Photophobia and Corneal Crystal Density in Nephropathic Cystinosis: An In Vivo Confocal Microscopy and Anterior-Segment Optical Coherence Tomography Study

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PURPOSE. To analyze the correlation between photophobia and corneal crystal density in nephropathic cystinosis using in vivo confocal microscopy (IVCM) and anterior-segment optical coherence tomography (AS-OCT).

METHODS. Forty eyes of 20 patients with nephropathic cystinosis aged 7 to 37 years were included in this study. Ophthalmologic investigations included clinician-assessed and self-assessed evaluations of photophobia, slit-lamp biomicroscopy analysis, the depth of crystal deposition (DCD) and the central corneal thickness (CCT) in the central cornea measured with AS-OCT, and IVCM analysis of the crystal density score (IVCM-CysS), inflammatory cell density (IVCM-inf), and nerve damage (IVCM-N). Age, sex, intraleukocyte cystine concentrations (ICC), and the need for renal transplantation were also recorded.

RESULTS. The average subjective and objective photophobia scores were 2.10 ± 1.28 and 1.70 ± 1.41, respectively. Using AS-OCT, the average percentage of crystal infiltration (OCT-CysP) and was $49.56 \pm 27.31\%$ (range, 11.45%–95.81%). The mean IVCM-CysS was 8.84 ± 4.34, the mean density of inflammatory cells (IVCM-inf) was 178.28 ± 173.00 cells/mm^2, and the mean IVCM-N score was 3.11 ± 2.11. Clinician- and self-assessed estimations of photophobia were correlated ($R^2 = 0.61$). No significant correlation was observed between clinician- and self-assessed photophobia scores and ICC or sex. There were significant correlations between clinician- and self-assessed photophobia scores and age, OCT-CysP, IVCM-CysS, IVCM-inf, and IVCM-N. The IVCM-CysS was also correlated with OCT-CysP ($R^2 = 0.27$), IVCM-inf ($R^2 = 0.37$), and IVCM-N ($R^2 = 0.56$).

CONCLUSIONS. In vivo confocal microscopy and AS-OCT are reliable tools to quantify cystinosis corneal crystals. In patients with nephropathic cystinosis, the intensity of photophobia is associated with the density of crystals, infiltration of inflammatory cells, and nerve damage within the cornea.

Keywords: photophobia, cystinosis, confocal microscopy, anterior-segment OCT

Cystinosis is a rare lysosomal storage disease characterized by the accumulation of cystine crystals in various tissues including the brain, kidney, bones, and eyes. Genetically, cystinosis is due to the mutation of the cystinosin (*CTNS*) gene (17p13) that codes for cystinosin, a transmembrane protein responsible for the transport of the cystine amino acid out of the lysosome.[1] Although cystine crystals can be found in all ocular structures, the pathognomonic and most frequently described ocular manifestation of cystinosis is crystal deposition in the conjunctiva and cornea.[2–4] This crystal accumulation begins in infancy, increases with age and gradually leads to photophobia, blepharospasm, superficial punctate keratopathy, and recurrent corneal erosions.[2,4,5] In older patients, filamentous keratopathy, band keratopathy, and peripheral corneal neovascularization can also occur.[1,3–5]

The first and most frequently reported ocular symptom in cystinosis is photophobia. This light sensitivity can rapidly impair patient's quality of life by interfering with the ability to carry out daily functions.[3,4] Photophobia has a complex mechanism involving the retinal ganglion cells, the visual cortex, the sympathetic system, and the spinal trigeminal nociceptive neurons.[5–9] Anterior-segment diseases such as iritis, cyclitis, keratoconjunctivitis, uveitis, and several corneal diseases may present with photophobia symptoms.[7,9,10] Although corneal cysteine crystal accumulation may explain photophobia in cystinosis, the exact pathophysiology of photophobia in relation to crystal deposition and corneal

tissue changes remains unclear.[3] Several imaging techniques have been developed to evaluate cystine corneal crystals. Gahl[3] was the first to establish as slit-lamp score allowing a semiquantitative analysis of corneal crystals. Our group has developed the use of in vivo confocal microscopy (IVCM) and anterior-segment OCT (AS-OCT) to directly analyze and quantify corneal crystals in cystinosis.[11,12] Anterior-segment OCT measures the depth of crystal deposition within the cornea without any contact with the eyes and IVCM quantifies crystal density in all corneal layers at a cellular level. Moreover, IVCM can also image other corneal tissue changes such as an infiltration of inflammatory cells or nerve damage, which might be involved in the pathophysiology of photophobia.[13] The objective of the present study was to correlate the results of corneal tissue changes with photophobia evaluation in order to investigate the mechanisms of photophobia in cystinosis and the relationships between symptoms and objective evaluation of crystal accumulation and location.

METHODS

Twenty patients with infantile nephropathic cystinosis were included in this study: 10 females and 10 males with a mean age of 17.10 years $\pm$ 9.55 (range, 7–37). This study was conducted at the Center for Clinical Investigations (CIC INSERM) at the Quinze-Vingts National Eye Center, Paris, France, with the approval of the institutional review board of Saint-Antoine University Hospital (CPP-Ile de France 5, national agreement 10793). The detailed protocol for this study complied with the Declaration of Helsinki. All subjects received information about the study and their written consent or the consent of their legal representative was obtained. The diagnosis of nephropathic cystinosis was based on a typical clinical history associated with an intraleukocyte cystine concentration (ICC) above 3 nmol half-cystine/milligram protein.

