Cystinosis: A 12-year-old boy with light sensitivity

Helen I. Myers, BS, Jaclyn M. Haugsdal, MD (../bio/authors/Haugsdal-Jaclyn.htm), Michael D. Wagoner, MD, PhD (http://www.medicine.uiowa.edu/dept_primary_apr.aspx?appointment=Ophthalmology%20and%20Visual%20Sciences&id=wagonerm)

March 4, 2015

Chief Complaint: Light sensitivity during outdoor activity

History of Present Illness: A previously healthy 12-year-old boy noticed a 6 to 12 month history of progressive photophobia during outdoor activities. Despite increasing use of sunglasses, his symptoms had worsened. More recently, he had become symptomatic indoors, particularly while watching television. In addition, he had intermittent redness and mild foreign body sensation in both eyes (OU) that was only mildly alleviated with the intermittent use of topical lubrication.

Past Ocular History: No prior history of ocular disorders or therapeutic interventions. He does not wear glasses or contacts.

Medical History: None

Review of Systems: Negative

Medications: Artificial tears OU as needed

Family History: No known ocular disease in either parent or the patient's 16-year-old sister. The mother emigrated from France as a child and the father was adopted.

Social History: Noncontributory.

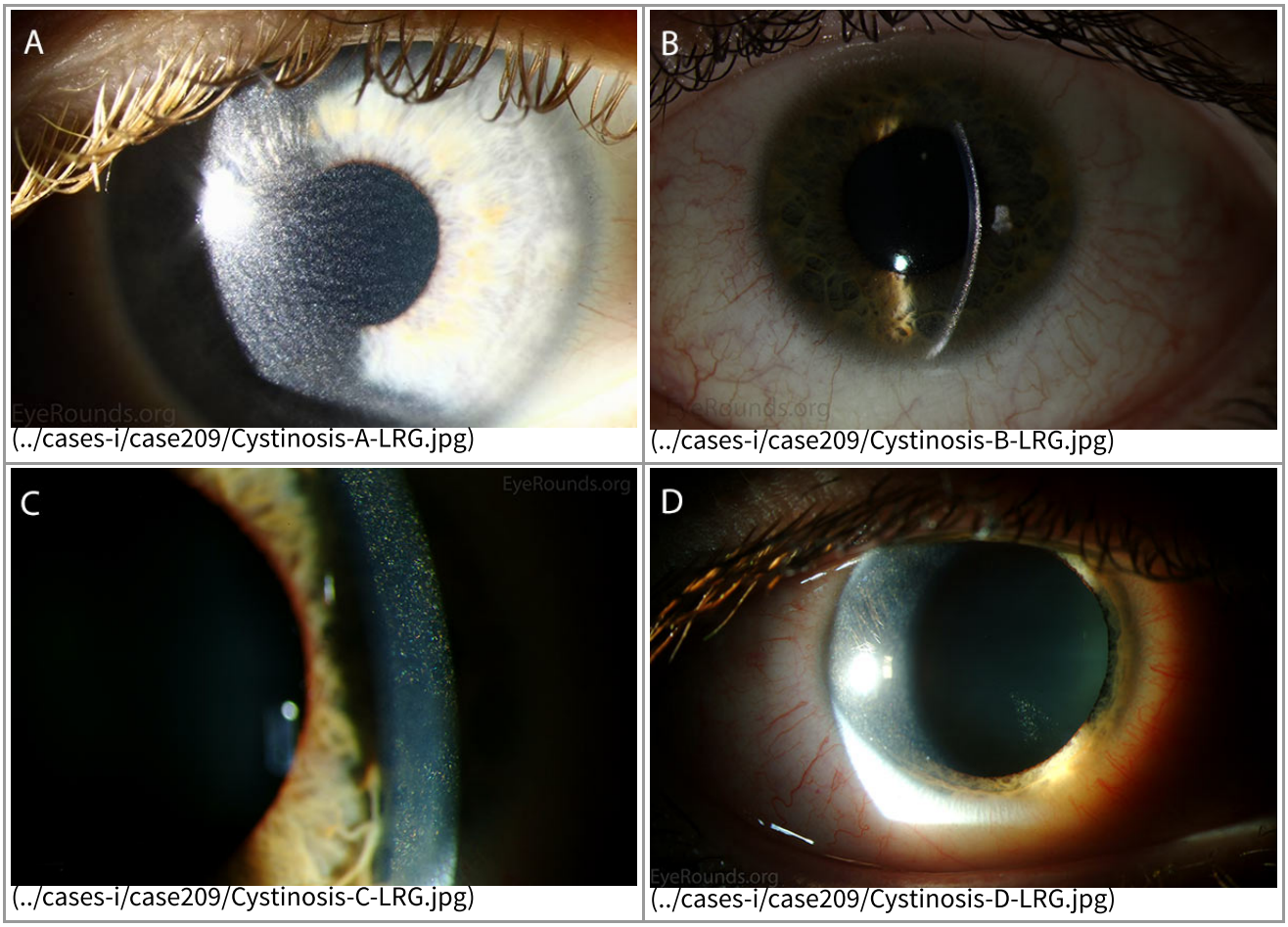
Ocular Exam

- Visual Acuity (without correction): $20/20^{-2}$ right eye (OD), $20/15^{-1}$ left eye (OS)
- Pupils: 5 mm in dark, 3 mm in light, brisk constriction OU. No relative afferent pupillary defect.

- Extraocular Motility: Full range of motion OU.
- Confrontation Visual Fields: Full OU.
- Intraocular Pressure: 12 mmHg OD; 15 mmHg OS
- Pachymetry: 598 microns OD; 582 microns OS

Slit Lamp Exam (Figure 1)

- Lids/lashes: Normal OU
- Conjunctiva/sclera: 1+ injection OU without crystal deposits
- Cornea: Diffuse subepithelial corneal crystals in the anterior stroma OU
- Anterior chamber: Occasional floating crystals OU
