Case Report

Ocular Involvement in Patients with Infantile Nephropathic Cystinosis

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Abstract

Cystinosis is a rare autosomal recessive lysosomal storage disease associated with high mortality and morbidity rates. The most distinctive ocular manifestations of cystinosis are photophobia, tearing, and blurred vision. Herein, we assessed the ocular involvement of four patients from two families diagnosed with infantile nephropathic cystinosis using optical coherence tomography (OCT) and *in vivo* confocal microscopy (IVCM). Anterior segment OCT demonstrated multiple hyperreflective punctate deposits, and IVCM revealed needle-shaped bright crystal deposits in the corneal stroma in all patients. Three patients also had crystal deposits in the epithelium, where epithelial cell disruption was observed. Crystal deposits around the subepithelial nerve plexus were noted in some sections. In one patient, round and needle-shaped bright deposits along with inflammatory cells were observed in the limbal region of the conjunctiva. Infrared fundus images of two female siblings revealed hyperreflective crystal-like deposits around the optic disc, macula, and peripheral retina, and enhanced depth imaging OCT showed accumulation of crystals in all layers of the retina.

Keywords: Infantile nephropathic cystinosis, *in vivo* confocal microscopy, optical coherence tomography

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Introduction

Cystinosis is a rare lysosomal storage disease with autosomal recessive inheritance and high mortality and morbidity.[1,2] It is caused by a mutation in the *CTNS* gene, which is located on chromosome 17p13.2 and encodes cystinosin, a membrane transport protein that transports cystine from lysosomes to the extracellular space.[1,3]

Cystinosis has three clinical forms: infantile (early-onset) nephropathic cystinosis, juvenile (late-onset) nephropathic cystinosis, and adult (ocular) cystinosis. Infantile nephropathic cystinosis accounts for approximately 95% of cases and is the most severe form.[1] Cystine crystals can accumulate in various organs, including primarily the eyes and kidneys, as well as the nervous system, thyroid gland, bones, muscles, bone marrow, pancreas, liver, lungs, and gonads.[4] These deposits can lead to numerous problems such as Fanconi syndrome, renal failure, rickets, retarded growth and development, learning disabilities, muscle atrophy, gastrointestinal symptoms, dysphagia, and hypothyroidism.[5,6]

In the eye, deposition can be seen in the cornea, conjunctiva, limbus, iris, anterior chamber, iridocorneal angle, lens capsule, ciliary body, choroid, and rarely in the retinal pigment epithelium and optic disc.[1] Clinically, it causes symptoms such as photophobia, tearing, and blurred vision.[7,8] Corneal deposition starts in the periphery and superficial layers and later progresses centrally and into the deeper corneal layers.[9] Gahl et al.[1] defined a scoring system to objectively evaluate the density of cystine deposits in the cornea. This corneal cystine crystal score (CCCS) ranges from 0 (no deposits) to 3 (full of deposits) with 0.25-unit intervals. In advanced cases, pathologies such as recurrent corneal epithelial erosions, corneal thinning, band keratopathy, filamentary keratitis, peripheral corneal neovascularization, posterior synechia, secondary pupillary block, glaucoma, papilledema, and reduced color and night vision may occur.[1,2,3]

In this case report, we discuss the ocular involvement of four patients from two families diagnosed with infantile nephropathic

cystinosis and present their *in vivo* laser confocal microscopy (IVCM) and anterior segment optical coherence tomography (OCT) findings.

Case Reports

Family 1

A couple with two children and no history of consanguineous marriage presented for photophobia in their sons, aged 6 and 9 years. Both boys had best corrected visual acuity (BCVA) of 20/20 in both eyes, and intraocular pressures (IOP) were approximately 12-15 mmHg bilaterally. On biomicroscopic examination, bilateral diffuse cystine crystal deposits in the cornea were observed in both patients (Figure 1). CCCS was 3 in both eyes in the younger sibling and 2 in both eyes in the older sibling. In Scheimpflug-Placido disc-based corneal tomographic imaging (Sirius®, CSO, Italy), central corneal thicknesses (CCT) in the right and left eyes were measured as 548 and 545 µm in the younger sibling and 580 and 570 µm in the older sibling, respectively. In manual measurements performed with anterior segment OCT (Topcon®, Japan), right and left CCT values were 560 and 546 µm in the younger sibling and 575 and 574 µm in the older sibling, respectively. No retinal involvement was observed. The patients exhibited physical growth retardation. It was learned that both patients had been diagnosed with cystinosis 4 years earlier and had since received systemic and topical cysteamine (Cystamin® 0.55%, Tobio Pharmaceuticals, 3 times daily) therapy. However, they had been unable to use topical cysteamine for the last 6 months because it was not available in our country. No mutation in the *CTNS* gene could be detected by clinical exome sequencing. In the deletion/duplication analysis, homozygous duplication of *CTNS* exons 6-8 was detected.

