal failure. The limited mobility of a breast-fed 5-month-old infant eliminates the first, while the lack of renal pathology except for that attributable to oxalate deposition makes oxalosis secondary to renal failure unlikely. We therefore conclude that this infant suffered a primary disturbance of oxalate metabolism. Further consideration of this aspect is beyond the scope of this article, but as Williams and Smith state, ‘the diagnosis of primary hyperoxaluria in the uraemic stage of the disease may be difficult to document by current methods’.

Oxalate crystals have been found to be deposited in many tissues of the body, including bone, heart, thyroid and testis, with little or no clinical significance. Heart block due to involvement of the cardiac conduction tissues has been reported, and presumably the pendular nystagmus noted by Gottlieb and Ritter resulted from macular involvement.

So far oxalate deposition in extrarenal tissues has been considered in conditions in which there has been a disturbance of oxalate metabolism, but its deposition in the eye can occur in the absence of a systemic disturbance. Thus oxalate crystals have been detected in the lens in association with phacolytic glaucoma and Morgagnian cataract and in the retina or adjacent tissue fluid in long-standing retinal detachments.

The above are all instances of calcium oxalate deposition in degenerate tissue, and in none of these cases has there been a generalised disorder of oxalate metabolism.

The first report of ocular involvement in primary hyperoxaluria was when Scowen and colleagues detected crystals in the ciliary body as an incidental post-mortem finding. Brini confirmed this finding in a young adult who died from primary hyperoxaluria, noting crystals in the stroma of the ciliary processes. Franceschetti in a description of a 9-year-old girl with primary hyperoxaluria, was the first to observe retinopathy.

In 1963 Timm observed inflammation of the extraocular muscles associated with crystalline
deposits in the walls of their vascular supply in a patient with oxalosis; the ciliary body, choroid, optic nerve, and retina were also involved. The deposits in this last tissue were situated in the ganglion cell layer. A second report by this author concerns an eye enucleated for secondary glaucoma. Crystals were seen in all layers of the retina (predominantly the inner), retinal arterial walls, optic disc, and ciliary body. Vitreous membranes and haemorrhage were observed in addition to ruberosis iridis. Later the remaining eye developed white spots in the retina followed by a proliferative retinopathy and vitreous haemorrhage. This patient was in renal failure, but unfortunately owing to the paucity of systemic and biochemical data the nature of the basic pathological process is not clear. The involvement of the inner retinal layers, retinal arteries, and the later development of proliferative retinopathy are at variance with other reports, and it is not known whether they represent a later stage or different pathological process to that observed by others.

Toussaint et al. reported the clinical and pathological findings of a male with primary hyperoxaluria. White spots were seen to develop at both retinal posterior poles 1 month before death. Crystals were observed between Bruch’s membrane and the retinal pigment epithelium and a few were seen to be intraepithelial. Crystals were present in the ciliary body stroma, only occasionally reaching the pigment epithelium.

In 1977 Gottlieb and Ritter observed multiple white retinal flecks in an infant with type I hyperoxaluria. Initially the maculae were spared, but by the age of 9 months pendular nystagmus and macular involvement was seen. Pathological examination was not performed.

Ocular involvement in secondary hyperoxaluria has been reported by Bullock and Albert and colleagues in a patient who died of renal failure following abdominal surgery under methoxyfluorane anaesthesia. A flecked retinopathy, which did not affect vision, was seen, while histological examination of the eyes revealed multiple birefringent crystals in the retinal pigment epithelium involving the posterior pole and extending to the mid periphery. A few crystals were also observed in the ciliary body.

Despite the limited number of patients with either primary or secondary oxalosis in whom a retinopathy has been observed an evolutionary pattern is apparent. Initially small white flecks (appearing as minute depigmented areas in the deeper retinal layers) are seen at the posterior retinal poles, later spreading peripherally and in 1 case centrally to involve the macula. The histopathological changes are similar in most reports, crystals being detected in either the ciliary body or retina or both. It is not possible to state unequivocally whether the crystals originate intra- or extra-cellularly, but it is our impression, and that of Bullock et al., that they begin intracellularly and later disrupt the cell. The acicular appearance supports this theory and may also account for the observations that crystals were situated in the ciliary body stroma, for, if the illustrations are studied, crystals are seen abutting on the pigmented ciliary epithelium and in fact may have arisen from this layer, particularly as crystals have been observed in these cells. Retinal pigment epithelial involvement has been noted in 3 reports including the present case.