All patients underwent a complete ophthalmologic evaluation of both eyes, including an evaluation of clinician- and self-assessed photophobia, best-corrected visual acuity (BCVA), slit-lamp examination with a photograph of the cornea and determination of Gahl's corneal cystine crystal score (0–3),[3] IOP measurement, and IVCM and AS-OCT evaluation of corneal crystals. All ophthalmologic evaluations were performed under controlled standardized room illumination conditions. For each patient, age, sex, ICC, and renal transplantation situation were also recorded.

Self- and Clinician-Assessed Evaluation of Photophobia

Self-assessed photophobia was evaluated by the patients themselves and graded according to photophobia scores previously published for vernal keratoconjunctivitis or other inflammatory ocular surface diseases[14,15]: Grade 0, no photophobia, no discomfort; Grade 1, slight difficulty with light causing occasional eye blinking; Grade 2, slight difficulty with light causing regular eye blinking; Grade 3, moderate difficulty with light requiring wearing sunglasses; Grade 4, severe difficulty with light requiring wearing sunglasses in a quasipermanent manner; Grade 5, extreme difficulty with light requiring the patient to remain inside, cannot bear natural light even with sunglasses. Clinician-assessed photophobia was evaluated with slit-lamp biomicroscopy with a score modified from a previous study[15]: Grade 0, no photophobia under the slit-lamp beam even with the largest slit; Grade 1, photophobia to moderate slit-lamp beam light; Grade 2, photophobia to the lightest slit-lamp beam; Grade 3, photophobia with inability to bear the blue slit-lamp beam; Grade 4, photophobia needing dark glasses and unable to open eyes inside the illuminated consultation room; Grade 5, unable to open eyes even inside the dark room.

Anterior-Segment OCT

Anterior-segment OCT analysis was performed with the RTVue SD-OCT (Optovue, Inc., Fremont, CA, USA), which provides 26,000 A-scans per second with a transverse resolution of 15 μm and an axial resolution of 5 μm. Anterior-segment scanning was achieved using an adapted lens, the corneal adaptor module (CAM-S), which was placed in front of the objective to focus the OCT beam on the anterior segment. All images of the central cornea were acquired using the high-resolution program. A corneal pachymetry map was also obtained to measure the central corneal thickness (CCT, μm). The depth of crystal deposition (DCD, μm) in the central cornea was evaluated using the measurement calipers provide by the AS-OCT software. Considering the variability of the corneal thickness, the depth of crystal deposition was expressed as a percentage of the corneal thickness (OCT-CysP: 0%–100%).

In Vivo Confocal Microscopy

Corneal IVCM images were obtained using the Rostock Cornea Module (RCM) of the Heidelberg Retina Tomograph (Heidelberg Engineering GmbH, Heidelberg, Germany) according to a previously validated method.[11,12] In vivo confocal microscopy (Heidelberg Engineering GmbH). images comprised 384 × 384 pixels covering an area of 400 × 400 μm. Before the examination, one drop of topical anesthetic (oxybuprocaine 0.4%; MSD-Chibret, Paris, France) and one drop of gel tear substitute (Lacrigel, carbomer 0.2%; Europhta, Monaco, Monaco) were applied. No corneal complications related to IVCM evaluation were noted in this study, and IVCM could be performed even in young children (as early as 6 years of age). An IVCM score was used to quantify crystal deposition in each corneal layer of the central cornea (rated 0–4 according to the percent number of deposits in the field of each image: 0, no crystal; 1, <25%; 2, 25%–50%; 3, 50%–75%; and 4, >75%); results were the mean of five images analyzed in a masked manner in each corneal layer. The crystal density score (IVCM-CysS) corresponded to the sum of each individual layer's mean score (superficial epithelium, basal epithelium, bowman's layer, anterior stroma, middle stroma, posterior stroma, and endothelium; 0–28).[11] Using the Cell Count software (Heidelberg Engineering GmbH), dendritic inflammatory cell density (IVCM-inf) was quantified at the level of the Bowman layer in the central cornea.[12] For each eye, five images were analyzed and the results presented as mean $\pm$ SD (IVCM-inf, cells/mm²). Subbasal corneal nerve plexus alterations were also evaluated in the central cornea using IVCM. We used a semiquantitative simple score derived from a multivariate analysis of five nerve parameters.[16] The density of subbasal nerves, width of long corneal nerves, number of branchings (the number of fibers connecting to long nerve fibers), tortuosity, and reflectivity were graded from 0 to 2 with 0.5 increments. Five images were analyzed and quantified for each eye in order to obtain an average nerve damage score, the IVCM-N maximum score of 10, for all patients.

