A clinicopathological study of ocular involvement in primary hyperoxaluria type I*

Kent W Small, Jon Scheinman, Gordon K Klintworth

Abstract
We performed a clinicopathological study on the eyes of a 3-year-old girl with primary hyperoxaluria type I. An examination one year before death disclosed a slightly diminished visual acuity in both eyes with black, geographic central macular, subretinal patches. Calcium oxalate was deposited predominantly in the retinal pigment epithelium of the posterior pole, where these cells were markedly hyperplastic and hypertrophied round foci of oxalate crystals. Oxalate crystals were exceedingly sparse in other ocular structures and were not associated with an apparent tissue reaction in these other locations. A collagenuous layer was evident between parts of the retinal pigment epithelium and the neurosensory retina, which contained occasional perivascular clumps of melanin laden cells. The predominant deposition of oxalate in the retinal pigment epithelium, with the exuberant response of these cells around the crystals, gives a clue to the pathogenic mechanisms of primary hyperoxaluria.

Calcium oxalate crystals may be deposited in the kidneys, eyes, bones, joints, skin, cardiac conduction system, and other tissues as a primary or secondary phenomenon. The term primary hyperoxaluria (primary oxalosis) refers to two rare genetic inborn errors of metabolism characterised by nephrocalcinosis, recurrent calcium oxalate nephrolithiasis, and an excessive urinary excretion of oxalic acid. Early diagnosis can be suspected by the finding of increased echogenicity of the renal papillae on ultrasonography before nephrocalcinosis is detectable on routine roentgenograms of the abdomen. Primary hyperoxaluria may be particularly severe when it presents during infancy with acute renal failure. Primary hyperoxaluria type I (McKusick 259900) (glycolic aciduria) is typified by an excessive urinary excretion of glyoxylic and glycolic acids and is due to a deficiency of alanine:glyoxylate aminotransferase (AGAT) (Fig 1). The AGAT gene has recently been sequenced and the mutation predicted to cause the disease in one-third of all patients with primary hyperoxaluria type I has been identified. The manifestations of primary hyperoxaluria type I vary markedly. This autosomal recessive disease usually becomes clinically evident during childhood or early adulthood with urolithiasis leading to end stage renal failure. A retinopathy characterised by tiny yellow glistening specks ('flecked' retina, crystalline retinopathy) or by large black geographic submacular lesions has been noted in one-third of patients with primary hyperoxaluria type I. End stage renal failure has invariably preceded or occurred concurrently with this funduscopic appearance, which has usually been limited to the posterior pole.

In a clinical series of 24 patients with primary hyperoxaluria we have previously shown the extreme clinical variability in the funduscopic appearance. One of the patients from our series died, and in this communication we report the histopathological findings in the two eyes that were obtained post mortem and compare them with those in previous studies.

Case report
The patient, a girl, was born weighing 3912 g, after an uncomplicated pregnancy and delivery to a healthy primigravida mother. She was healthy and developed normally until 8 months old, when she presented with weight loss, anorexia, and leathery and was found to have primary hyperoxaluria type I with anuric renal failure. Treatment was begun with intensive haemodialysis, supplemental pyridoxine, electrolyte manipulations, and dietary restriction of oxalate and ascorbate according to our previously described protocol. At 15 months of age a renal transplantation was performed with a living relative as a donor.

The patient gradually developed recurrence of calcium oxalate in her renal graft and died two years later of renal failure. At 2 years of age we performed an ophthalmic examination, which has been previously reported (Fig 2). An electroretinogram was normal.


Figure 1 Metabolic pathways for primary hyperoxaluria type I (PH1) deficient peroxisomal alanine:glyoxylate aminotransferase and primary hyperoxaluria type 2 (PH2) deficient extraperoxisomal D-glyceric acid dehydrogenase. DGDH=D-glyceric acid dehydrogenase, LDH=lactate dehydrogenase, AGAT=alanine:glyoxylate aminotransferase, NADH=reduced nicotinamide adenine dinucleotide. NAD+=nicotinamide adenine dinucleotide.

