Ocular Complications of Infantile Nephropathic Cystinosis

Rachel Bishop, MD, MPH

Ocular complications are among the most common cause of discomfort and disability in patients with cystinosis, affecting virtually all individuals with nephropathic cystinosis if left untreated.[1,2] Photophobia results from accumulation of cystine crystals within the corneal tissue. Compliance with recommended therapy can reverse this change, resulting in resolution of symptoms.[3] Other ocular structures also suffer from cystine accumulation,[4-6] and early and diligent systemic and local treatment prevents the most severe, irreversible, complications including vision loss.

Anterior Segment ("Front of Eye") Findings

Corneal changes are the most common, and most commonly symptomatic, ocular complication in cystinosis. There is evidence for crystal accumulation in all layers of the cornea, with cornea stroma involvement being the most significant examination finding. Corneal crystals are typically present in the corneal periphery by 16 months of age, and advance to saturate the cornea by early adolescence if left untreated.[7] Although difficult to appreciate on slit-lamp examination, crystals can be visualized in corneal epithelial cells by in vivo confocal microscopy[8] and histopathology.[6] Corneal crystals diffract incoming light, causing it to scatter, creating the photophobia (or light sensitivity) classic to this condition, with severity of photophobia related to density of stromal crystal deposit. Dense corneal stromal changes appear to destabilize the corneal epithelium, resulting in punctate keratopathy, filamentary keratitis, and recurrent epithelial erosions, all of which can cause pain, and in some cases, corneal scarring, impairing vision.[1,9,10] Systemic cysteamine therapy does not reach the avascular corneal tissues, necessitating the use of topical therapy in the form of drops or gel. When used properly, topical treatment can reverse corneal crystal accumulation and, thereby, improve or resolve both photophobia and ocular discomfort (**Figure 1**).[1] Crystals also accumulate in other anterior segment structures,[10] including the conjunctiva, iris, and ciliary body. Conjunctival crystals are responsive to topical cysteamine therapy. In severe untreated or undertreated cases, band keratopathy, peripheral corneal neovascularization, posterior synechiae, and pupillary block with secondary glaucoma can result. Some of these conditions require specialized surgery to manage[11,12] and often result in vision loss (**Figure 2**).

Posterior Segment ("Back of Eye") Findings

Intracellular cystine crystals have been identified in nearly all ocular structures on postmortem examination, including the retina, choroid, and optic nerve.[6] In an untreated or under-treated patient, the impairment of retinal function can result in a pigmentary retinopathy, appearing as a mottled pattern to the retinal pigment epithelium on fundus examination, and manifesting as decreased color and night vision, and significant visual field loss, typically in the midperiphery and may advance to central vision impairment (**Figure 3**).[5] Decreased signal on electroretinogram also captures this change. As the retina and choroid are well vascularized, these changes occur less frequently in patients receiving effective systemic therapy. Another condition that affects patients with cystinosis is increased intracranial pressure. This can cause papilledema even among those receiving appropriate systemic cysteamine therapy,[4] and is one of the reasons patients require regular ophthalmologic examinations. Papilledema can progress to cause visual field impairment and vision loss, and is best managed in concert with the primary treatment team, often with the help of neurology or neuro-ophthalmology (**Figure 4**).

Conclusions in Ocular Findings

Several points bear consideration and might guide future efforts:

(1) It is essential that patients with cystinosis receive regular eye examinations by ophthalmologists skilled in identifying ocular changes and guiding therapy. These skills are not difficult to learn, and online and/or printed materials can assist ophthalmologists who rarely care for these patients. Yearly eye examinations are typically advised, with more frequent examinations necessary for

From the National Eye Institute, National Institutes of Health, Bethesda, MD

Please see the author disclosures at the end of the article.

