Ultrasound Biomicroscopy of the Eye in Cystinosis

Nils Mungan, MD, FRCSC; Ken K. Nischal, FRCOphth; Elise Héon, MD, FRCSC; Leslie MacKeen, CRA; J. Williamson Balfe, MD, FRCPC; Alex V. Levin, MD, FRCSC

Objective: To describe the ocular ultrasound biomicroscopy (UBM) findings in patients with cystinosis.

Methods: Six patients with infantile nephropathic cystinosis, aged 16 to 25 years, and 6 controls (matched for age and spherical refractive error) were examined clinically and with UBM. Scleral reflectivity, corneal and iris thickness, central anterior chamber depth, angle width, trabecular meshwork to ciliary process distance, and ciliary sulcus width were measured.

Results: No patient had glaucoma or posterior synechiae, but all had crystals in the trabecular meshwork apparent with gonioscopy. Using UBM, the cornea and iris appeared similar in both groups, but the scleral reflectivity was increased in patients ($P = .003$). The angle was narrower in patients (mean ± SD, $20° ± 7°$) than controls ($31° ± 5°$, $P < .001$). The anterior chamber was shallower in patients ($2556 ± 197$ µm) than controls ($2968 ± 284$ µm, $P < .001$). The ciliary sulcus was closed or narrow in all patients ($83 ± 112$ µm) compared with controls ($339 ± 135$ µm, $P < .001$), with a reduction in the trabecular meshwork to ciliary process distance.

Conclusions: This report of ocular UBM findings in cystinosis demonstrated narrowing of the angle and a ciliary body configuration similar to that reported for plateau iris syndrome. Gonioscopy demonstrated crystals in the trabecular meshwork. These findings may explain the predisposition of these patients to glaucoma.


INFANTILE NEPHROPATHIC cystinosis is a rare autosomal recessive disorder characterized by excessive intracellular accumulation of cystine crystals throughout the body. Excretion of free cystine from lysosomes is deficient owing to a mutation in the CTNS gene located at 17p13. This gene codes for cystinosin, a putative lysosomal membrane protein carrier. The chief clinical manifestation of this condition is renal Fanconi syndrome by 1 year of age, progressing to end-stage renal disease in early adolescence. Systemic cysteamine medication forestalls renal failure, but its effect on other organs is uncertain. Advances in renal transplantation methods have improved patient survival, but this has led to an increasing prevalence of long-term extrarenal complications. These complications include blindness, myopathy, endocrine dysfunction, and neurologic deterioration.

Blindness, usually due to corneal disease, retinopathy, and/or glaucoma, has been considered the most common and debilitating of these complications. Up to 33% of patients eventually experience loss of driving vision, and 14% become legally blind. Corneal crystals are invariably present by 1 year of age, often causing discomfort but rarely affecting vision. Topical cysteamine can help prevent and reverse corneal crystal deposition. The commonly observed (75%-100%) pigmentary retinopathy causes a variable degree of electroretinographic changes and visual loss, which remain untreatable at present. Recently, glaucoma has been described in association with cystinosis. Although observed in only 6% of adult patients, glaucoma is potentially treatable. Further investigation of its mechanisms is therefore warranted. The glaucoma may be the result of angle closure with pupillary block due to posterior synechiae. Other ocular abnormalities that may predispose patients to glaucoma include “thickening” and “stiffening” of the iris stroma and fixed miotic pupils.

We performed ultrasound biomicroscopy (UBM) to define the anterior segment characteristics in patients with cystinosis.
PATIENTS AND METHODS

This study was approved by the Research Ethics Board of The Hospital for Sick Children, Toronto, Ontario, and all subjects provided informed consent. Because older patients are more likely to have accumulated ocular pathological changes over time, the oldest surviving patients with a diagnosis of infantile nephropathic cystinosis were identified from the nephrology clinic database and recruited. Patients were invited to participate in descending order of age. Exclusion criteria consisted of inability of the patient to cooperate with UBM or presence of coexistent eye disorders not attributable to cystinosis. An equal number of controls, matched for age and spherical refractive error, were studied with UBM. Controls consisted of healthy volunteers recruited from the University of Toronto, Toronto, Ontario, community.