TABLE. Age, Sex, Ethnic Origin, ICC, Average BCVA (logMAR), Subjective Photophobia Score, Objective Photophobia Score, and Gahl Slit-Lamp Score in the Patients Examined

	Mean, Patients Examined
Age, y, mean ± SD	17.10 ± 9.55
Sex, no. female (%)	10 (50%)
Race, no. (%)	
Caucasian	20 (100%)
ICC analysis	1.56 ± 0.99
Mean BCVA, logMAR	0.09 ± 0.17
Subjective photophobia score	2.10 ± 1.28
Objective photophobia score	1.70 ± 1.41
Gahl slit-lamp score	2.11 ± 0.50

Statistical Analysis

The statistical values of the different parameters (mean value ± SD) were calculated. The correlation between the photophobia scores and patients' general information (age, sex, and ICC), OCT-CysP, IVCM-CysS, IVCM-inf, and IVCM-N were measured using spearman correlation with GraphPad PRISM (GraphPad Software, Inc., La Jolla, CA, USA). Probability values P less than 0.05 were considered significant.
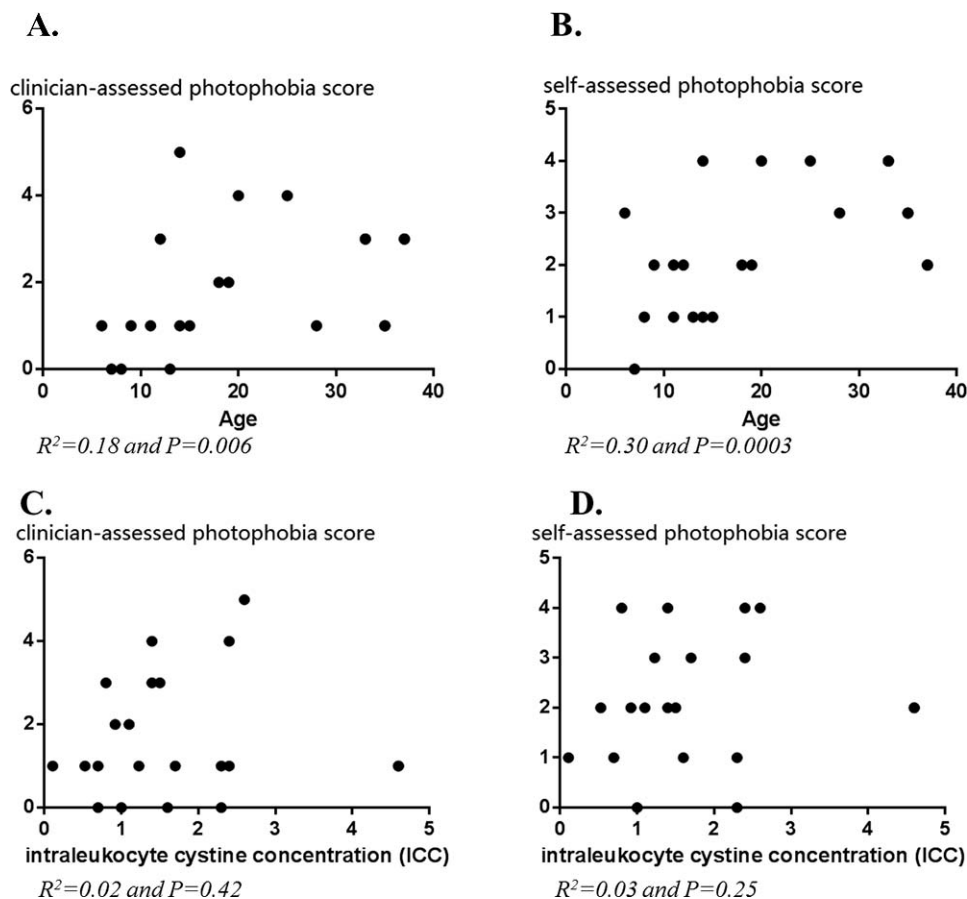
RESULTS

Photophobia Scores and Demographic Data

There were 10 men and 10 women with a mean age of 17.10 ± 9.55 years and an ICC of 1.56 ± 0.99 half-cystine/mg protein. The mean BCVA (logMAR) was 0.09 ± 0.17. Mean self-assessed photophobia was 2.10 ± 1.28 and mean clinician-assessed photophobia was 1.70 ± 1.41. The average Gahl slit-lamp score was 2.11 ± 0.50. Five patients had undergone a renal transplantation. The Table summarizes demographic data. The photophobia scores were moderately associated with the patient's age (Fig. 1A, clinician-assessed score: $R^2 = 0.18$ and $P = 0.006$; Fig. 1B, self-assessed score: $R^2 = 0.30$ and $P = 0.0003$). However, there was no correlation between ICC and photophobia scores (Fig. 1, clinician-assessed score: Fig. 1C, $R^2 = 0.02$, $P = 0.42$; self-assessed score: Fig. 1D, $R^2 = 0.03$, $P = 0.25$). A medical history of renal transplantation was also correlated with the self-assessed photophobia score ($R^2 = 0.32$, $P = 0.04$). Figure 2 shows OCT and IVCM images of the cornea of a 35-year-old male patient with nephropathic cystinosis. Photophobia was graded at 3 and 3 for clinician- and self-assessed photophobia scores, respectively.

