WPSOS Consensus Statement – Ocular Manifestations Of Cystinosis

WHAT IS CYSTINOSIS?

Cystinosis is a rare, autosomal recessive metabolic disorder caused by pathogenic variants in the gene *CTNS* located on chromosome 17p13.22. This gene encodes a lysosomal membrane transport protein, cystinosin, which is responsible for the transport of the amino acid cystine, out of lysosomes.[1] *CTNS* dysfunction results in the widespread intracellular accumulation of cystine crystals in tissues and organs, with early clinical manifestations affecting the kidney and the eye. Other functions of cystinosin influencing autophagic flux, oxidative stress, mitophagy, apoptosis and inflammation also have a role in the pathology of cystinosis.[2]

The worldwide incidence of cystinosis is 1:100,000 to 1:200,000,[3] whilst in some regions, founder effects can push the incidence up to 1:26,000[4] and, in communities with high levels of consanguinity, the incidence can be as high as 1:3,613.[5]

HOW MANY TYPES OF CYSTINOSIS ARE THERE ?

There are three clinical phenotypes of Cystinosis :

Infantile nephropathic cystinosis (INC) the commonest type occurring in approximately 95% of cases. This is also the most common, identifiable cause of renal Fanconi syndrome in infancy, due to renal proximal tubular dysfunction, clinically presenting with failure to thrive and hypophosphatemic rickets. Untreated, end-stage renal failure occurs by the end of the first decade of life. Ocular involvement is first seen with corneal and conjunctival cystine crystals visible on slit-lamp examination as young as 5 months of age.[6] Rapid accumulation of cystine crystal occurs in the first years of life leading to all patients having crystals visible in the cornea by 16 months of age. By the end of the second decade and beginning of the third decade of life, most of the patients demonstrate diffuse infiltration of corneal crystals.[6]

Intermediate (juvenile) cystinosis occurs in approximately 5% of cases, where renal involvement and ocular involvement are later in onset;[7] milder form compared to INC.

Adult-onset, non-nephropathic (ocular) cystinosis is very rare and manifests only corneal and conjunctival cystine crystal accumulation and no systemic manifestations. In comparison to INC, the rate of accumulation of crystals in ocular tissues is slower.

In Nephropathic Cystinosis, systemic treatment with oral cysteamine (mercaptamine) has significantly altered the rate of progression of the disease and delayed or prevented onset of complications, particularly when instituted early.[8] Patients are surviving well into their 50's from combination of cysteamine treatment and renal allograft.[9] Furthermore, in a retrospective study of 100 consecutive patients attending over a 21 year period, death rates were reduced from 49% in those receiving cysteamine for less than 8 years duration to 8% in those receiving it for 8 years of more.[10]

WHAT IS THE OCULAR INVOLVEMENT?

Signs and Symptoms

All ocular tissues accumulate cystine crystals, although most noticeable in the cornea. Photophobia is the commonest ocular symptom of cystinosis and is attributed to the deposition of crystals in the cornea, resulting in inflammatory cell infiltration, and corneal nerve damage.[11] This can result in ocular irritation, blepharospasm and epiphora. Patients may also have blepharitis and meibomian gland dysfunction.[12] Symptoms of photophobia may be observed in young children, but more typically begins in the second decade and increases from third decade onwards with increasing crystal deposition.[13,14]

Visual acuity is often initially normal but may also start to decline beginning in the third decade due to progressive corneal and ocular surface damage.

In untreated or delayed systemic treatment cases, retinal involvement may result in nyctalopia, peripheral field loss, and reduced visual acuity secondary to a progressive maculopathy. Cystinosis-related retinopathy may also contribute to glare and photophobia.[15] Corneal damage tends to precede retinal disease.

Anterior segment:

Cornea

In early infancy, corneal cystine crystal deposits may be detected in the peripheral anterior cornea by careful slit lamp examination. They appear as fine, refractile crystal deposits that progressively accumulate over the first 2 decades of life. Over time these deposits progress more centrally and deeper into the corneal stroma until all corneal layers contain crystals.[16] Early corneal complications include superficial punctate keratopathy. In the third decade, a filamentary keratitis may develop. With continued progression from the third decade onwards, corneal neovascularization occurs with lipid deposits.[13] Corneal endothelial damage from advanced disease may result in corneal edema. End stage corneal disease is associated with band-shaped keratopathy typically seen after the 4th decade, extensive corneal vascularization and scarring and corneal decompensation.[17]

Conjunctiva

Cystine crystals appear early and accumulate throughout the conjunctiva.[18] Though harder to see than in the cornea, they may be observed as fine golden-yellow deposits on bulbar and tarsal conjunctiva and at the limbus.