Patients underwent a complete clinical eye examination including gonioscopy. The conjunctiva, cornea, iris, and fundus were photographed. Ultrasound biomicroscopy was performed on supine subjects with undilated eyes who were instructed to fixate with the fellow eye on a distant ceiling target. After topical anesthesia, an eyecup was inserted and filled with 2.5% methylcellulose. A UBM (Humphrey Instruments Inc, San Leandro, Calif) with a 50-MHz transducer set at a gain of 60 dB, a delay of 2.24 mm, and a time-gain control of 5 dB/mm was used. Scans were performed radially at the limbus at the 3-, 6-, 9-, and 12-o’clock positions and axially over the center of the pupil. The probe was kept as perpendicular as possible to the structure being examined by using standard criteria. The appearance of the cornea, sclera, angle, iris, and ciliary body were assessed qualitatively. Measurements of central corneal thickness, minimum iris thickness, and central anterior chamber depth were performed using the built-in functions of the UBM device. The angle and trabecular meshwork to ciliary process distance were measured using previously described methods. The width of the ciliary sulcus was defined as the maximum distance from the posterior surface of the iris to the anterior surface of the ciliary process along a line perpendicular to the iris surface. All quantitative measurements (other than corneal thickness and anterior chamber depth) were made at the 6-o’clock position.

Scleral reflectivity was quantified using Adobe Photoshop 3.0 for MacIntosh (Adobe Systems Inc, San Jose, Calif). The mean luminosity of the image pixels in a 1.25 by 0.5-mm area (based at the scleral spur) was measured using the program’s built-in scale of 0 (darkest) to 255 (brightest).

Measurements in patients and controls were compared with a t test.

RESULTS

A total of 6 patients aged 16 to 25 years (mean [SD] age, 19±4 years) and 6 controls aged 17 to 30 years (mean [SD] age, 21±5 years) were included (P=.16). Results are summarized in Table 1 and Table 2. Two pairs of patients were siblings: patients 3 and 4 and patients 5 and 6. All patients had functioning renal grafts except for patient 6 (hemodialysis). All patients were using cysteamine eyedrops at a frequency ranging from once daily to a maximum of 4 times a day (hourly administration is recommended). Patients 1 and 2 were taking systemic cysteamine, patients 3 and 4 had previously taken systemic cysteamine, and patients 5 and 6 had never taken systemic cysteamine. Each group had an equal distribution of iris color (3 blue, 3 brown) and sex (4 males, 2 females). Spherical equivalent refractive error was similar in the 2 groups (patients: +0.23±0.49 diopters [D]; range, −0.50 to +1.13 D; controls: −0.17±0.35 D; range, −1.00 to +0.25 D).

All patients had normal or near-normal visual acuity despite the invariable presence of dense full-thickness corneal crystals and retinopathy. Patients 3, 5, and 6 had band keratopathy. All patients had obvious iris crystals, but none had glaucoma, posterior synechiae, or other pupillary abnormalities. Patient 3 had marked peripheral iris transillumination defects. Patient 6 had large peripheral iris pigment epithelial cysts in the left eye. Patients 4 and 5 each had trace quantities of crystals on the anterior lens capsule of one eye. On gonioscopy, the angle was open in all patients examined. Patient 4 was unable to cooperate with gonioscopy. Rare crystals in the trabecular meshwork were observed in all. All patients had mild-to-moderate retinopathy except for patient 3, who had a bull’s-eye maculopathy in both eyes.

Ultrasound biomicroscopy findings in patients and controls are summarized in Table 2. Despite the dense crystal deposition observed clinically, the cornea and iris appeared similar in patients and controls, although control patients had slightly greater corneal (P=.04) and iris (P=.03) thickness. Neither iris nor corneal crystals could be visualized by UBM even when present on clinical examination. The scleral reflectivity was significantly increased in patients compared with controls (P=.003, Figure 1). The anterior chamber was shallower in patients, and the angle was narrower. The ciliary sulcus was abnormal, being absent or narrow in all patients (Figure 2). The trabecular meshwork to ciliary process distance was also reduced in patients. Although quantitative measurements were only taken at the 6-o’clock position, other meridians appeared similar. Patient 6 had large iris pigment epithelial cysts, which were responsible for localized narrowing of the angle at the 3-o’clock position (Figure 3).

