
Adolescent cystinosis: a clinical and specular microscopic study of an unusual sibship

ROBERT T. DALE, GULLAPALLI N. RAO, JAMES V. AQUAVELLA, AND HENRY S. METZ

From the Departments of Ophthalmology, Park Ridge Hospital, and the University of Rochester School of Medicine and Dentistry, Rochester, New York, USA

SUMMARY Six members of a sibship originally consisting of 8 offspring lived to teenage. Five of these developed the adolescent form of cystinosis. Since adolescent cystinosis is autosomal recessive, such a high incidence of affected members is of uncommon occurrence. Depending on whether the sibship size (n) is known as 6 or 8, it should occur only in approximately 1·5% or 5·8% of sibships of corresponding size. Specular microscopy was used to study the corneal stroma of all 3 of the living, affected members of this sibship and the conjunctiva of one of the siblings. Vivid, needle-shaped crystals were observed in the corneal stroma. Smaller, variably shaped crystals were observed in the conjunctiva. The crystals seen with specular microscopy fit the description of those studied with light and electron microscopy.

Cystinosis is a rare, recessively inherited disturbance in amino acid metabolism characterised by the intralysosomal deposition of cystine crystals in the eye, bone marrow, lymph nodes, leucocytes, and internal organs. It occurs in 3 clinical forms: an infantile nephropathic type, an adolescent or intermediate nephropathic type, and an adult benign type. In all 3 forms cystine crystals are deposited in the corneal stroma and the conjunctiva. We describe here a most unusual sibship afflicted with the adolescent form of cystinosis, a sibship which has not yet been reported in the ophthalmic literature.

Clinical specular microscopy has opened up the realm of in-vivo observation of structural changes in the cornea. However, its use has been limited exclusively to the study of corneal endothelium until now. We applied this technique to study and photograph changes in corneal stroma and conjunctiva in the living, affected members of this sibship. To our knowledge this represents the first reported use of specular microscopy to demonstrate stromal and conjunctival pathology of any type.

Case reports

The sibship in this report originally consisted of 5 brothers and 3 sisters, only 4 of whom are still alive.

Correspondence to Dr G. N. Rao, 1160 Chili Avenue, Rochester, NY 14624, USA.

One of the females was born prematurely at 7½ months of gestation and died at the age of 2 days. Necropsy disclosed a traumatic subarachnoid haemorrhage with no evidence of cystinosis. The second was a male infant who died 17 days after birth. Again no necropsy evidence was found for cystinosis. The necropsy diagnosis was supplicative pericarditis. While cystinosis could not be diagnosed in either of these infants, they did not live to the age of expected risk of the disease which in all of the affected siblings has been adolescence. Of the remaining 6 siblings 5 have the adolescent form of cystinosis.

Case 1

A 19-year-old male died in 1972 of undiagnosed renal failure. He had bilateral nephrectomies and a splenectomy followed by dialysis. His only ocular complaint was photophobia, but a slit-lamp examination was never performed. Although renal biopsies were done and the kidneys were removed, the renal histology showed no cystine crystals. A bone marrow examination was never done. At necropsy there was no evidence of cystinosis. The eyes and bone marrow were not studied in the necropsy.

Case 2

A 16-year-old brother died in 1972, also of undiagnosed kidney disease. His kidney disease similarly required bilateral nephrectomies and
dialysis. The immunosuppressive therapy which was
given to prevent rejection of the transplanted kidney
resulted in mucormycosis involving the heart, lung,
and brain, which was the immediate cause of death.
Although photophobia was documented during his
life, a slit-lamp examination was not done. Bone
marrow examination was also not performed. There
was no evidence of cystine crystals in the kidneys
either from an open renal biopsy or from examination
of the kidneys at necropsy. The eyes and bone
marrow were not studied at the time of necropsy.

After the death of the second sibling all the remain-
ing brothers and sisters were hospitalised in 1973 for
evaluation of what was obviously a potentially fatal
familial kidney condition of still undetermined cause.

Case 3
During this admission to hospital the first diagnosis
was made by slit-lamp examination in the now 18-
year-old sister. Characteristic cystine crystals were
seen both in the corneal stroma and in the bulbar
conjunctiva. A bone marrow examination also
revealed cystine crystals. She was asymptomatic at
that time with the exception of photophobia and has
remained so. She now has only mild kidney dys-
function not requiring dialysis or kidney transplant.
Ocular examination on 23 July 1980 revealed an
uncorrected visual acuity of 20/20 OD and 20/30 OS,
unimproved by correction. (The mild amblyopia is
causd by a monofixation syndrome.) Slit-lamp
examination revealed the cystine crystals first seen in
1973. In the central cornea the cystine crystals were
seen both superficially and deeply with an area of
relative clearing in the mid-stroma. Peripherally,
the crystals were seen throughout the corneal stroma
in all layers. A dilated funduscopic examination by both
direct and indirect ophthalmoscopy was unremark-
able with the exception of an area of hypertrophy of
the retinal pigment epithelium in the temporal
equatorior region of the right fundus and in the
periphery of the left fundus.

