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

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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.[1–4] It occurs in 3 clinical forms: an infantile nephropathic type, an adolescent or intermediate nephropathic type, and an adult benign type.[5–7] In all 3 forms cystine crystals are deposited in the corneal stroma and the conjunctiva.[1] 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.[8–10] 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.

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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 suppurative 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 remaining 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 dysfunction 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 caused 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 unremarkable with the exception of an area of hypertrophy of the retinal pigment epithelium in the temporal equatorial 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 immunosuppression. 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 examination 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 appearances 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 proteinuria and a complete Fanconi syndrome in all affected siblings. IgM and complement have been

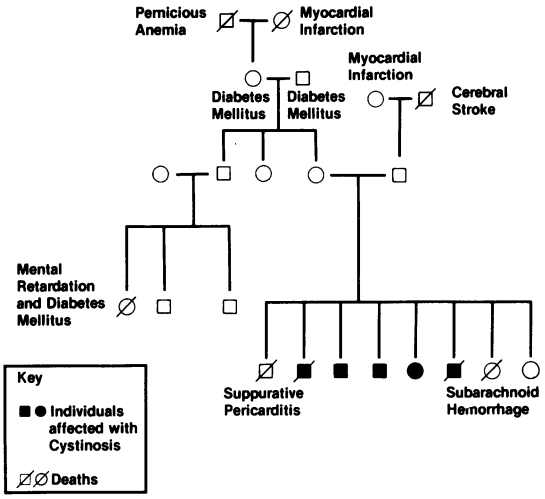

Fig. 1 *Family pedigree of sibship. Five of 8 siblings are affected with cystinosis. However, only 6 of those reached the age of expected risk in adolescence. Note the absence of consanguinity or other family history of cystinosis.*

identified in the kidneys of the 3 affected siblings who are still alive.

The family pedigree (Fig. 1) shows no history of cystinosis on either parental side. Both parents denied any family history of consanguinity. The mother denied any history of spontaneous abortions. The father is of Greek ancestral origin and the mother is German-Hungarian.

Materials and methods

Cases 3, 4, and 5 were examined by the technique of clinical specular microscopy. A Syber clinical specular microscope was used to which a Nikon camera was attached. The photography was performed with Kodak Tri-X 400 film. The overall magnification of this system was 104 times. At least 20 pictures were obtained in each of the eyes in all these 3 cases. The central region of the cornea was photographed in cases 3, 4, and 5. In case 5 the bulbar conjunctiva of the right eye was also photographed by applanating the dipping cone against the conjunctiva approximately 3 mm from the temporal side of the limbus in the right eye in the horizontal meridian. The examination of the conjunctiva in the other 2 cases was not performed. The methods used were essentially the same as for the examination of corneal endothelium.

Results

Cystine crystals were observed and photographed in the corneal stroma of the 3 living affected siblings. In

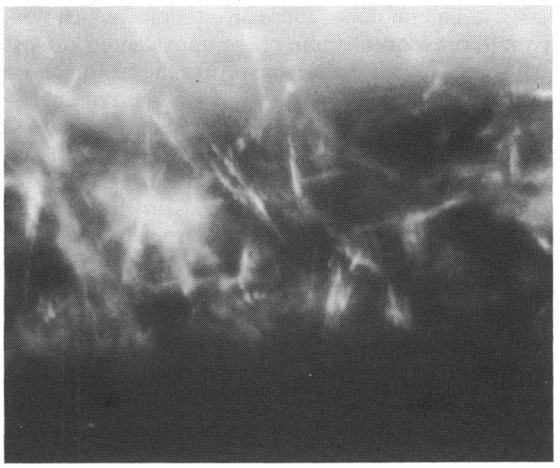

Fig. 2 *Elongated fusiform shaped crystals arranged irregularly in the superficial stroma of the cornea.*

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

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.*

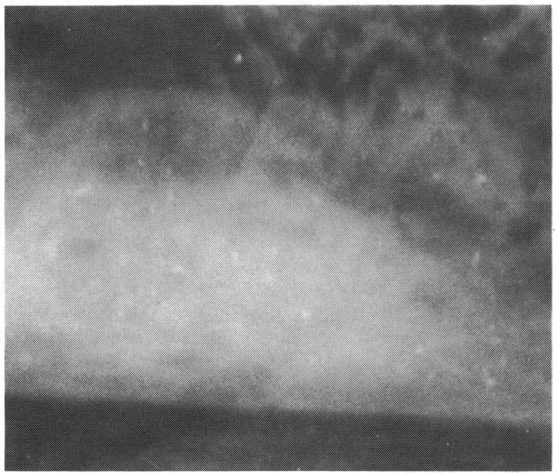

Fig. 4 *Cystine crystals in the conjunctiva, which are much smaller than those in the cornea and have a rectangular or variable shape.*

endothelium of all 3 patients showed a mild degree of 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,[11] it is of interest that the photophobia subjectively decreased in one sibling after renal transplant. Retinopathy has been reported in cystinosis,[12 13] 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.[1] 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,[1 14 15] 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*[1]

	Infantile	*Adolescent*	*Benign*	*Present sibship*
General symptoms				
Onset of symptoms	6–10 mo	18 mo–17 yr	None	Late teens
Growth	Impaired	Variable	Normal	Mildly impaired
Skin pigmentation	Usually fair	Variable	Normal	Decreased
Bone marrow cystine crystals	Present	Present	Usually present	Present
Ocular				
Retinopathy	Present	Variable	Absent	Absent
Crystalline deposits in cornea and conjunctiva	Present	Present	Present	Present
Photophobia	Present	Variable	May be present	Present
Renal				
Tubular dysfunction (Fanconi syndrome)	Present	Often incomplete	Absent	Present
Glomerular failure	Present	Present at later age infantile form	Absent	Present
Inheritance	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive

the term $5pq^4$ in the binomial expansion $(p+q)^{n-1}$ provides the expected ratio.[16] 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 $35p^3q^4$ 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.[17 18] 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.[18] 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.

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