Evolution of Ocular Manifestations in Nephropathic Cystinosis: A Long-Term Study of a Population Treated With Cysteamine

Pascal Dureau, MD, PhD; Michel Broyer, MD; and Jean-Louis Dufier, MD

ABSTRACT

Background: Nephropathic cystinosis is characterized by an accumulation of cystine crystals within most body tissues. Renal transplantation and oral cysteamine have improved the general prognosis of the disease, and ocular manifestations are now the most common complication. This long-term follow-up study describes the sequence of ocular manifestations in patients with nephropathic cystinosis treated with oral and topical cysteamine.

Methods: Data were recorded for all patients with cystinosis examined between 1980 and 2000. For each patient, photophobia and visual acuity were evaluated and slit-lamp and fundus examinations were performed. For some patients, an electroretinogram was also performed.

Results: Twenty-nine patients were observed during this period. They received oral and topical cysteamine. Photophobia and loss of visual acuity generally began by 10 years of age but were severe only after 15 years of age. Peripheral corneal epithelial infiltration appeared in the first few years of life. Infiltration evolved toward the depth and center of the cornea during the second decade of life. Retinopathy was present in 51.7% of the patients, with 3 cases of maculopathy and 3 cases of flattening on electroretinogram.

Conclusions: Photophobia and corneal infiltration, although generally severe after 15 years of age, could be treated with topical cysteamine and corneal transplantation. Retinal infiltration, previously described as frequent and potentially blinding, is currently observed in only half of these patients, with mild visual impairment. This could be related to the treatment with oral cysteamine reaching the retinal vascularization.


INTRODUCTION

Nephropathic cystinosis is a rare autosomal recessive metabolic disorder characterized by a defect in lysosomal cystine transport. This condition leads to the intralysosomal accumulation of cystine crystals within most tissues. The responsible gene (CTNS) encodes a 367 amino acid transmembrane protein. The most common form of the disease is infantile with renal tubular Fanconi syndrome, growth retardation, and renal failure. Renal transplantation, generally performed by 10 years of age, has improved the life expectancy of these children, permitting evaluation of the long-term effects of cystinosis on non-renal tissues.
The corneal accumulation of needle-shaped cystine crystals is characteristic,6 beginning in the superficial layers and periphery of the cornea and progressing toward the endothelium and center.5 These lesions begin early in life.7 The other ocular tissues (ie, conjunctiva, lens, iris, retina, and choroid) are otherwise generally involved by cystine deposits.2-8 The retinopathy begins in the first few years of life with patches of peripheral depigmentation,2 and is constant after 7 years of age.9 Later macular involvement leads to definitive visual loss.7

Treatment with oral cysteamine delays the general complications of cystinosis,10 but is ineffective for ocular manifestations.11 However, topical cysteamine can delay or even reduce the deposition of crystals in the cornea.12,13

This long-term follow-up study describes the evolution of ocular lesions in a large group of patients with nephropathic cystinosis treated with oral and topical cysteamine.

PATIENTS AND METHODS

A retrospective study was conducted that included each patient with nephropathic cystinosis examined between 1980 and 2000. All of the patients were referred by the pediatric nephrology department of our institution, either at diagnosis (generally in the first 2 years of life) or at the onset of ocular symptoms. Follow-up examinations were performed yearly. All of the patients were seen by the authors and had received oral cysteamine (50 mg/kg/d) since the time of diagnosis. Renal transplants were noted. For patients examined after 1985, cysteamine eye drops had been administered (6 times a day) since the onset of ocular symptoms.

The number of ocular examinations and the age at each were noted for the patients. Best-corrected visual acuity was determined if age permitted, photophobia was evaluated, and slit-lamp and fundus examinations were performed. Twelve patients received an electoretinogram. The severity of photophobia was graded according to the patient's estimation as 0 (no photophobia), 1 (photophobia limited to bright light), 2 (photophobia limited to room light), or 3 (photophobia limited to dim light). Corneal infiltration by crystals was graded on a scale of 0 to 3 separately for epithelium, stroma, and endothelium. Grade 1 infiltration was defined as 1 to 10 crystals per 1 × 1-mm slit-lamp beam. Grade 2 was defined as 10 to 50 crystals, and grade 3 as more than 50 crystals. The need for keratoplasty was noted. The deposition of crystals in the conjunctiva and iris was noted as absent or present. The fundus was examined with indirect and direct ophthalmoscopy. Peripheral or macular retinopathy was noted as absent or present. The data related to all of the examinations performed for a given patient were included in the study to appreciate the overall evolution of the disease.

RESULTS

Twenty-nine patients were examined during this 20-year period. Renal transplantation had been performed for 13 patients. The mean number of examinations for each patient was 3.7. Age at the time of examination ranged from 7 months to 26 years (mean, 10.2 years). Ten patients were examined one time, 10 from two to five times, and 9 more than five times.