- Iris: Crystals visible in the crypts OU
- Lens: Localized crystals on anterior lens capsule inferiorly OU.



(../cases-i/case209/Cystinosis-A-LRG.jpg)
(../cases-i/case209/Cystinosis-B-LRG.jpg)
(../cases-i/case209/Cystinosis-C-LRG.jpg)
(../cases-i/case209/Cystinosis-D-LRG.jpg)

> ***Figure 1.*** *Punctate, needle-shaped crystals diffusely present throughout the corneal surface. They are mostly localized to the epithelium and anterior stroma as evident with the slit beam. Crystals initially appear in the corneal anterior periphery and move posteriorly and centrally as they accumulate (1). The crystals may also appear on the endothelium and throughout the anterior chamber such as on the iris or anterior lens capsule as demonstrated here.*

Fundus Exam

- Vitreous: Clear OU
- Disc: Normal OU
- Macula: Normal OU
- Vessels: Normal OU

- Periphery: Normal OU

Laboratory Testing

- Leukocyte cystine: 5 nmol half-cystine/mg protein (normal ≤ 0.2 nmol)

Diagnosis and Clinical Course

The presence of corneal crystals, in conjunction with increased levels of leukocyte cystine, leads to the diagnosis of cystinosis. The onset of ocular symptoms, in the absence of systemic signs and symptoms, is consistent with a diagnosis of intermediate (juvenile or late-onset) nephropathic cystinosis.

The patient was started on cysteamine HCl 0.44% (Cystaran®) ophthalmic solution every hour while awake and he was referred to a pediatric nephrologist who prescribed cysteamine bitartrate (Cystagon®) 450 mg orally, 4 times daily. The leukocyte cystine measurements were reduced to < 1.0 nmol half-cystine/mg protein 5 hours after taking medication.

Over the next 20 years, the visual acuity remained 20/20 in both eyes, with complete resolution of all subjective symptoms. He eventually developed renal involvement and required renal transplantation at age 25 due to end-stage renal disease. He did not develop any other systemic manifestations of the disorder.