0022-3476/$ - see front matter. © 2016 Published by Elsevier Inc.
http://dx.doi.org10.1016/j.jpeds.2016.12.055

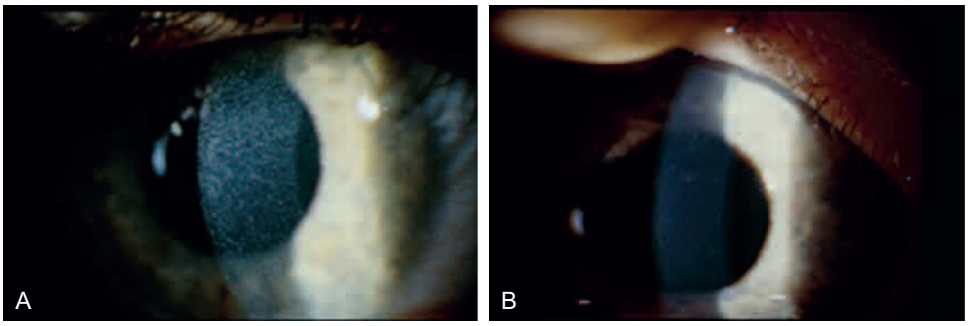

Figure 1. Corneal crystal accumulation **A,** pre-treatment, and **B,** post-treatment with topical cysteamine drops over a 16-month period.

some patients. Although imaging techniques such as slit-lamp photography and anterior segment optical coherence tomography are helpful (and recommended) in managing patients and tracking progress of treatment, these are not essential to providing care to patients if unavailable.

(2) Patients vary in the frequency of topical cysteamine dosing that is needed for effective corneal crystal control, but most patients are well managed on a regimen of 6-10 doses per day of cysteamine drops. More frequent dosing is often required to initially reduce corneal crystal load in severely affected patients. In Europe, cysteamine gel is used successfully with the frequency of 4 doses per day.[13] Approved cysteamine drug formulations vary by country, and for those patients without access to commercially available topical treatments (drops or gel), compounded formulations are often used, though with variable success.

(3) The age at which to start topical cysteamine therapy is controversial. Some experts speculate that early topical treatment with a cysteamine agent, perhaps at low frequency, might prevent corneal crystal accumulation if initiated before there is clinical evidence of corneal crystals. Standard practice is to initiate topical therapy on first evidence of corneal crystals on eye examination.[14]

(4) Research exploring potentially preventative therapy regimens, whether with current or future drug formulations, is warranted, as is research exploring less arduous delivery methods that would be equally or more effective than current treatments.

(5) There is significant benefit to patients by using multidisciplinary team management, including ophthalmology and nephrology, allowing for easy communication between specialists and with patients, and optimal patient care. ■

Author Disclosures

The author declares no conflicts of interest, real or perceived.

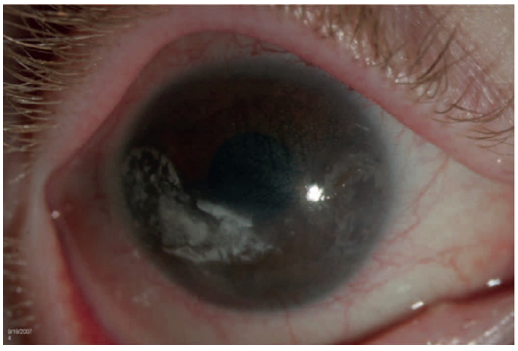

Figure 2. Band keratopathy and corneal neovascularization.

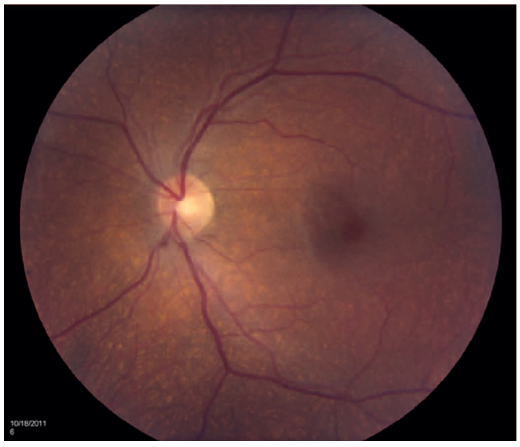

Figure 3. Retinal pigment epithelial mottling.