Family 2

A couple with two children and a history of consanguineous marriage presented for photophobia in their two daughters, aged 14 and 18 years. In both patients, BCVA ranged from 16/20 to 20/20 and IOP ranged from 14 to 16 mmHg. On biomicroscopic examination, both patients had cystine crystal deposits in the corneas of both eyes. CCCS was 3 in both eyes in the younger sibling and 2 in both eyes in the older sibling. On corneal tomographic imaging, CCT in the right and left eye was measured as 530 and 536 µm in the younger sibling and 524 and 518 µm in the older sibling, respectively. Manual CCT measurements obtained with anterior segment OCT in the right and left eye were 532 and 546 µm in the younger sibling and 534 and 533 µm in the older sibling, respectively. Both patients also had retinal cystine deposits surrounding the optic disc, around the vascular arcades, and in the peripheral regions that were more pronounced on infrared images (Spectralis®, Heidelberg Engineering, Germany) (Figure 2). OCT sections obtained in enhanced depth imaging mode (EDI-OCT; Spectralis®, Heidelberg Engineering, Germany) revealed cystine deposits in the ganglion cell layer (GCL), inner nuclear layer (INL), inner plexiform layer (IPL), and outer plexiform layer (OPL), but no involvement in the choroid (Figure 3).

It was learned that both of the patients had received systemic and topical cysteamine therapy for a diagnosis of cystinosis and underwent kidney transplantation (the older sibling in 2013 and the younger in 2017). A homozygous c.18_21del/p.Thr7PhefsTer7 rs786204501 variant in exon 3 of the *CTNS* gene was detected by clinical exome sequencing.

Anterior Segment OCT and IVCM Imaging

On anterior segment OCT, all of the patients had diffuse hyperreflective punctate deposits in the stromal layer (Figure 4). On IVCM (Rostock Cornea Module®, Heidelberg Engineering, Germany), diffuse bright needle-shaped crystal deposits were observed in the stroma in all patients. Three patients had crystal deposits in the epithelium, and epithelial cell disruption was observed in these regions. Crystal deposits around the subepithelial nerve plexus were observed in some sections. In one patient, bright round and needle-shaped deposits and inflammatory cells were observed in the limbal region of the conjunctiva (Figure 5).

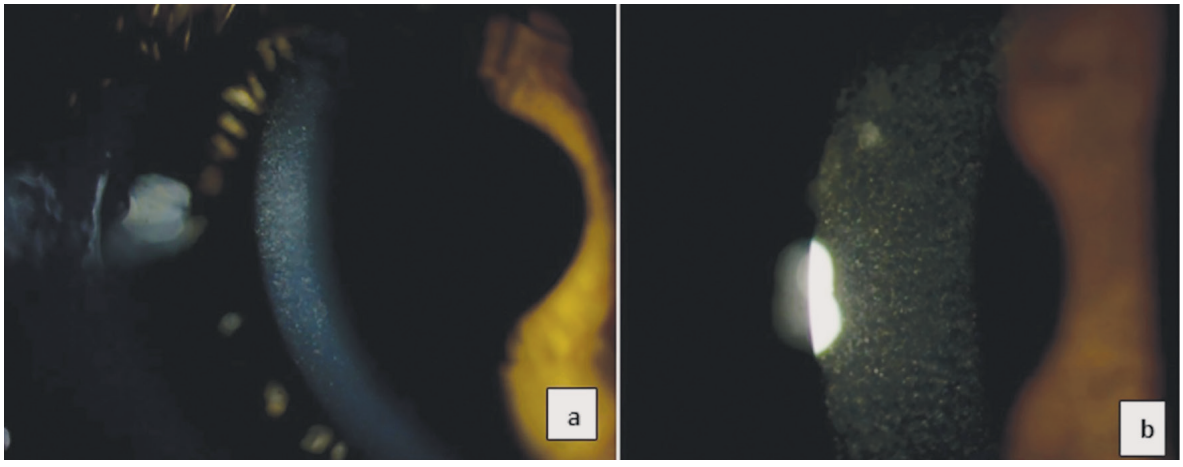

Figure 1. Anterior segment photographs of the diffuse cystine crystal deposits in the cornea taken at 10x (a) and 16x (b) magnification