Discussion

Cystinosis is a metabolic disorder resulting from autosomal-recessive inherited genetic defects in the *CTNS* gene (2). Cystinosis has been attributed to 112 identified mutations, including missense, nonsense and splice mutations, deletions and insertions (2,3). In patients affected by cystinosis, transport of the amino acid cystine from inside lysosomes is impeded due to improper functioning of protein transporter coded for by the *CTNS*. Following routine protein degradation inside the lysosome, cystine accumulates instead of being transported outside of the lysosome and recycled. Cystine is poorly soluble and form crystals with accumulation. This leads to cell damage, cell death and eventual organ damage (4-8).

Three distinct forms of cystinosis exist. All three forms can result in anterior segment crystal deposition, but only the nephropathic forms affect the posterior segment (9).

1. Nephropathic cystinosis, also known as infantile, classic and early-onset cystinosis, is the most severe form of the disease. It typically present in the first 6-12 months of life with renal involvement including Fanconi syndrome (disease of the proximal renal tubules resulting in glycosuria, metabolic acidosis, phosphaturia, and aminoaciduria) and renal loss of salt and water (1,10). All cases require renal transplantation in childhood (10). Growth failure is also a common early finding. The eyes are often affected early in the disease course with cystine crystals depositing in the cornea causing photophobia, blepharospasm and occasionally corneal erosions. Crystals also deposit in the conjunctiva, iris, trabecular meshwork, anterior capsule, optic nerve and retina. Though irritating, the corneal crystal deposits do not affect visual acuity (1,10). Retina abnormalities occur in some patients as early as infancy and include retinal pigment epithelium hypopigmentation, appearing as a "salt and pepper" type fundus which may result in an abnormal visual field (11). Other organs affected include the thyroid, pancreas, muscle and central nervous system (10).

2. Intermediate nephropathic cystinosis, also known as juvenile or late-onset cystinosis, is less common than the infantile form and includes the same spectrum of disease but with later onset and less severity, particularly with respect to the systemic manifestations. Nonetheless, end-stage renal disease, such as that which occurred in our patient, may occur, requiring transplantation in early adulthood (2).

3. Non-nephropathic cystinosis, also known as adult or ocular cystinosis results in isolated ocular signs and symptoms and do not experience the effects on other organs (2).

Cystinosis can be diagnosed clinically, particularly with the finding of corneal crystals on slit-lamp examination. The diagnosis may be confirmed on laboratory testing with an elevated serum leukocyte cystine measurement.

Reference Levels	
3.0 – 23.0 nmol half-cystine/mg protein	Nephropathic cystinosis
1.0 – 3.0 nmol half-cystine/mg protein	Non-nephropathic cystinosis
≤ 1.0 nmol half-cystine/mg protein	Heterozygotes for CTNS mutation
≤ 0.2 nmol half-cystine/mg protein	Normal value

Treatment

Cystinosis is treated with daily cysteamine, which reacts with cystine inside the lysosome to convert it to both cysteine and a cysteine-cysteamine disulfide resembling lysine. These molecules can then be transported out of the lysosome (1,12) Oral cysteamine does improve symptoms and delay organ damage, but end-stage renal disease often still results. Oral cysteamine has also been shown to prevent retinopathy; therefore, it is recommended that all patients begin oral cysteamine therapy at the time of diagnosis (11). Systemic cysteamine has no effect on corneal crystal deposition, but cysteamine eye drops are very effective at dissolving corneal and conjunctival crystals and relieving the associated symptoms when used frequently (every 1-2 hours while awake) (1,13). Genetic testing and prenatal counseling are available.

Differential Diagnosis

- Cystinosis
- Schnyder crystalline corneal dystrophy
- Bietti crystalline corneoretinal dystrophy
- Infectious crystalline keratopathy
- Lymphoproliferative disorders
- Medication-induced corneal deposits

Diagnosis

Epidemiology

- The incidence of nephropathic cystinosis, the most common form, is about 1 in 100,000 – 200,000 individuals.
- A higher incidence of 1 in 26,000 has been observed in the province of Brittany, France.