Case 4
The diagnosis of adolescent cystinosis was made in a
26-year-old male with chronic renal failure in 1973
when his remaining siblings were hospitalised. The
diagnosis was similarly made by ocular and bone
marrow examination. At that time he was clinically
well. However, by 1977 he had become severely
symptomatic from his chronic renal failure, and a
cadaver renal transplant had to be done. Since then
he has had progressive functional deterioration due
to biopsy-documented chronic rejection. As in his
deceased brother, cystine crystals were not observed
on open renal biopsy nor in the excised kidney. His
most recent ophthalmological examination was
performed on 23 July 1980, when he still complained
of photophobia. His best corrected visual acuity was
20/30 OD and 20/25 OS. Slit-lamp examination
revealed multiple refractile cystine crystals in the
corneal stroma and bulbar conjunctiva of both eyes.
These were also seen in the superficial and deeper
layers of the central corneal stroma and throughout
the stroma in the periphery. In addition, early central
posterior subcapsular cataracts were also seen, which
were probably secondary to prolonged systemic
administration of corticosteroids for immunosup-
pression. The anterior segment was otherwise
normal. Ocular motility was normal. A dilated
examination of the fundus by both direct and indirect
ophthalmoscopy was unremarkable.

Case 5
A 20-year-old brother was also diagnosed as having
cystinosis by ocular and bone marrow examination
when the family was screened in 1973. But unlike his
other affected siblings his renal biopsy did reveal
cystine crystals. Photophobia is a significant symptom
even in this patient, and according to the patient there
has been relief from this symptom since receiving his
cadaver renal transplant in 1980. After the transplant
he suffered a renal rejection thought to be due to
cytomegalovirus infection, which was cultured from
his urine. Fortunately the condition was reversed
with persistence of reasonable kidney function. At
the last examination he had a visual acuity of 20/20
in both eyes without correction. Slit-lamp examination
revealed numerous cystine crystals in the corneal
stroma and bulbar conjunctiva of both eyes similar in
appearance and location to those in cases 3 and 4. The
anterior segment was otherwise unremarkable except
for minimal bilateral posterior subcapsular cataracts.
Ocular motility was normal. Dilated fundus exa-
mination with direct and indirect ophthalmoscopy was
normal.

In addition a 26-year-old sister was also screened
for cystinosis in 1973. Her bone marrow and slit-lamp
examinations were negative. A renal biopsy was not
done. Since this examination the slit-lamp appear-
ces continue to be normal. She is the only living
unaffected sibling.

General physical examination of the affected
siblings disclosed that they all have lighter hair and
skin pigmentation than either of their parents. Also,
all of the affected children are shorter than, or as
short as, the mother, who is 5 feet 5 inches (165 cm)
tall. The unaffected sister is 5 feet 8 inches
(173 cm) tall, and her hair is as dark as her parents'.
Laboratory evaluations revealed massive pro-
teinuria and a complete Fanconi syndrome in all
affected siblings. IgM and complement have been
Cystine crystals were observed and photographed in the corneal stroma of the 3 living affected siblings. In the cornea crystals were elongated and fusiform in shape, had an irregular orientation, and appeared much more numerous in the superficial stroma (Fig. 2). However, a smaller number of similarly needle-shaped, irregularly orientated crystals were also seen deeply scattered near the regions just above Descemet's membrane and the endothelium (Fig. 3). Some smaller, variably shaped crystals were also seen in the corneas of the 3 patients in the same stromal areas. These were also most abundant superficially in the central cornea than in deeper stroma immediately anterior to Descemet's membrane. The corneal stroma

Fig. 2  Elongated fusiform shaped crystals arranged irregularly in the superficial stroma of the cornea.

Fig. 3  Cystine crystals in the deep corneal stroma. These crystals were needle-shaped and irregularly orientated and were sparsely distributed compared to those in the superficial stroma.
Adolescent cystinosis: a clinical and specular microscopic study of an unusual sibship

Variability in the size of the endothelial cells. Cystine crystals were also observed in the conjunctiva of case 5 (Fig. 4). However, they were far less numerous than in the cornea and were seen sparsely scattered in an irregular manner. None of these were needle-shaped or fusiform. Some were rectangular, but others were of variable shape and size. The conjunctival crystals were also noticeably smaller than the fusiform crystals seen in the stroma.

Discussion

This sibship conforms to the characteristics of the intermediate or adolescent type of cystinosis (Table 1). Photophobia was severe and was in fact the only ocular symptom. Because severe photophobia may hasten the decision to do a kidney transplant in some patients, it is of interest that the photophobia subjectively decreased in one sibling after renal transplant. Retinopathy has been reported in cystinosis, but there is no evidence for this in any of the siblings. The patients also showed mild growth retardation and a mild decrease in skin pigmentation, features which are typically severe in the infantile form. The presence of massive proteinuria, which is unusual in cystinosis, and the detection of IgM and complement in the kidney will be the subject of another report on the sibship (R. C. Pabico, personal communication).