COMMENT

Ultrasound biomicroscopy was performed on eyes of 6 older patients with cystinosis. Ultrasound biomicroscopy did not reveal any evidence of increased iris thickness, posterior synechiae, or anterior iris bowing. However, the ciliary processes were closely apposed to the peripheral iris, with narrowing of the ciliary sulcus. This finding is similar but not identical to the findings in plateau iris syndrome described by Pavlin and coworkers. In that condition, the ciliary body is rotated ante-
riorily and pushes the peripheral iris forward, narrowing the angle. The fact that the iris is pushed forward by the ciliary body and not by posterior aqueous pressure explains the failure of peripheral iridotomy to open the angle. Our patients had significantly narrower angles than controls but not to a degree considered at risk for closure (≤10°). The trabecular meshwork to ciliary process distance was reduced. This distance, which is also decreased in plateau iris syndrome, was described by Pavlin and colleagues as a port through which the thickness of the iris must pass. If the trabecular meshwork to ciliary process distance is small, it is possible that thickening of the iris could close the angle even in the presence of a relatively deep central anterior chamber and absence of iris bombe. Wan and coworkers reported a patient with cystinosis who developed increased intraocular pressure, a shallow anterior chamber, and iris bombe. A trabeculectomy and iridectomy were performed. At surgery, the iris was found to be thick, rigid, and relatively immobile. Histopathologic examination showed dense infiltration of the iris stroma by crystals. Although this is an isolated case report, other studies describe iris or angle abnormalities that may predispose to the development of glaucoma in patients with cystinosis. Posterior synechiae were observed in 9 of 36 patients (aged 16 to 34 years) at the National Eye Institute, and 2 of these 9 progressed to glaucoma. The cause of posterior synechiae is unknown, because inflammation has never been documented in cystinosis, either clinically or histologically. Increased thickness of the iris stroma has been described in 4 patients, but how thickness was assessed is not stated. Two other studies have reported fixed miotic pupils as the only iris abnormality observed, which may represent hidden posterior synechiae, a thick “stiffened” iris, or both. Increased corneal thickness has been described by Katz and coworkers and may contribute to narrowing of the angle.

The cause of the abnormal ciliary body configuration in our patients is unknown. Possibilities include ciliary body thickening, iris-ciliary body adhesions, or a developmental anomaly. Ciliary body thickness appeared normal on UBM, although this is difficult to measure objectively. Histopathologic examination of cystinotic eyes does demonstrate necrosis of the iris pigment epithelium and ciliary body epithelium, which may then scar together. This necrosis could also explain the iris transillumination defects observed in 1 of our patients. Finally, because cystinosis leads to other developmental anomalies, such as markedly short stature, it is possible that the anterior segment of the eye also grows ab-

### Table 1. Clinical Characteristics of Patients With Cystinosis

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Visual Acuity†</th>
<th>Slitlamp Examination</th>
<th>Gonioscopy</th>
<th>Trabecular Meshwork</th>
<th>Crystals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Conjunctiva Crystals</td>
<td>Cornea Crystals</td>
<td>Iris Crystals</td>
<td>Lens Crystals</td>
</tr>
<tr>
<td>1/M/16</td>
<td>20/20 OD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>20/20 OS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>2/F/16</td>
<td>20/20 OD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>20/20 OD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>3/M/16</td>
<td>20/20 OD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>20/20 OS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>4/M/17</td>
<td>20/20 OD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>20/20 OS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>5/F/22</td>
<td>20/20 OD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>20/20 OS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>6/M/25</td>
<td>20/25 OD</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>20/30 OS</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
</tbody>
</table>

* Plus sign indicates finding present; minus sign, finding absent; and NA, not assessed.
† Best-corrected Snellen acuity.
‡ Shaffer grading of angle.