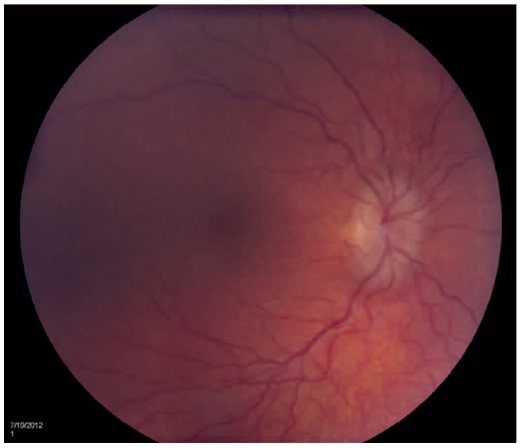

Figure 4. Papilledema.

Reprint requests: Rachel Bishop, MD, MPH, National Eye Institute, National Institutes of Health, 31 Center Dr, Bethesda, MD 20892. E-mail: bishopra@nei.nih.gov

References

1. Gahl WA, Kuehl EM, Iwata F, Lindblad A, Kaiser-Kupfer MI. Corneal crystals in nephropathic cystinosis: natural history and treatment with cysteamine eye drops. Mol Genet Metab 2000;71:100-20.
2. Gahl WA, Thoene JG, Schneider JA. Cystinosis. N Engl J Med 2002;347:111-21.
3. Kaiser-Kupfer MI, Fujikawa L, Kuwabara T, Jain S, Gahl WA. Removal of corneal crystals by topical cysteamine in nephropathic cystinosis. N Engl J Med 1987;316:775-9.
4. Dogulu CF, Tsilou E, Rubin B, Fitzgibbon EJ, Kaiser-Kupper MI, Rennert OM, et al. Idiopathic intracranial hypertension in cystinosis. J Pediatr 2004;145:673-8.
5. Tsilou ET, Rubin BI, Reed G, Caruso RC, Iwata F, Balog J, et al. Nephropathic cystinosis: posterior segment manifestations and effects of cysteamine therapy. Ophthalmology 2006;113:1002-9.
6. 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;52:97-105.
7. Labbé A, Niaudet P, Loirat C, Charbit M, Guest G, Baudouin C. In vivo confocal microscopy and anterior segment optical coherence tomography analysis of the cornea in nephropathic cystinosis. Ophthalmology 2009;116:870-6.
8. Liang H, Baudouin C, Tahiri Joutei Hassani R, Brignole-Baudouin F, Labbé A. Photophobia and corneal crystal density in nephropathic cystinosis: an in vivo confocal microscopy and anterior-segment optical coherence tomography study. Invest Ophthalmol Vis Sci 2015;56:3218-25.
9. Kaiser-Kupfer MI, Caruso RC, Minkler DS, Gahl WA. Long-term ocular manifestations in nephropathic cystinosis. Arch Ophthalmol 1986;104:706-11.
10. Tsilou ET, Rubin BI, Reed GF, Iwata F, Gahl W, Kaiser-Kupfer MI. Age-related prevalence of anterior segment complications in patients with infantile nephropathic cystinosis. Cornea 2002;21:173-6.
11. Kaiser-Kupfer MI, Datiles MB, Gahl WA. Corneal transplant in boy with nephropathic cystinosis. Lancet 1987;1:331.
12. Wan WL, Minckler DS, Rao NA. Pupillary-block glaucoma associated with childhood cystinosis. Am J Ophthalmol 1986;101:700-5.
13. Buchan B, Kay G, Heneghan A, Matthews KH, Cairns D. Gel formulations for treatment of the ophthalmic complications in cystinosis. Int J Pharm 2010;392:192-7.
14. Bishop R. Personal communication. Cystinosis: ophthalmological symposium for patients and physicians. Salzburg, Germany: Cystinosis Foundation Germany; 2015.