Photophobia and Gahl Slit-Lamp Score

In the 20 patients analyzed, the clinician- and self-assessed evaluations of photophobia were correlated ($R^2 = 0.61$, $P <$

A.

clinician-assessed photophobia score

$R^2=0.18$ and $P=0.006$

B.

self-assessed photophobia score

$R^2=0.30$ and $P=0.0003$

C.

clinician-assessed photophobia score

intraleukocyte cystine concentration (ICC)

$R^2=0.02$ and $P=0.42$

D.

self-assessed photophobia score

intraleukocyte cystine concentration (ICC)

$R^2=0.03$ and $P=0.25$

FIGURE 1. Scatterplots of photophobia scores, age, and ICC. There were correlations between age (years) and clinician-assessed photophobia score ($R^2 = 0.18$ and $P = 0.006$, [A]), and self-assessed photophobia score ($R^2 = 0.30$ and $P = 0.0003$, [B]). No correlation was observed between ICC and clinician- ($R^2 = 0.02$ and $P = 0.42$, [C]) and self-assessed ($R^2 = 0.03$ and $P = 0.25$, [D]) photophobia scores.

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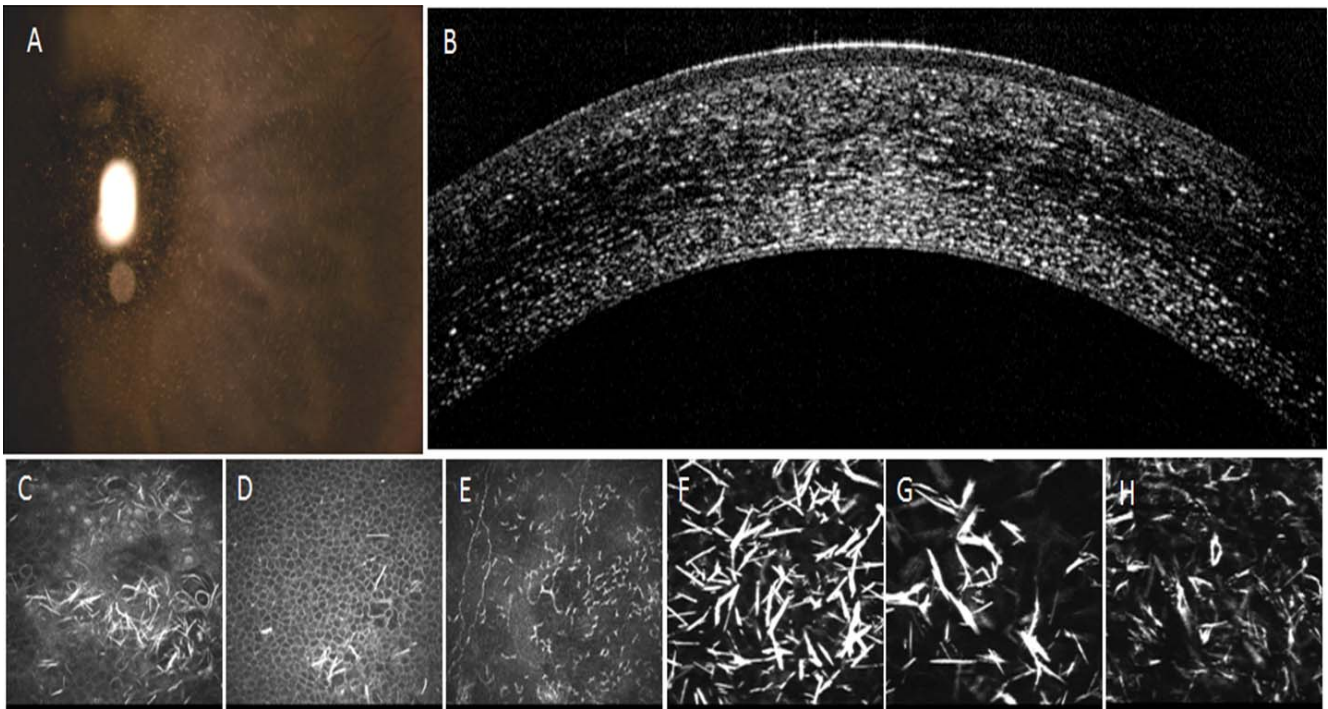
FIGURE 2. Example of a 35-year-old male patient with nephropathic cystinosis. Photophobia was evaluated at 3 and 3 for self- and clinician-assessed photophobia scores, respectively. Slit-lamp photography of the cornea showing corneal crystals (**A**). In the AS-OCT image (**B**), OCT-CysP was 91.50%. Using IVCM, crystals were detected in the superficial epithelial layer ([**C**], image IVCM score: 3), the basal layer ([**D**], image IVCM score: 1), the Bowman layer ([**E**], image IVCM score: 3) and the anterior, intermediate, and posterior stroma ([**F–H**], images IVCM score: 4). The IVCM-CysS for this patient was 17.6 (sum of each individual corneal layer's mean score).

0.0001). The Gahl slit-lamp score was also moderately correlated with self-assessed photophobia (Fig. 3B, $R^2 = 0.20$, $P = 0.0043$) but not with the clinician-assessed photophobia score (Fig. 3A, $R^2 = 0.02$, $P = 0.36$).