Signs

- Ocular: cystine crystals in the cornea, conjunctiva, iris, anterior chamber, optic nerve, retina; corneal epithelial erosions; peripheral retinal depigmentation ("salt and pepper" appearance of fundus)
  - Visual acuity is not affected by the corneal deposits.
  - Visual field defects may occur in association with peripheral pigmentary retinopathy.
- Systemic: Delayed puberty, growth failure, rickets, hyothyroidism, hepatosplenomegaly

Symptoms

- Ocular: Photophobia, epiphora, foreign body sensation, blepharospasm
- Renal: Polyuria, polydypsia, vomiting, constipation, weakness
- Other: Nausea and vomiting, constipation, weakness, difficulty with walking and swallowing in later disease

Treatment

- Oral cystine depleting therapy: cysteamine bitartrate (Cystagon ®), dose titrated to reduce cystine concentration to less < 1.0 nmol half-cystine/mg protein 5-6 hours after medication administration.
- Cysteamine eye drops 0.44% solution Q1H while awake if possible.
- Avoid bright light, use sunglasses and artificial tears as needed.
- See complete treatment guidelines (https://cystinosis.org/images/family-support/resources/CRN_Standards_12pgloRes.pdf)

References

1. Tsilou E, Zhou M, Gahl W, Sieving PC, Chan CC. Ophthalmic manifestations and histopathology of infantile nephropathic cystinosis: report of a case and review of the literature. Surv Ophthalmol. 2007;52(1):97-105.
2. Nesterova G, Gahl WA. Cystinosis. 2014. In: GeneReviews [Internet]. Seattle, WA: University of Washington.
3. Online Mendelian Inheritance in Man OMIM Number: 606272. March 19, 2010. Baltimore, MD: Johns Hopkins University. Available from: http://omin.org/ (http://omin.org/).
4. Gahl WA. Bashan N, Tietze F, Bernardini I, Schulman JD. Cystine transport is defective in isolated leukocyte lysosomes from patients with cystinosis. Science. 1982;217(4566):1263-5.
5. Gahl WA, Tietze F, Bashan N, Steinherz R, Schulman JD. Defective cystine exodus from isolated lysosome-rich fractions of cystinotic leucocytes. J Biol Chem. 1982;257(16):9570-5.
6. Jonas AJ, Smith ML, Allison WS, Laikind PK, Greene AA, Schneider JA. Proton-translocating ATPas and lysosomal cystine transport. J Biol Chem. 1983;258(19):11727-30.
7. Jonas AJ, Smith ML, Schneider JA. ATP-dependent lysosomal cystine efflux is defective in cystinosis. J Biol Chem. 1982;257(22):13185-8.
8. Thoene JG, Oshima RG, Ritchie DG, Schneider JA. Cystinotic fibroblasts accumulate from intracellular protein degradation. Proc Natl Acad Sci. 1977;74(10):4507-7.
9. Online Mendelian Inheritance in Man OMIM Number: 219750. April 19, 2011. Baltimore, MD: Johns Hopkins University. Available from: http://omin.org/ (http://omin.org/).
10. Schneider JA, Katz B, Melles RB. Update on nephropathic cystinosis. Pediatr Nephrol. 1990;4(6):645-53.
11. Tsilou ET, Rubin BI, Reed G, Caruso RC, Iwata F, Balog J. Nephropathic cystinosis: posterior segment manifestations and effects of cysteamine therapy. Ophthalmology. 2006;113(6):1002-9.

12. Markello TC, Bernardini IM, Gahl WA. Improved renal function in children with cystinosis treated with cysteamine. N Eng J Med 1993;328(16):1157-62.
13. Labbe A, Baudoiun C, Deschenes G, Loirat C, Charbit M, Guest G. A new gel formulation of topical cysteamine for the treatment of corneal cystine crystals in cystinosis: the Cystadrops OCT-1 study. Mol Genet Metab. 2014;111(3):314-20.

Suggested Citation Format

Myers HI, Haugsdal JM, Wagoner MD. Cystinosis: A 12-year-old boy with light sensitivity. March 4, 2015; Available from: http://EyeRounds.org/cases/209-Cystinosis.htm

last updated: 03/04/2015

University of Iowa Carver College of Medicine
Department of Ophthalmology & Visual Sciences
200 Hawkins Dr.
Iowa City, IA 52242