So far only the clinicopathological changes which sometimes occur in hyperoxaluria have been discussed, but it is interesting to consider a few factors which may influence calcium deposition in the eye and its predilection for the pigment epithelium.

The metabolic precursors of oxalic acid in man are ascorbic acid, glyoxylate and certain aromatic amino acids (tryptophan, tyrosine, and phenylalanine). Just under half the daily urinary excretion of oxalate is derived from ascorbic acid via a pathway which is ill understood but probably does not involve glyoxylate as an intermediary. Whether such a pathway exists in the eye is unknown, but this possibility should be considered, firstly because owing to active transport the concentration of ascorbic acid in human aqueous is 20 times that of plasma, and secondly because retinal microsomes in certain vertebrates have been shown to concentrate ascorbic acid via an energy dependent process. The concentration of this substance in the vitreous is much lower than in the aqueous but is still higher than in the plasma. Ascorbate levels in aqueous and vitreous were found to be decreased in naphthalene-fed rabbits, this being attributed to oxidation of ascorbate and its subsequent breakdown to oxalate. Calcium oxalate crystals were deposited in the vitreous and on the inner surface of the retina but not in the deeper retinal tissues. It is difficult to imagine that intraocular oxidation of ascorbate to oxalate has a significant role in hyperoxaluria, particularly as the site of deposition (pigment epithelium of ciliary body and retina) may be considered to be ‘upstream’ to the regions of ascorbate transport or concentration. Furthermore, involvement would be expected either to be generalised or to occur in regions of high ascorbate concentration rather than in the characteristic localised pattern observed.

Since there is no evidence that oxalate is synthesised locally, and since most membranes are per-
measurable to this substance, it is reasonable to suggest that it diffuses into the pigment epithelium from the submacular choroidal circulation. Why the pigment epithelium should be selectively involved is not known. As the low solubility of calcium oxalate is hardly altered between pH 5 and 8.2, intracellular pH changes cannot be significant, but whether other ions which could affect its solubility are present, or whether naturally occurring inhibitors to crystal growth such as exist in the urine are absent, is unknown.

Calcium influences many vital cellular activities including enzymatic and membrane-linked functions, so that it is important for cytoplasmic calcium to be protected from the considerable fluctuations in concentration to which extracellular calcium is subject. The Ca\(^{2+}\) content of the extracellular fluid at 10^{-3}M is at least a thousand times that of the cytosol (10^{-9} to 10^{-7}M), and, while both mitochondria and microsomes are rich in this cation, how much of this remains in its ionised state in these organelles is unknown. In order to maintain a constant cytosol Ca\(^{2+}\) level mechanisms exist to control its movement in and out of the cell and into the mitochondria and microsomes. The homeostatic mechanism is liable to be overwhelmed, however, by the influx of large amounts of oxalate which complex with the ionic intracellular calcium and precipitate to form poorly soluble crystals.

The acicular pattern of crystal formation observed indicates intracellular origin, and we therefore suggest that in the first instance oxalic acid diffuses into the retinal pigment epithelium, where for reasons as yet unknown precipitation as its insoluble calcium salt occurs. Once initiated, crystallisation continues apace in the continued presence of oxalate, further Ca\(^{2+}\) being derived presumably from the extracellular fluid. This mechanism has been suggested to account at least in part for the hypocalcaemia encountered in association with the soft tissue precipitation of calcium oxalate in oxalic acid poisoning, and it is tempting to speculate that the finding of a serum calcium level of 1.26 mmol/l in the present case prior to dialysis, which is unusually low even for acute renal failure, may have had a similar basis.

After the injection of microspheres into the carotid artery of rhesus monkeys a high concentration was observed in the macular regions relative to the retinal periphery. This greater vascularity of the submacular choroid has also been noted in man, both blood pressure and flow being higher in this region. As the evidence reviewed in this article indicates that both calcium and oxalate are blood-borne, we felt that the selective involvement of the macular region and ciliary body, in the absence of local biochemical factors, simply reflects the high vascularity of these 2 regions.

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