Iris

Cystine crystals are also seen deposited on the iris stroma. In more advanced cases uveitis may develop with posterior synechiae, iris thickening, iris pigment epithelial loss and transillumination defects.[13] Progressive deposition of crystals in the ciliary body may result in thickening and anterior rotation resulting in progressive narrowing of the angle[19] with a configuration very similar to plateau iris syndrome.

Lens

Cystine crystals may occasionally be seen deposited on the anterior lens capsule. Those patients with nephropathic cystinosis with renal transplantation may develop posterior subcapsular lens opacities from significant systemic steroid medications.

Posterior Segment

Posterior segment complications were commonly seen in patients who were historically untreated or undertreated with systemic cysteamine.

Retina and Retinal Pigment Epithelium

Pigmentary retinopathy may be observed with retinal pigment epithelial defects (RPE) and mottling of the RPE, observed in the peripheral retina and this may be observed as early as 6 months of age.[20] Maculopathy and cystoid macular oedema may develop.[21]

Retinal cystine crystal deposits may be observed on fundoscopy in older patients beginning in the third decade.[20]

A pigmentary retinopathy resembling retinitis pigmentosa may be observed in advanced cases.

Choroid

Cystine crystals are present in the choroid.[22] Choroidal neovascularization has occasionally been found.[23]

Optic Nerve

Papilledema is well known to occur in cystinosis and may or may not be symptomatic. The incidence varies from 5%[24] to 13.6%.[12] The cause remains elusive, but may be related to treatment with cyclosporine, growth hormone, corticosteroids, vitamin D, complications of renal failure, hypercoagulability and venous sinus thrombosis, arachnoid villi dysfunction due to thrombosis or cystine crystal accumulation,[24] or Chiari 1 malformation[25].

Investigations

A full ophthalmological assessment including:

- Visual acuity
- Contrast sensitivity, both of which decline with increasing severity of disease.[26]
- Patient and clinician assessed photophobia.[27]
- Anterior segment examination with slit lamp biomicroscopy (hand-held slit lamp examination in infancy directed at the peripheral cornea may be helpful in identifying early crystal deposits).
- Intraocular pressure measurement.
- Posterior segment examination.[28]

Quantifying cystine crystals:

Quantifying crystal load in cornea and retina may provide the clinician with additional information about disease status and response to or compliance with treatment. Advanced imaging techniques can facilitate this, but are not mandatory.

Cornea

Various methods have been devised for quantifying cystine crystal load in the cornea. A variety of techniques can be used to measure this as below

- Corneal Cystine Crystal Score (Gahl Score)[6]
- Anterior segment OCT (Corneal Crystal Depth).[29 30]
- Corneal densitometry: Using Scheimpflug imaging [31] or AS-OCT with appropriate software.[32]
- In-vivo confocal microscopy.[29]

Retinal Imaging

Optical Coherence Tomography: Choroidal and retinal crystals best visualized with SD-OCT.[15] The crystal score may be a good biomarker for disease control.

Other imaging investigations

- Wide-angle retinal imaging and autofluorescence provides an excellent means of identifying pigmentary abnormalities in the retinal periphery.
- Optic nerve appearance may also be documented in order to assess for papilledema and optic nerve drusen.
- OCT scans of the optic nerve is also helpful for monitoring optic nerve swelling.
- Indocyanine green video-angiography to optimally identify choroidal neovascular membrane in the presence of dense corneal crystal deposits.[23]
- Visual Field Testing: Formal visual field testing may be carried out when there is evidence of retinal or RPE involvement or symptoms such as night blindness or monitoring of raised intracranial pressure.

- Electrodiagnostic testing: Electroretinography may be required if there is evidence of retinal involvement or symptoms of visual loss or night blindness.
- Visual Evoked Potentials may be considered if there is evidence of optic nerve swelling and raised intracranial pressure.

Table 1: Summary of Ocular Complications and suggested investigations / imaging.