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Results

Histopathological examination of the eyes disclosed numerous, pitch black foci in the posterior portion of the fundus (Fig 2). By light microscopy these dense black foci consisted of multiple layers of hyperplastic and hypertrophic retinal pigment epithelium (Fig 3). Numerous calcium oxalate crystals were present within the clumps of retinal pigment epithelial cells and were dramatically demonstrated when viewed under polarised light because of their birefringence. Some crystals in the retinal pigment epithelium stained with alizarin red at pH 7.0 but not at pH 4.2, thus confirming that the crystals were composed of calcium oxalate.35 Very few birefringent crystals were noted in the pigment epithelium anterior to the equator of the eye. A collagenous layer was evident on the surface of some reactive retinal pigment epithelial cells in the macula. Choroidal neovascularisation was not present.

Most of the overlying neurosensory retinal and other ocular structures were normal except for autolytic degeneration of the photoreceptors.

Liver tissue, analysed by Professor C Danpure, showed no alanine:glyoxylate aminotransferase activity, confirming the diagnosis of primary hyperoxaluria type I.
Discussion
In addition to our case we know of histopathological reports on the eyes of seven cases of primary hyperoxaluria reviewed in Table 1. None have reported choroidal neovascularisation as was previously suggested by Meredith et al.

Table 1  Pathological reports on ocular findings in primary hyperoxaluria

<table>
<thead>
<tr>
<th>Case</th>
<th>Reference</th>
<th>Years</th>
<th>Age at onset of symptoms</th>
<th>Renal failure</th>
<th>Renal transplant</th>
<th>Age at death</th>
<th>Funduscopice findings in posterior pole</th>
<th>Crystal locations</th>
<th>RPE hyperplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Scowen et al.</td>
<td>1959</td>
<td>1 year</td>
<td>Yes</td>
<td>No</td>
<td>23 years</td>
<td>Not described</td>
<td>Ciliary body (scanty)</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>Timm</td>
<td>1963</td>
<td>Childhood</td>
<td>Yes</td>
<td>No</td>
<td>23 years</td>
<td>Not described</td>
<td>Extracocular muscles, lacrimal glands, ciliary body, choroid, retina, optic nerve (especially vessels)</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>Timm</td>
<td>1976</td>
<td>Not stated</td>
<td>Yes</td>
<td>Yes</td>
<td>26 years</td>
<td>Flecked retina</td>
<td>RPE, sensory retina, ciliary body</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>Toussaint et al.</td>
<td>1976</td>
<td>10 years</td>
<td>Yes</td>
<td>Yes</td>
<td>33 years</td>
<td>Flecked retina</td>
<td>RPE ciliary body</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>Fielder et al.</td>
<td>1980</td>
<td>5 months</td>
<td>Yes</td>
<td>No</td>
<td>6 months</td>
<td>Flecked retina</td>
<td>RPE</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>Meredith et al.</td>
<td>1984</td>
<td>6 months</td>
<td>Yes</td>
<td>No</td>
<td>7 months</td>
<td>'Ring of yellowish lesions'</td>
<td>RPE, iris sensory retina, ciliary body, conjunctiva</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>Speiser et al.</td>
<td>1988</td>
<td>4 months</td>
<td>Yes</td>
<td>No</td>
<td>6 months</td>
<td>Black ringlets</td>
<td>RPE sensory retina</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>Small, Scheinman, Klintworth</td>
<td>1991</td>
<td>9 months</td>
<td>Yes</td>
<td>Yes</td>
<td>3 years</td>
<td>Black geographic lesions</td>
<td>RPE</td>
<td>Mild</td>
</tr>
</tbody>
</table>

RPE = retinal pigment epithelium.
knowledge this is the first histopathological report of a patient with enzymatically confirmed primary hyperoxaluria type I. In contrast to previously reported cases, the eyes of our patient were characterised by: (1) an exuberant retinal pigment epithelial reaction round the crystals which was seen funduscopically as geographic black lesions; (2) the collagenous layer between the retinal pigment epithelial cells and the neurosensory retina which correlated with the clinically apparent thin white layer located between the neurosensory retina and the retinal pigment epithelium; and (3) the paucity of oxalate crystals in the remaining ocular structures.

We acknowledge the pioneering biochemical and molecular genetic work of Christopher Danpure on this disease and thank him for performing the enzyme assays on our patient. This work was supported in part by Research Grant ROI-EYO147 from the National Eye Institute.

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