American Academy of Optometry
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Resident’s Day Case Report Proposal
Erin Bender, O.D.
Lebanon VAMC Resident

ABSTRACT: Ocular (non-nephropathic) cystinosis is a rare, autosomal recessive metabolic disease that manifests as a crystalline keratopathy unlike nephropathic forms which are associated with renal disease. Diagnosis is accomplished through physical exam, urinalysis and serology.

CASE HISTORY

Patient Demographics: 62 year old Caucasian male

Chief Complaint: photophobia, night-time glare: both eyes

Ocular/Medical History:

Medical: post-traumatic stress disorder, Hepatitis C, coronary artery disease, diverticulosis of the colon, degeneration of intervertebral disc.

Ocular: previously diagnosed anterior stromal dystrophy OU

Medications: Citalopram, Albuterol, Ibuprofen, Isosorbide, polyethylene glycol, ASA 325 mg, Metoprolol, triamcinolone cream

Other salient information: initial presentation to eye clinic in Nov 2003 with anterior stromal crystals present and dense OU, monitored biennially from start date. Family Medical History unremarkable for renal disease per patient.

PERTINENT FINDINGS

Clinical:

VA: OD 20/20 cc -0.75 sphere add +2.25 sphere
    OS 20/20 cc -0.25-0.75x045 add +2.25 sphere

CORNEA: refractive crystalline deposits within the anterior 1/2 of cornea both eyes, crystals extending from limbus to limbus and onto conjunctiva with minimally increased concentration peripherally both eyes.


Laboratory studies: ordered WBC cystine levels, taken on 8/9/2011, awaiting results.

Radiology studies: none

Others: Corneal photography demonstrating crystalline deposits
DIFFERENTIAL DIAGNOSIS: Crystalline Keratopathy

Primary/Leading:

1. Ocular Cystinosis: autosomal recessive, bilateral cystine crystalline deposition. Particles are refractile, polychromatic. Commonly more dense in peripheral cornea extending across the anterior 1/3 to 2/3 of corneal stroma. Crystals tend to cause symptoms of corneal irritation and photophobia.

Others:

2. Schnyder’s crystalline dystrophy: autosomal dominant, bilateral, white, green or red polychromatic crystals, associated with hypercholesterolemia, central and mid peripheral crystalline deposits
3. Streptococcal Keratitis: stromal infiltrates often associated with corneal grafts or corneal surgical procedures and chronically inflamed corneas.
4. Multiple Myeloma: corneal accumulation of immunoglobulins clinically presenting as corneal crystals in the epithelium
5. Bietti crystalline dystrophy: autosomal recessive, sparkling yellow/white deposits at the limbus and also seen in the retina causing progressive night blindness and visual field loss. More common in Asian ancestry.

DIAGNOSIS AND DISCUSSION

Elaborate on the condition

- **Ocular Cystinosis**: Corneal crystals can present prior to age 1 and are almost always present beyond the age of 16 months. Corneal crystals increase with age. Crystals tend to have a growth pattern that begins superficially and progresses to the endothelium as well as beginning at the periphery and extending centrally. Side effects of crystal formation: photophobia, blepharospasm, corneal erosion: secondary to breakdown of epithelial surface.
- Basic defect is an impairment of lysosomal membrane transporter, cystinosin, which leads to the accumulation of the amino acid cystine within several structures resulting in a multi-organ condition.
- Cystinosis is divided into 3 categories:
  - **Nephropathic (Infantile) Cystinosis**: Characterized by renal Fanconi syndrome (polyuria, polydipsia, dehydration and acidosis), rickets, poor glomerular function, poor growth and deposition of cystine crystals in multiple locations throughout the body including several structures of the eye: cornea, conjunctiva, retina. Signs presenting often at 3 to 6 months old. Incidence is 1 case per 100,000 to 200,000 live births.
- **Intermediate cystinosis**: Characterized by similar features of nephropathic cystinosis however it presents at a later age ~ 10 to 15 years of age and typically less severe.