Photophobia and OCT Depth of Crystal Deposition

The average OCT-CysP was $49.56 \pm 27.31\%$ for a mean CCT of 558.63 ± 48.83 μm. The OCT-CysP was correlated with the two evaluations of photophobia (Fig. 4A, $R^2 = 0.33$, $P = 0.0001$ for the clinician-assessed evaluation and Fig. 4B, $R^2 = 0.49$, $P < 0.0001$ for the self-assessed evaluation).

Photophobia and IVCM Scores

The mean IVCM-CysS was 8.84 ± 4.34 and a moderate but significant correlation was found between the IVCM-CysS and the OCT-CysP ($R^2 = 0.27$ and $P = 0.0006$; Fig. 5). A correlation was observed between clinician- and self-assessed photophobia scores, and the density of crystal deposition evaluated with the IVCM-CysS (Fig. 6A, $R^2 = 0.21$, $P = 0.003$ for the clinician-assessed score and Fig. 6B, $R^2 = 0.33$, $P = 0.0001$ for the self-assessed score). The mean IVCM-inf was 178.28 ± 173.00 cells/mm². For patients with a high photophobia score, the inflammatory cell count could reach more than 800 cells/mm²

A.

B.

$R^2 = 0.02$ and $P = 0.36$

$R^2 = 0.20$ and $P = 0.0043$
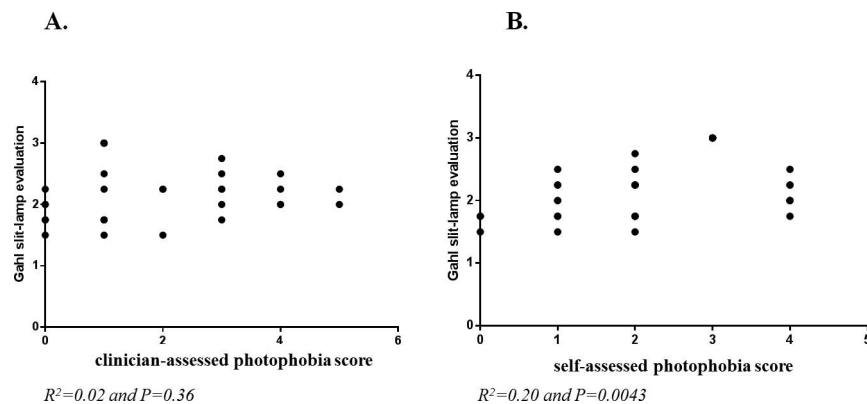
FIGURE 3. Scatterplots of self- and clinician-assessed photophobia versus the Gahl slit-lamp score. The average self-assessed photophobia score evaluated by the patients was 2.10 ± 1.28, the average clinician-assessed photophobia score was 1.70 ± 1.41, and the two scores were strongly correlated ($R^2 = 0.61$ and $P < 0.0001$). Although the clinician-assessed score did not correlate with the Gahl score ($R^2 = 0.02$ and $P = 0.36$, [**A**]), self-assessed photophobia correlated with the Gahl slit-lamp score ($R^2 = 0.20$ and $P = 0.0043$, [**B**]).

A.

B.

$R^2=0.33, P=0.0001$
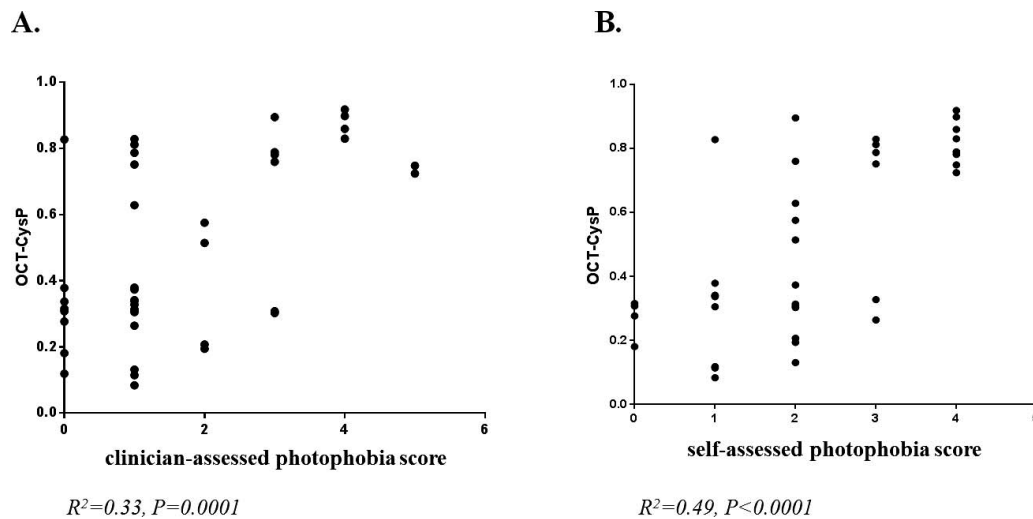
$R^2=0.49, P<0.0001$

FIGURE 4. Scatterplots of photophobia scores versus crystal deposit thickness (OCT-CysP) evaluated with AS-OCT. The correlations were significant between OCT-CysP and both clinician-assessed ([**A**], $R^2 = 0.33$, $P = 0.0001$) and self-assessed photophobia scores ([**B**], $R^2 = 0.49$, $P < 0.0001$).