### Table 2. Ultrasound Biomicroscopy Measurements in Patients With Cystinosis and Controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient Eyes (n = 12)</th>
<th>Control Eyes (n = 12)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scleral reflectivity, U†</td>
<td>200 ± 33 (150-244)</td>
<td>157 ± 22 (105-179)</td>
<td>.003</td>
</tr>
<tr>
<td>Corneal thickness, µm</td>
<td>560 ± 31 (320-625)</td>
<td>595 ± 43 (533-683)</td>
<td>.04</td>
</tr>
<tr>
<td>Anterior chamber depth, µm</td>
<td>2556 ± 197 (2231-2769)</td>
<td>2968 ± 284 (2663-3519)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Iridocorneal angle, °</td>
<td>20 ± 7 (12-34)</td>
<td>31 ± 5 (21-36)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Iris thickness, µm</td>
<td>284 ± 62 (162-381)</td>
<td>343 ± 65 (260-507)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ciliary sulcus width, µm</td>
<td>83 ± 112 (9-286)</td>
<td>339 ± 135 (143-603)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Trabecular meshwork to ciliary process distance, µm</td>
<td>672 ± 165 (428-961)</td>
<td>1067 ± 169 (764-1368)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* All values are given as mean ± SD (range); t test was used to compare groups.
† Units of brightness measured using Adobe Photoshop 3.0 (see the “Patients and Methods” section).
normally. The pathogenesis of growth retardation in cystinosis remains unknown and is not simply related to renal failure.

Other observations on UBM are consistent with the known pathology of cystinosis. Corneal crystals on microscopy are fine, needle-shaped, and less than 20 µm long, whereas scleral crystals are larger and more rectangular. The resolution of our UBM is 60 µm, which may explain why increased reflectivity was detected in the sclera but not the cornea.

Gonioscopy revealed the presence of crystals in the trabecular meshwork, a finding that to our knowledge has not previously been reported. It is possible that these crystals could accumulate and eventually contribute to glaucoma.

We did not find any patient with glaucoma or posterior synechiae, so we could not investigate those abnormalities directly. Our patients had less severe visual loss than patients in some previous studies, although all had dense corneal crystals and retinopathy. Possible explanations for this discrepancy include differences in patient age (although our patients were older than patients in studies finding mild visual loss), use of systemic or topical cysteamine, or genotype. Molecular genetic analysis has not been performed on our study patients. Finally, we could only study a small number of patients, even at our major pediatric nephrology referral center. However, the incidence of cystinosis is only 1 per 100000 to 1 per 200000 live births, rendering a larger study difficult.

We report several new observations regarding the anterior segment in cystinosis. Crystals were present in the trabecular meshwork and may contribute to glaucoma. The sclera exhibits increased reflectivity on UBM. An abnormal ciliary body configuration similar to plateau iris syndrome occurs, suggesting that if angle closure should develop in a patient with cystinosis, peripheral iridotomy alone may fail to reverse it. Patients with cystinosis should be followed up by an ophthalmologist not only for corneal and retinal complications but also to monitor for the possible development of glaucoma, pos-

![Figure 1. A, 23-year-old control; B, patient 2 (age, 16 years); and C, patient 6 (age, 25 years). Scleral reflectivity was increased in patients vs controls and was proportional to clinically observed crystal deposition in the cornea. Band keratopathy (arrows) is present. The same setting of the instrument (transfer function 7) was used to print these 3 images.](image1)

![Figure 2. A-C, Images of 3 controls; D-F, 3 unrelated patients. Note absent (D, E) or narrow (F) ciliary sulcus in patients with narrowing of the iridocorneal angle. All these images have been printed using transfer function 1, which brightens the image to highlight the ciliary process detail but reduces the contrast in scleral reflectivity.](image2)

![Figure 3. Large iris pigment epithelial and ciliary body cysts are producing localized narrowing of the iridocorneal angle at the 3-o'clock position in patient 6.](image3)
terior synechiae, or progressive angle narrowing. Ultrasound biomicroscopy may help identify individuals at risk for glaucoma. The association of these findings and the risk of developing glaucoma require further evaluation.

Accepted for publication June 20, 2000.

Corresponding author: Alex V. Levin, MD, FRCSC, Department of Ophthalmology, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (e-mail: avlevin@sickkids.on.ca).

REFERENCES