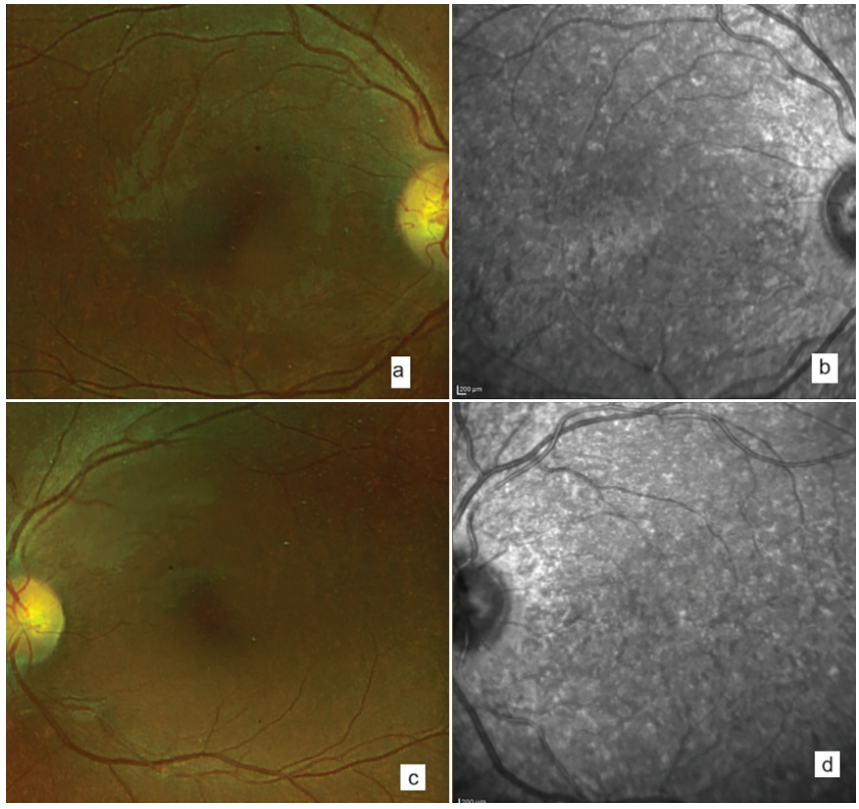

Figure 2. Color and infrared fundus photographs of the right eye (a, b) and left eye (c, d) showing cystine crystal deposits in the macula and optic disc pallor

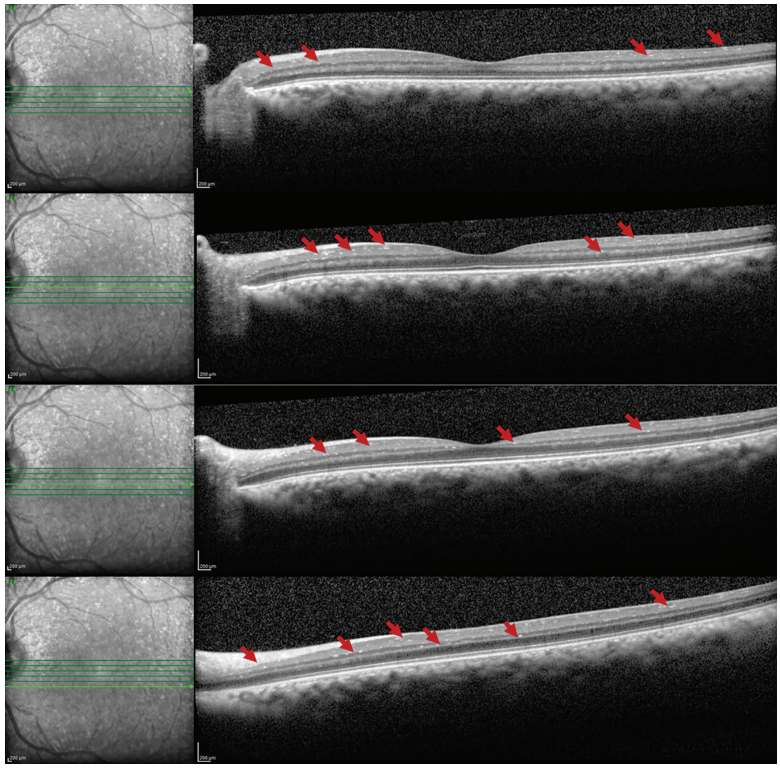

Figure 3. Cystine crystal deposits (red arrows) in the different retinal layers shown on optical coherence tomography sections obtained in enhanced depth imaging mode