(Fig. 2E). The photophobia scores were correlated with IVCM-inf (Figs. 6C, 6D, $R^2 = 0.42$, $P < 0.0001$ and $R^2 = 0.22$, $P = 0.002$ for the clinician and self-assessed scores, respectively). The mean nerve damage score was 3.11 ± 2.11. For the patients with high photophobia scores (Fig. 2E), the nerves were markedly altered but often difficult to evaluate due to the presence of crystals and numerous inflammatory cells infiltrating the cornea. We found positive correlations between IVCM-N and photophobia scores (Figs. 6E, 6F, $R^2 = 0.19$, $P = 0.005$ and $R^2 = 0.16$, $P = 0.01$ for the clinician-assessed and self-assessed scores, respectively).

Density of Crystals, Infiltration of Inflammatory Cells, and Nerve Damage

We also analyzed the correlations between the different IVCM parameters: The density of crystals (IVCM-CysS) was correlated to the density of dendritic inflammatory cells (IVCM-inf) ($R^2 = 0.37$ and $P < 0.0001$, Fig. 6G) and the nerve damage score (IVCM-N; $R^2 = 0.56$ and $P < 0.0001$, Fig. 6H). The IVCM-inf was also correlated to the IVCM-N ($R^2 = 0.29$ and $P = 0.0003$, Fig. 6I).

DISCUSSION

Photophobia is the most frequently reported ocular symptom in cystinosis.[2,3] The presence of corneal cysteine crystals induces light scattering at the level of the cornea and could be the main factor explaining photophobia in these patients. However, other factors associated with the deposition of cystine crystals might be involved. Due to the presence of cystine crystals, corneal tissues suffer from hypoxia with limbal and eventually corneal neovascularization.[4,17] Thus, our objective was to analyze the relationship between photophobia and corneal tissue alterations including density of crystals, inflammatory cell infiltration, and nerve alterations.

We observed significant correlations between photophobia and age. Moreover, the density of corneal crystals was correlated to both age and photophobia scores (clinician- and self-assessed). As previously demonstrated, corneal crystal deposits progressively increase with age in patients with cystinosis.[1] Thus, these results emphasize the role of corneal crystals in the etiology of photophobia in these patients.

However, there was no relationship between photophobia or corneal crystal infiltration and ICC. Although the precise level of ICC is difficult to determine in clinical practice, the absence of a correlation between ICC and corneal crystal deposits is mainly due to the systemic treatment with oral cysteamine, which decreases systemic cystine levels but has no effect on corneal deposits.[4,5] Consequently, ICC dosage does not provide reliable information concerning the ocular surface status of patients with cystinosis.[18,19]

Two photophobia scores (self- and clinician-assessed) were used in the present study and a positive correlation was observed between these two scores. This result associated with the good correlation between photophobia and corneal crystal density makes the self-evaluation of photophobia a valuable criterion for ocular surface treatment and evaluation of complications. Given that only ophthalmologists can
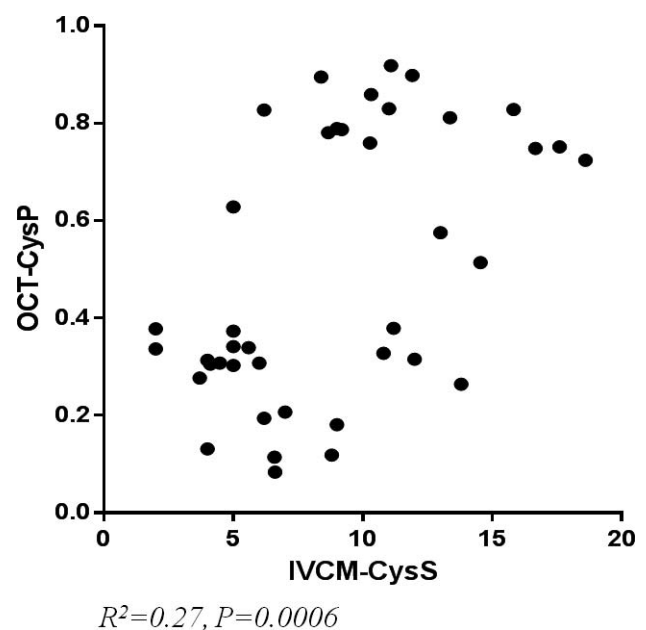