Anterior Segment Complications		**Suggested Imaging / Investigations***
Cornea	• Needle-shaped crystal deposits; • Punctate keratopathy • Filamentary keratitis • Corneal oedema • Corneal neovascularisation Corneal thinning • Band keratopathy	• Slit lamp imaging / photography • Anterior Segment OCT • Corneal Densitometry • In vivo confocal microscopy
Conjunctiva	• Fine golden-yellow crystalline deposits • Conjunctival injection	• Slit lamp photography
Iris	• Iris crystals • Iris synechiae • Plateau Iris / secondary angle closure glaucoma • Uveitis	• Anterior segment OCT • Anterior segment ultrasound biomicroscopy
Lens	• Crystalline anterior lens capsule deposits	• Slit lamp imaging / photography
Posterior Segment Complications		**Suggested imaging / investigations**
RPE	• Peripheral RPE hypopigmentation • Pigment mottling	• Wide angle retinal imaging and autofluorescence
Retina	• Intraretinal crystal deposits • Pigmentary retinopathy • Subretinal neovascular membrane	• SD-OCT macula • ERG • Visual fields • ICG angiography
Optic nerve	• Papilledema	• Ultrasound B scan • Autofluorescence imaging • OCT disc • Visual fields
Choroid	• Crystalline deposits	• SD-OCT

*Not all imaging / investigations are necessary and will depend on age of patient, co-operation and equipment available.

WHAT IS THE MANAGEMENT?

Guidance on clinical management of cystinosis have been published. [27] [28] Initially, patients present to nephrologists due to early renal complications. Cystinosis should be suspected in renal Fanconi syndrome (failure to thrive, glycosuria, polyuria / polydipsia, electrolyte imbalance, dehydration, rickets). Early referral to ophthalmology can help confirm the diagnosis clinically.

Molecular diagnosis by genetic testing for biallelic pathogenic *CTNS* gene variants can be performed with a high sensitivity and specificity, [33] although this may not always be available. Over 140 CTNS variants have been described with geographic variation, for example, in Western Europe and North

America the most common variant is a large 57 kb deletion, although in the Middle East this variant is rare and the c681G>A (p.E227E) is more common. Cystinosis is noted for a genotype-phenotype correlation with the vast majority of variants causing the more severe infantile form. Only 15 and 4 variants have been described causing intermediante/juvenile and ocular cystinosis respectively, so far.[34] Genetic testing through Next Generation Sequencing may be performed in suspected cases. Newborn genetic testing has also been trialed in Germany[35] and in England (www.generationstudy.co.uk/conditions-we-test-for/all-conditions?letter=C). Genetic testing affords the possibility of very early diagnosis, genetic counselling and future pre-natal diagnosis enabling better outcomes as a result of earlier initiation of treatment.

Measurement of elevated white cell cystine levels (>2 nmol half-cystine/mg) also confirms the diagnosis, but access to specialized laboratories is required.[8] Patients with intermediate (juvenile onset) cystinosis may have a more insidious onset of renal complications and ophthalmologists may be the first to suspect cystinosis in this group of patients through identifying the corneal crystals prompting urgent referral to paediatric nephrologists for further investigation.

Systemic Treatment

Once the diagnosis of cystinosis is made, infants and children are administered systemic cysteamine orally by their nephrologists coupled with electrolyte replacement therapy. Early initiation of oral cysteamine significantly delays onset of and may even prevent end-stage renal failure. Oral cysteamine is typically administered 6 hourly but delayed release cysteamine is also available as a twice daily preparation. There are significant gastrointestinal side effects with these such as nausea and vomiting, flatulence and halitosis. As cystinosis is a multisystem disorder, other specialists are involved, for example:

- Endocrinologists - growth and metabolic bone disease, thyroid and pancreatic function, puberty and fertility.
- Neurologists – myopathies, central and peripheral nervous system disorders, raised intracranial pressure.
- Orthopaedics – skeletal problems, scoliosis, fractures, rickets/osteomalacia
- Gastroenterology and dieticians – feeding difficulties, appetite, GI symptoms
- Psychologists – general psychological and educational support
- Specialist nurses to support holistic care. This depletes the lysosome of cystine through alternative transport routes reducing cystine levels in tissues and organs. This treatment is not effective in reducing corneal crystal deposition, but is almost certainly critical in reducing the retinal complications of cystinosis.[20]

Ocular Treatment

Systemic cysteamine reduces retinal complications but is unable influence progression of corneal disease. Topically applied cysteamine 0.55% is effective in reducing corneal crystal load[6] but requires frequent administration (10-12 times a day), need for refrigeration, and unexposure to light. Many patients struggle to administer this treatment at the required frequency[12] contributing to its ineffectiveness.[36] Other concerns include the poor stability of the drug, which readily oxidises to ineffective cystamine[37] and possible poor penetration of the drug into the cornea.[38] To improve duration of exposure of the cornea to topically applied cysteamine, a viscous preparation containing carmellose sodium and cysteamine 0.55% and benzalkonium chloride has shown greater efficacy than an aqueous compounded eyedrop preparation in reducing crystal density and photophobia[39] and has been licensed for treatment of corneal cystine crystals at a four times daily dosing. Improvement in drug presence on the ocular surface may be achieved by insertion of punctal plugs, which may also enable a reduced frequency of administration of non-viscous preparations of topical cysteamine.