Discussion

Ocular involvement is among the most common causes of symptoms and morbidity in patients with cystinosis.[1] The most prominent feature of ocular involvement in cystinosis is diffuse crystal deposition in the cornea. IVCM and OCT enable a detailed assessment of the depth and morphology of these crystals.[10,11] Ozdemir et al.[10] demonstrated the presence of needle- and fusiform-shaped crystal structures in the anterior and posterior stroma using anterior segment OCT and IVCM imaging in a 36-year-old male patient diagnosed with cystinosis. No cystine deposits were detected in the corneal epithelial and endothelial layers. Keidel et al.[11] revealed widespread crystal deposition in all levels of the stroma using anterior segment OCT in 88 eyes of 45 patients. We also observed diffuse stromal deposits in all 4 patients in this study, but there were also deposits in the epithelium in 3 patients. Disruptions in the epithelial cells were noted in areas of dense crystal deposition.

In addition to the cornea, cystine crystals may also accumulate in the retina and choroid in cystinosis. Al Abdulsalam[12] reported OCT findings of dome-shaped crystal deposits in the outer retinal layers in the subfoveal region in a 19-year-old female patient with cystinosis. Keidel et al.[13] detected cystine crystals

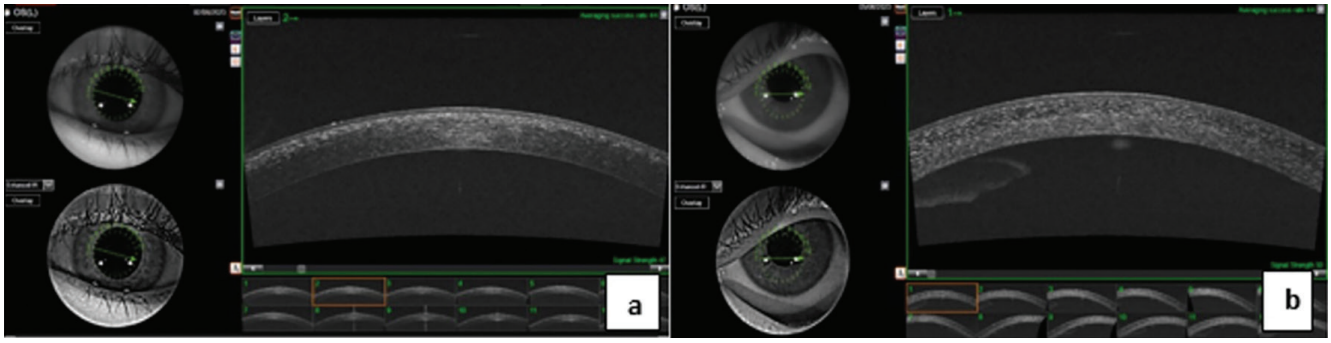

Figure 4. Anterior segment optical coherence tomography images showing cystine crystal deposits in the (a) epithelium and anterior stroma and (b) anterior, middle, and posterior stroma