$R^2=0.27, P=0.0006$

FIGURE 5. Scatterplots of the IVCM-CysS investigated by IVCM versus OCT-CysP evaluated with AS-OCT.
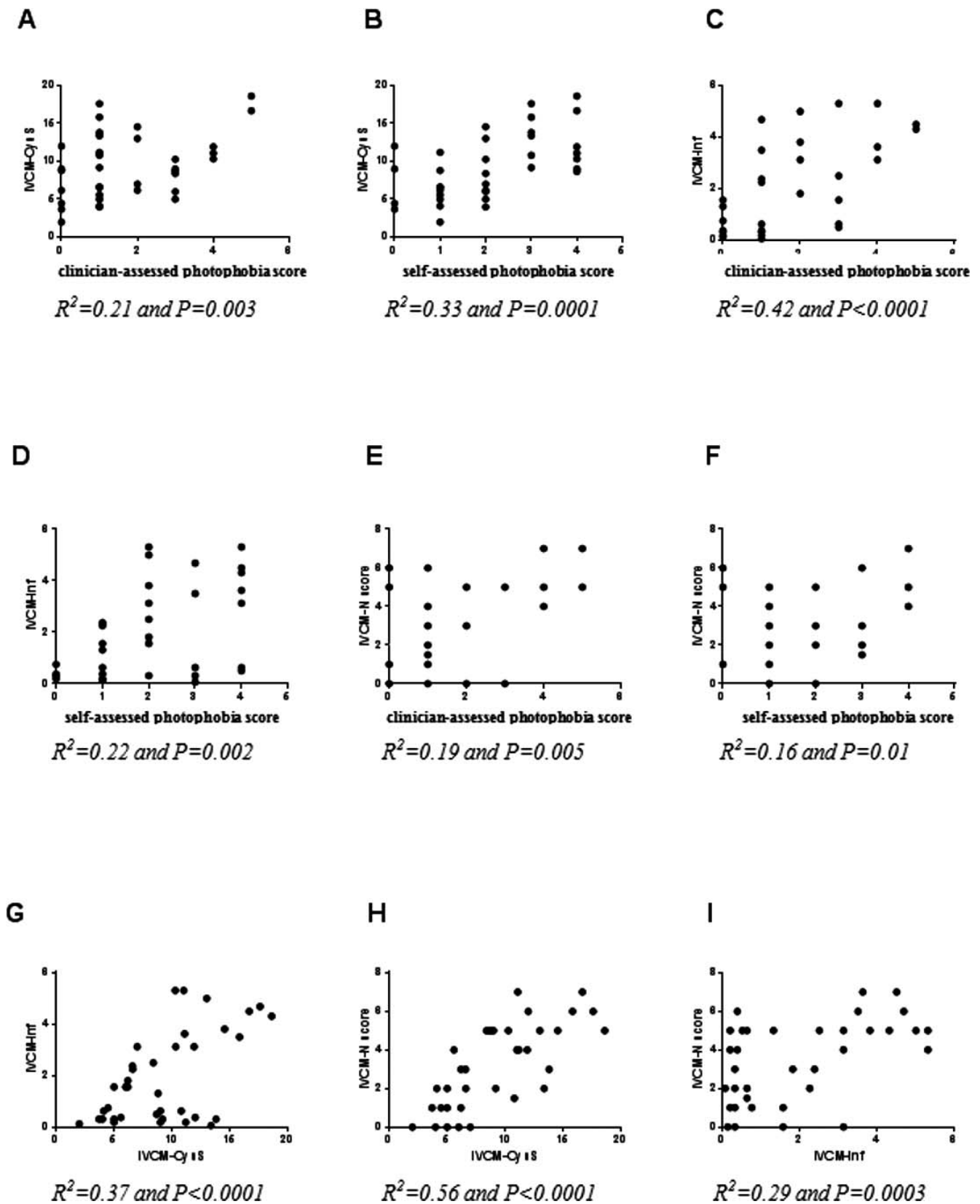
FIGURE 6. Scatterplots between the photophobia evaluations versus IVCM patterns. There were significant correlations between the IVCM-CysS and the clinician-assessed ([**A**], $R^2 = 0.21$, $P = 0.003$) and self-assessed photophobia scores ([**B**], $R^2 = 0.33$, $P = 0.0001$). The two photophobia scores were also correlated with the density of inflammatory cells (IVCM-inf; clinician-assessed score, $R^2 = 0.42$, $P < 0.0001$, [**C**]; self-assessed score, $R^2 = 0.22$, $P = 0.002$, [**D**]) and with nerve alterations (IVCM-N; clinician-assessed score, $R^2 = 0.19$, $P = 0.005$, [**E**]; self-assessed score, $R^2 = 0.16$, $P = 0.01$, [**F**]). The IVCM-CysS was correlated to the IVCM-inf ($R^2 = 0.37$, $P < 0.0001$, [**G**]) and the IVCM-N ($R^2 = 0.56$, $P < 0.0001$, [**H**]). Finally, the IVCM-inf was correlated to IVCM-N ($R^2 = 0.29$, $P = 0.0003$; [**I**]).

precisely evaluate photophobia and corneal crystal density, the evaluation of photophobia by the patient could be are liable surrogate marker that can be used by other specialists, in particular nephrologists, in the follow-up of cystinosis patients.

The first scoring system developed for the quantification of corneal cystine crystals was the Gahl slit-lamp score. It is a semiquantitative photographic score that was developed to analyze the density of corneal crystals by comparison with a library of slit-lamp photographs of corneas with scores ranging from 0 to 3 at 0.125 or 0.25 increments.[3] Our group previously demonstrated the advantage of IVCM over the slit lamp to quantify and analyze crystal deposition in patients with nephropathiccystinosis.[11,12] The results of the present study confirm our previous findings showing a direct and strong correlation between IVCM scores of corneal crystal deposits and the main ocular surface symptom: photophobia.