- **Non-nephropathic (Adult) cystinosis (Ocular Cystinosis)**: Characterized only by the presence of corneal crystals however crystals are present within bone marrow and conjunctiva.

  - Major diagnostic features for all forms include **elevated cystine concentrations in polymorphonuclear leukocytes and corneal crystalline deposits**.

  - **GENETICS**: CTNS (cystine transport nephrotic syndrome) gene mapped to chromosome 17p13. Same gene is involved in all forms of cystinosis. Differences in the clinical manifestations are a result of mutations that happen within the single gene.

    - Two deletions of severe forms are associated with nephropathic cystinosis
    - Intermediate and ocular cystinosis are associated with one severe mutation that causes nephropathic cystinosis and one less severe mutation; therefore, part of the transport function of cystinosin remains intact.

  - **LAB FINDINGS**: Leukocyte cystine values:

    - Nephropathic range: 3.0 to 23.0 nmol half-cystine/mg protein
    - Non-nephropathic range: 1.0 to 3.0 nmol half-cystine/mg protein
    - Heterozygotes range: <= 1.0 nmol half-cystine/mg protein
    - Normal range: <= 0.2 nmol half-cystine/mg protein

  - **OUTCOMES**:

    - Nephropathic cystinosis: untreated, lifespan estimated to be no longer than 10 years.
    - Intermediate cystinosis: untreated, lifespan estimated to be about 15 to 25 years.
    - Ocular cystinosis: untreated, normal lifespan.

  - Retinal involvement is a late stage finding in nephropathic cystinosis. Crystals can continue to deposit and invade multiple other structures as the disease progresses including anterior chamber, iris, ciliary body, choroid, fundus and optic nerve head. End stage disease can show pigmentary retinopathy and photoreceptor degeneration resulting in poor visual function that is irreversible.

**Expound on unique features**

- Nephropathic cystinosis accounts for 5% of childhood renal failure.

**TREATMENT/MANAGEMENT**

**Treatment and response to treatment**

- Cysteamine bitartrate, an aminothiol, is treatment of choice for nephropathic and intermediate forms. Early intervention with this medication has the potential to drastically slow the progression of glomerular damage. Can potentially reduce cells the cystine content in affected cells by about 90%.
Dosage: ORAL, initial treatment: 10 mg of free base/kg body weight per day (divided over 6 hour dosing times). Increase weekly by 10 mg/kg/day until reaching target dose, 60 to 90 mg/kg/day.

Target treated leukocyte cystine content under 1.0 nmol of half cystine/mg protein.

Oral cysteamine therapy NOT affective against corneal crystal formation.

Cysteamine hydrochloride drops used to dissolve corneal crystals and administered 10 to 12 times per day. Response has shown photophobia reduction within weeks of therapy.

Refer to research where appropriate

- Cystinosis Research Network: organization designed to support and aid in patient care along with furthering laboratory studies to help improve treatments and find a cure. In 2010 Survey Data Analysis Report for nephropathic cystinosis, a total of 192 cases were used:
  o 94% had corneal crystals
  o Average age of nephropathic cystinosis diagnosis = 3.4 years (min prenatal, max 25)
  o Average age of crystal identification = 4.5 years

- Study from 2008 by the American Society of Nephrology including late-onset nephropathic and non-nephropathic patients
  o Renal Fanconi syndrome was lacking in presentation in 6 out of 14 patients, only abnormality being proteinuria.
  o Interfamilial variability reported: challenged the need for intervention and familial screening even in the ocular, “benign” form. Ocular form noted in one family member with no renal involvement at age 59 years with brother reaching end stage renal disease at age 28 years.

Bibliography, literature review encouraged

CONCLUSION

Clinical pearls, take away points if indicated

- Etiology of crystalline keratopathy should be explored due to association with potentially life threatening conditions such as cystinosis and multiple myeloma.
- Especially in the intermediate form, many of the symptoms can go unnoticed by the patient and potentially the doctor. Corneal crystals will be present and if observed should have testing performed to rule out cystinosis diagnosis.
- Renal damage is irreversible at time of discovery therefore early intervention is imperative.