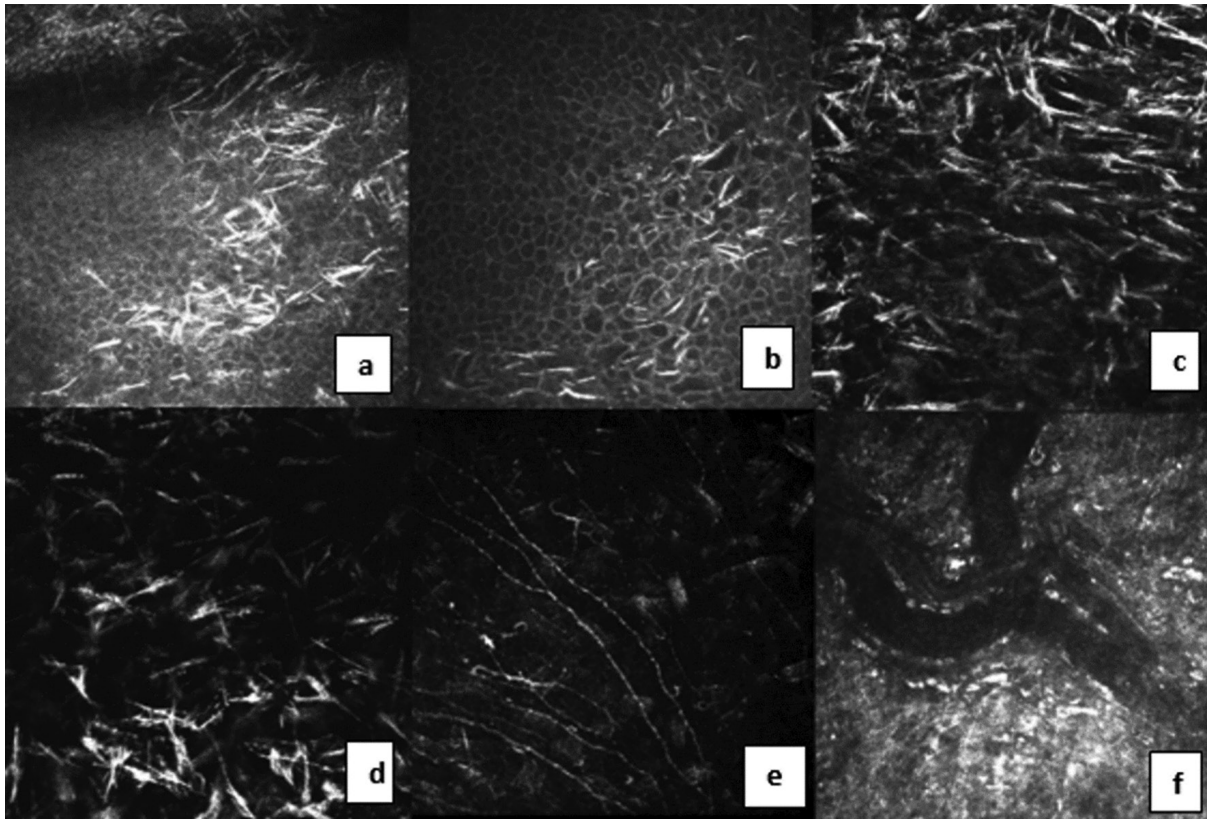

Figure 5. *In vivo* confocal microscopy images showing (a) hyperreflective crystals in the epithelium, (b) disruption of epithelial cells, (c, d) stromal deposits, (e) cystine crystal deposits around the subepithelial nerve plexus, and (f) punctate and linear hyperreflective deposits in the conjunctiva and limbal region

in the fovea on fundus examination and stated that on OCT imaging, these deposits were densest in the choriocapillaris, followed by the GCL, INL, IPL, and choroid. Among our patients, no significant retinal pathology was observed in the boys, while the girls had widespread cystine crystals in the GCL, IPL, INL, and OPL on posterior segment OCT sections and fundus autofluorescence.

Cystinosis is treated with cysteamine, which is available in oral and topical form. Oral cysteamine therapy may slow the progression of renal and retinal findings, but its effect on the cornea is limited because of its avascular structure. In contrast, topical cysteamine both relieves symptoms and helps dissolve crystals in the cornea.[1,14] Early-onset, long-term cysteamine therapy delays end-stage renal failure, reduces the risk of extrarenal complications, and improves survival rates.[15] Among our cases, we believe the diagnosis of the boys at age 2 and 5 and the resulting early initiation of treatment prevented the occurrence of renal complications.

Calculations based on IVCM and OCT deposit analysis have been shown in the literature to offer a more objective and accurate assessment during disease progression and may serve as biomarkers in the future.[11,16] Vercauteren et al.[17] compared corneal thickness measurements taken by anterior segment OCT and corneal tomography in patients with cystinosis and found that corneal tomography measurements were much higher. Therefore, they suggested that anterior segment OCT should be taken as a basis for prognosis and evaluation of treatment response. In our patients, CCT measurements performed with anterior segment OCT did not show a marked deviation from corneal tomography measurements.

In the literature, studies of cystinosis patients consist of limited cases series. Our study demonstrated for the first time with IVCM that crystals accumulated in the corneal epithelium. In conclusion, cystinosis is a rare lysosomal storage disease with autosomal recessive inheritance, and the morphology, extent, and depth of cystine crystals deposited in the cornea and retina can be objectively demonstrated at the tissue and cellular level with IVCM and OCT.

Ethics

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: S.Ü., A.B.O., B.B., Concept: S.Ü., A.B.O., B.B., Design: A.B.O., E.T.K., B.B., Data Collection or Processing: S.Ü., S.G., A.B.O., E.T.K., B.B., Analysis or Interpretation: A.B.O., E.T.K., B.B., Literature Search: S.Ü., S.G., A.B.O., E.T.K., B.B., Writing: S.Ü., A.B.O., B.B.

Conflict of Interest: No conflict of interest was declared by the authors.

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