Medscape EDUCATION

# Nephropathic Cystinosis

Cystinosis is a rare autosomal recessive disorder characterized by the accumulation of cystine within cells.[1,2] Caused by mutations in the *CTNS* gene encoding the lysosomal membrane transport protein cystinosin, it is a multisystemic disease that results from cystine accumulation that occurs primarily in the kidneys, but also in other tissue and organs, including the eyes, bone marrow, liver, spleen, pancreas, thyroid, muscle, and brain. Cystinosis belongs to the family of lysosomal storage disorders, and like other diseases in this category, initial manifestations generally appear several months after birth.[2]

The most severe and common form of cystinosis is the infantile form or nephropathic cystinosis, which accounts for 95% of cases.[3] Between 6 to 12 months of age, children typically develop Fanconi syndrome, a renal tubular disorder characterized by a severe fluid and electrolyte disturbance, proteinuria, growth retardation, and rickets.[2,3] Extra-renal manifestations include diabetes, myopathy, neurological defects, and ocular pathology. The 2 other clinical forms are juvenile, which is similar to the infantile form but with slower progression and presents at about age 12 to 15 years, and ocular non-nephropathic, typically diagnosed during adulthood and where patients present only with ocular anomalies.

## Ocular Manifestations

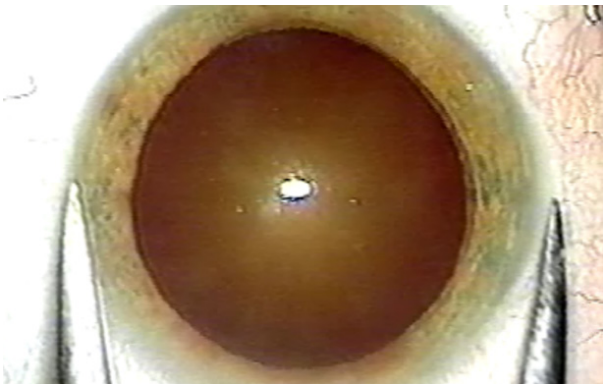
In nephropathic cystinosis, cystine crystal deposition will occur in multiple organs as the disorder progresses, with the kidneys and eyes being affected first.[3] All forms of cystinosis affect ocular structures, including the cornea, conjunctiva, iris, ciliary body, choroid, retina and optic nerve. However, the most frequently described manifestation is cystine crystal deposition in the cornea, which leads to photophobia, corneal erosions, and keratopathies. Corneal cystine crystals are not detectable at birth although they begin in infancy, in the anterior periphery of the cornea and then progress centrally and posteriorly.[3] They may be visible through a slit lamp examination by 12 months and are always present by the age of 18 months.[5]

Symptoms of photophobia and blepharospasm are generally observed from mid-childhood to early adolescence. Superficial punctate and filamentary keratopathy is commonly observed in adolescent and adult patients. Band keratopathy, peripheral corneal neovascularization and posterior synechiae associated with iris thickening are primarily seen in older adults.[5] Depigmentation of the peripheral retina with pigment epithelial mottling is a common complication that is generally observed by about age 20, but it has been detected in children as young as 6 months of age. Retinopathy will lead to retinal blindness in about 10% to 15% of patients.[5]

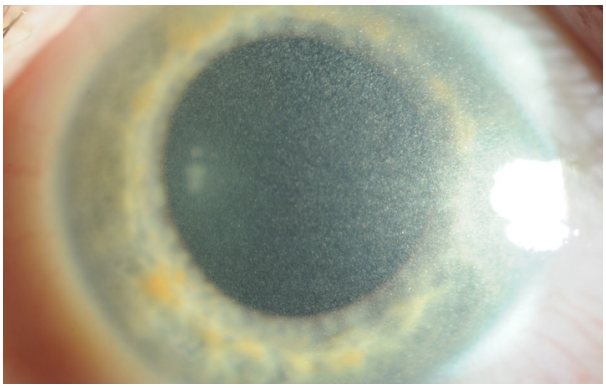
**Ocular Manifestations of Nephropathic Cystinosis**

*Images courtesy of Natalie A. Afshari, MD*

### Normal Cornea



### Cystinosis



## Treatment

Early detection, treatment, monitoring and follow-up are essential for ensuring increased life expectancy and a better quality of life. There is no curative treatment for cystinosis, and management is largely supportive and directed towards controlling symptoms.

- The mainstay of treatment is with oral cysteamine, which reduces the intralysosomal cystine concentration[4,6]
- Oral cysteamine slows the progression of the disease and increases life expectancy but it is not curative. It has no effect on proximal tubulopathy and does not prevent end-stage renal failure.[4]
- Due to the poor vascular system in the cornea, oral cysteamine does not effectively control ocular accumulation of cystine crystals in the eyes.
- Cysteamine must be applied directly to the eyes to have any real impact, and 2 formulations are available that can dissolve cystine crystals.
- The FDA approved a cysteamine ophthalmic solution in 2012 that contains 6.5 mg/ml (0.65%) of cysteamine hydrochloride (CH), which is equivalent to 4.4 mg/ml (0.44%) of cysteamine, as the active ingredient.[6]
- It requires frequent administration -- either every waking hour, or 6 to 12 times per day. [3,6] This formulation contains cysteamine which oxidizes at room temperature and must be refrigerated.
- A second formulation is a viscous ophthalmic solution that contains 0.37% of cysteamine (equivalent to 0.55% cysteamine hydrochloride).[6] Approved by the FDA in 2020, it has a dosing schedule of 4 times per day.
- The chemical stability of the formulation allows it to be kept at room temperature for up to 7 days after it is open, although refrigeration is still required for long-term storage.[3,6]
- There are currently no standardized guidelines or recommendations for detecting ocular cystinosis, management, and follow-up assessments.[3]

## References


1. Shams F, Livingstone I, Oladiwura D, et al. Treatment of corneal cystine crystal accumulation in patients with cystinosis. Clin Ophthalmol. 2014;8:2077-84.
2. Gahl WA, Thoene JG, Schneider JA. Cystinosis. N Engl J Med. 2002;347:111-21.
3. Biswas S, Gaviria M, Malheiro L, et al. Latest clinical approaches in the ocular management of cystinosis: a review of current practice and opinion from the Ophthalmology Cystinosis Forum. Ophthalmol Ther. 2018;7:307-322.
4. Cherqui S. Cysteamine therapy: a treatment for cystinosis, not a cure. Kidney Int. 2012;81:127-9.
5. Elmonem MA, Veys KR, Soliman NA, et al. Cystinosis: a review. Orphanet J Rare Dis. 2016;11:47.
6. Liang H, Labbé A, Baudouin C, et al. Long-term follow-up of cystinosis patients treated with 0.55% cysteamine hydrochloride. Br J Ophthalmol. 2021;105:608-613.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