Topical cysteamine preparations do have significant side effects that adversely affect compliance including stinging on application, watering, conjunctival injection, and blurring of vision, which is more pronounced with the viscous preparation due to the prolonged duration of contact with the ocular surface.[40] It is therefore important to counsel patients and families regarding these expected side effects. Regular use of topical lubricants may also help alleviate some of the side effects.
It is important to evaluate the tear meniscus; crystals can be deposited in any ocular tissue including lacrimal gland and dry eyes may contribute to the stingy sensation. Anecdotally placing a preservative free articial tear in the eye prior to placing the cysteamine drop may reduce the stinging in come cases.

Recording symptoms of photophobia, compliance with treatment and assessment of corneal crystal density at each visit is essential for ongoing care. Patient reported outcome measures may also provide valuable feedback to the clinician, for example using the Quality of Vision Questionnaire,[41] which has been show to correlate with the RCCCS score.[15]

Headaches maybe due to glaucoma; the possibility of angle closure glaucoma due to plateau iris syndrome must be considered and appropriate treatment considered.

Advanced corneal disease has had mixed results from surgical management such as penetrating keratoplasty including recurrent crystal deposits in the graft[42] and experience is limited to a few case reports.[42 43]

Posterior segment examination is important to monitor retinal complications but, importantly, to rule out raised intracranial pressure. If papilloedema is found, referral to neurology and neuro-imaging is required with ongoing monitoring of patients with papilloedema at an increased frequency to assess response to treatment.

Multidisciplinary Team Working

Cystinosis is multisystem metabolic disorder with significant co-morbidities beyond the kidney and eye and ophthalmologists must be part of a wide-ranging multidisciplinary team involved in the care of children with this disorder and to collaborate to achieve the best outcomes.

SUMMARY ESSENTIALS FOR MANAGING OCULAR MANIFESTATIONS OF CYSTINOSIS

When faced with a patient suspected or diagnosed with cystinosis, the following steps are critical for effective ophthalmic management:

1. **Confirm Diagnosis**: Perform a slit-lamp examination (hand-held in infants) to detect corneal cystine crystals, visible as early as 5 months in infantile nephropathic cystinosis and by 16 months in all cases. Coordinate with nephrologists for systemic evaluation, including genetic testing for *CTNS* variants or white cell cystine level measurement, if available.
2. **Assess Ocular Involvement**: Conduct a comprehensive ophthalmological exam, including visual acuity, contrast sensitivity, intraocular pressure, and anterior/posterior segment evaluation. Quantify corneal crystal load using the Corneal Cystine Crystal Score (Gahl Score) or anterior segment OCT, and monitor retinal health with fundoscopy and spectral-domain OCT (SD-OCT) to detect retinopathy or papilledema.
3. **Initiate Treatment**: Prescribe topical cysteamine 0.55% eye drops (preferably viscous formulation, dosed four times daily) to reduce corneal crystal density and photophobia. Counsel patients and families on side effects (stinging, tearing, blurred vision) and strategies to improve compliance, such as topical lubricants or punctal plugs. Ensure systemic cysteamine therapy is managed by nephrologists to prevent retinal and systemic complications.
4. **Monitor Regularly**: Schedule follow-up visits to assess photophobia, treatment compliance, and crystal load (using slit-lamp or imaging). Monitor for posterior segment complications (e.g.,

retinopathy, maculopathy) and papilledema, referring to neurology with neuroimaging if papilledema is detected. Use patient-reported outcome measures (e.g., Quality of Vision Questionnaire) to guide care. Always keep the possibility of glaucoma in the back of your mind especially towards the end of the second decade onwards.

5. **Collaborate Multidisciplinary**: Work within a multidisciplinary team, including nephrologists, neurologists, endocrinologists, dieticians, psychologists and pharmacists, to address renal, neurological, metabolic comorbidities, nutrition, and psychosocial aspects. Regular communication ensures holistic care, particularly in pediatric patients requiring early and consistent intervention.
6. **Transition to adult services**: As cystinosis is lifelong, special arrangements to involve the young person in their care and to transition them from from paediatric care to adult care in a structured way should start from the age of 12-14 years.[44] This may include important discussions around shared decision making, psychosocial aspects and fertility. A structured transition process lends itself to improved engagement through this critical period in the young person's life.[45]

These steps, tailored to the patient's age and disease severity, are essential to mitigate ocular complications, preserve vision, and improve quality of life in cystinosis.

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