It is of particular interest to ophthalmologists that the condition went undiagnosed in the first 2 siblings until a slit-lamp examination was made on one of the sisters. In this sibship the most reliable diagnostic tests were slit-lamp and bone marrow examinations, and they were equally reliable. Renal biopsy was not reliable, since it demonstrated cystine crystals in only one sibling; however, the cystine content of the renal tissues was never measured. Even medical necropsy was unreliable because the eyes and bone marrow were not examined.

All 3 forms of cystinosis are autosomal recessive, which means that a probability of 25% exists for each offspring being affected. Yet in this sibship only one individual who reached adolescence is unaffected. Can this be explained? To find out how common or uncommon this is, one should determine the expected proportion of sibships of size 6 that will have 5 affected members. In making such a calculation it is presumed that the 2 deceased brothers died of cystinosis. The 2 siblings who did not reach adolescence are omitted, so the sibship size (n) is 6. Because of the bias of ascertainment, the eldest affected sibling is also omitted (n-1). With single ascertainment, since it can be assumed that not all of the existing sibships with cystinosis have been located, if:

n = 6, sibship size
p = 3/4, probability of being unaffected, and
q = 1/4, probability of being affected.

Table 1  Sibship compared with the 3 major types of cystinosis

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Infantile</th>
<th>Adolescent</th>
<th>Benign</th>
<th>Present sibship</th>
</tr>
</thead>
<tbody>
<tr>
<td>General symptoms</td>
<td>6-10 mo</td>
<td>18 mo-17 yr</td>
<td>None</td>
<td>Late teens</td>
</tr>
<tr>
<td>Onset of symptoms</td>
<td></td>
<td>Variable</td>
<td>Normal</td>
<td>Mildly impaired</td>
</tr>
<tr>
<td>Growth</td>
<td>Impaired</td>
<td>Variable</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Skin pigmentation</td>
<td>Usually fair</td>
<td>Variable</td>
<td>Normal</td>
<td>Present</td>
</tr>
<tr>
<td>Bone marrow cystine crystals</td>
<td>Present</td>
<td>Usually present</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Ocular</td>
<td>Present</td>
<td>Variable</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Crystalline deposits in cornea and conjunctiva</td>
<td>Present</td>
<td>Variable</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Photophobia</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Renal</td>
<td>Present</td>
<td>Present</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Tubular dysfunction (Fanconi syndrome)</td>
<td>Present</td>
<td>Often incomplete</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Glomerular failure</td>
<td>Present</td>
<td>Present at later age</td>
<td>Absent</td>
<td>Absent</td>
</tr>
<tr>
<td>Inheritance</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
<td>Autosomal recessive</td>
</tr>
</tbody>
</table>
the term $5p^4$ in the binomial expansion $(p+q)^{n-1}$ provides the expected ratio. Calculated, this is 0.0146. Since cystinosis is recessively inherited, this means that approximately 1-5% of cystinosis sibships with 6 members will have 5 affected individuals.

If the 2 offspring who died in infancy had lived past teenage without developing cystinosis, sibship size (n) would then be 8. The term $35p^4q^4$ in $(p+q)^{n-1}$ would provide the ratio. This is approximately 5.8%. Thus, either with n=6 or n=8, while not genetically or statistically impossible, this sibship would have to be considered distinctly uncommon.

Cystinosis presents some very characteristic features in the external eye and early recognition of these features may give a clue to make a prompt diagnosis. Slit-lamp examination is virtually pathognomonic of the disease. Light microscopic and ultrastructural studies performed on the corneas have helped us to understand this pathological process better. With the advent of clinical specular microscopy it is now possible to make in-vivo observations on cellular alterations. The application of this technique in our study provided us with information on the configuration and distribution of cystine crystals both in the corneal stroma and bulbar conjunctiva. The appearance of these crystals seems to fit the description from light microscopic and ultrastructural studies of this condition. The elongated needle-shaped crystals in the corneal stroma and the rectangular crystals in the conjunctiva are typical. It seems reasonable to suggest that the difference in size and shape between the crystals in the cornea and conjunctiva may be due to the greater compactness of the corneal stroma compared with the looseness of the conjunctival lamina propria. Electron microscopy has shown these crystals always to be intracellular within lysosomal organelles. These observations, however, are beyond the scope of specular microscopy.

Although some of these changes can be observed with the slit-lamp, specular microscopy offers better magnification with the possibility for a more detailed examination. The magnification approximates to the lower range of light microscopy and obviates the need for invasive procedures such as biopsy. Our observations have shown that the use of the clinical specular microscope is not limited to endothelium but can be applied to examination of other structures of the outer eye. To our best knowledge this is the first demonstration of its application for studying corneal stromal and conjunctival pathology.

We express our appreciation to Rufino C. Pabico, MD. University of Rochester Medical Center, for allowing us to do ophthalmological studies on his patients, and to Edmond A. Murphy, MD. Chief of Genetics at the Johns Hopkins Hospital. for his genetic opinion of this sibship.

References

Adolescent cystinosis: a clinical and specular microscopic study of an unusual sibship.

R. T. Dale, G. N. Rao, J. V. Aquavella and H. S. Metz

doi: 10.1136/bjo.65.12.828