Using IVCM we were able to analyze all the corneal layers at the cellular level not only for crystal density but also for corneal inflammatory cell infiltration and nerve alterations. Interestingly, the number of dendritic inflammatory cells in the Bowman layer was correlated to the objective and subjective photophobia scores. Meanwhile, inflammatory cell density was correlated to crystal density and nerve damage. Using IVCM in healthy volunteers, Zhivov et al.[20] found that the density of inflammatory cells within the central part of the cornea was less than 50 cells/mm^2. In some patients of the present study, inflammatory cell density could reach 800 cells/mm^2. These eyes also had the highest scores for photophobia and nerve alterations. This corneal tissue inflammation has also been described in an animal model of cystinosis. The cystinosis (CTNS$^{-/-}$) knockout mouse developed cystine crystals in multiple tissues, including the cornea.[21,22] In this model, older CTNS$^{-/-}$ mice (7 months and older) showed the presence of inflammatory cell infiltrates in the corneal stroma that stained positively for CD45 associated with progressive keratocyte disruption.[23] In the present study, dendritic inflammatory cell infiltration was greater in adult patients and was mainly observed in the Bowman layer. Conversely to mice, no inflammatory cells were found in the stroma, but the IVCM analysis performed in vivo may be less sensitive than immunohistology to observe inflammatory cells in the stroma, particularly when numerous hyperreflective structures such as cystine crystals are present.

Among all ophthalmologic diseases, the most common cause of photophobia is inflammation of the anterior segment of the eye.[7,9,10,24] This may be related to a stimulation of the ciliary muscle fibers by inflammatory mediators and direct irritation of the trigeminal afferents.[25] Other mechanisms such as corneal inflammation with stimulation of corneal nerve endings at the level of the ocular surface have also been implicated in severe photo-oculoallodynia.[26] Similarly, nonsteroidal anti-inflammatory drugs are also effective in decreasing postoperative ocular photophobia by acting on ocular inflammation.[27] The result of the present study showing a direct correlation between dendritic cell infiltration and photophobia may emphasize the implication of corneal inflammation in the mechanisms of photophobia in cystinosis patients. To date, except the use of cysteamine eye drops, there is no specific treatment for reducing photophobia in patients with cystinosis. The use of anti-inflammatory eyedrops in association with cysteamine eyedrops could be a useful therapeutic option in order to alleviate these ocular surface symptoms.

The activation of the trigeminal nociceptive pathway is closely associated with photophobia.[26,28] We are currently unable to detect trigeminal activation directly using clinically available methods, but corneal nerve alterations can be observed using IVCM.[13,16] These morphologic alterations might possibly reflect, partly and/or indirectly, nerve changes or excessive nerve stimulation. In the present study, although we used a simple semiquantitative nerve alteration score that may limit the sensitivity of our analysis, nerve alterations were correlated to photophobia scores and to the density of corneal crystals and inflammatory cells. In patients with cystinosis, the decrease in density and the morphologic damage observed in corneal subbasal nerves were possibly a complication of the deposits of cystine crystals within the cornea. Interestingly, these nerve alterations have already been observed in another disease associated with the accumulation of abnormal materials within corneal tissue. In a case of chlorpromazine deposit-induced photophobia, the authors showed delineated peripheral nerve plexus and fibers in the superficial and subepithelial stroma.[29] Using IVCM, we could observed morphologic subbasal nerve alterations in the Bowman layer of patients with cystinosis. Interestingly, in patients at an early stage of cystinosis, corneal subbasal nerves appeared normal in morphology. Later, with more crystal deposits, nerve damage was directly correlated to the presence of corneal crystals. Although we could not determine if crystals were directly responsible for nerve alterations or if they resulted from corneal tissue inflammation and hypoxia, these changes might increase patient corneal and ocular surface pain as well as photophobia.

The role played by new imaging techniques, such as AS-OCT and IVCM, in cystinosis ophthalmologic complication analysis is increasing. With IVCM, it is possible to visualize the presence of corneal crystals directly in all corneal layers and combine this analysis with an evaluation of inflammatory cell infiltration and corneal nerve damage. The density of crystals can thus be evaluated precisely and the IVCM scores can be used to follow patients.[12] Because there is a strong correlation between AS-OCT and IVCM results for crystal quantification, noncontact AS-OCT might be used in very young patients (<5 years old) or very sensitive patients who could not support any contact method such as IVCM or any light such as when using the slit lamp. Moreover, the OCT analysis of crystal deposition thickness could be performed by less experienced ophthalmologists for the follow-up of cystinosis patients.

In the present study, 20 patients with nephropathic cystinosis have been evaluated. Although this may represent a large cohort of patients with nephropathic cystinosis, the small number of patients may limit the correlations observed between the different parameters. With this limitation in mind, this study is the first to evaluate the relationship between photophobia and corneal changes in nephropathic cystinosis. In those patients, the mechanism of photophobia might involve not only corneal crystal deposits, but also an infiltration of inflammatory cells and corneal nerve alterations.

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