The mean age at which photophobia was first noticed was 7.7 years (standard deviation, ± 3.6 years). Figure 1 illustrates the evolution of photophobia according to age. By 10 years of age, most of the patients complained of photophobia. Severe photophobia (grade 3) occurred only after 15 years of age and required symptomatic treatment (lubricants or tinted glasses).

Figure 2 illustrates the evolution of visual acu-
Figure 2. Visual acuity (mean of the two eyes) according to age. Examinations in which visual acuity was not measured (i.e., young children) were excluded.

Figure 3. Severity of corneal infiltration according to age for the (top) epithelium, (middle) stroma, and (bottom) endothelium. Infiltration was graded as 0 (no crystals), 1 (1 to 10 crystals per 1 x 1-mm slit-lamp beam), 2 (10 to 50 crystals), or 3 (more than 50 crystals).

ity (mean of the two eyes) according to age. There was a decrease in visual acuity with time, but most of the patients had relatively good vision (> 20/40) until age 20. Poor visual acuities (< 20/60) were noted only after 20 years of age.

Epithelial corneal infiltration by cystine crystals was the first sign of the disease. All of the patients had epithelial infiltration at all stages of the evolution, even in the first few months of life, beginning in the peripheral cornea. This infiltration rapidly evolved toward grades 2 and 3 with central corneal deposits in the first few years of life (Fig. 3). The mean age at which stromal infiltration was first noticed was 6.14 years (± 2.06 years), and it was rapidly followed by endothelial infiltration (7.9 ± 3.53 years). As for the epithelium, stromal and endothelial deposits of crystals in the peripheral cornea began to involve the center. Bilateral corneal transplantation was performed for one patient at the age of 21 years, with a final visual acuity of 20/20 in the right eye and 20/30 in the left eye 2 years later.

The mean age at which peripheral retinopathy was first noticed was 10.19 years (standard deviation, ± 4.4 years), generally as patches of depigmentation in the temporal retina. Among the 29 patients, 14 (48.3%) had no retinal infiltration after a follow-up ranging from 2.86 to 21.07 years (mean, 10.03 years). Figure 4 illustrates the presence of peripheral retinopathy according to age. All of the patients without peripheral retinopathy had a visual acuity of 20/40 or better, whereas only 69.4% of the patients with peripheral retinopathy had a visual acuity of 20/40 or better (P < .05). In 3 patients a macular infiltration was noticed, with a visual acuity inferior to 20/60, at the ages of 4.8, 8.9, and 12 years, respectively. Among the 12 electroretinograms performed, 3 were flattened (mean age of the patients, 15.12 years), corresponding to peripheral retinopathy (2 patients) or peripheral and central retinopathy (1
patient). The results of an electroretinogram were normal for the 9 other patients (mean age of the patients, 7.21 years).

Conjunctival infiltration was noted 12 times (mean age of the patients, 12.5 years) and iris infiltration was noted 21 times (mean age of the patients, 10.2 years).

No difference in evolution was noticed between patients who had received renal transplants and those who had not (data not shown).

**DISCUSSION**

Infantile nephropathic cystinosis is the most common and severe form of cystinosis. Renal transplantation and treatment with cysteamine have improved the life expectancy of these patients, and ocular manifestations are now the most common complication. 14 This series of 29 patients observed since 1980 has illustrated the actual evolution of these manifestations.

Photophobia generally appeared before 10 years of age and became severe in the middle of the second decade. This is consistent with the findings of previous series, 1,7,13,14 although cysteamine eye drops can provide some degree of improvement in photophobia. 15,16

Impairment of visual acuity is generally mild for a long period of time in nephropathic cystinosis, 14,15,17,18 although some cases of severe blindness have been reported. 19 In the current study, most of the patients had good visual acuity (≥ 20/40) for at least 20 years. Only one patient had poor visual acuity (20/400), at two successive examinations, after 20 years. The decrease in visual acuity can be related to the storage of corneal cystine crystals or to retinopathy, observed only after several years of evolution.

Corneal infiltration by cystine crystals was observed in accordance with the previously described sequence: 5,7 the infiltration progresses from the surface toward the depth of the cornea, and from the periphery toward the center. The endothelial infiltration is an important step in the disease, as it can be accompanied by corneal edema and epithelial erosions. The most severe corneal infiltrations are observed essentially after 15 years of age and can lead to corneal transplantation with good optical results, although there is a risk of recurrent infiltration in the graft. 20

Renal transplantation 18 and treatment with oral cysteamine 11 have no influence on corneal infiltration, but topical cysteamine can slow down or reverse cystine deposits. 1,12,13 Nevertheless, as we observed, compliance with topical cysteamine treatment is often poor in the long-term because of the frequent instillations required to reach effectiveness. 1

The retinopathy of cystinosis was first described by Wong et al. 2 as patches of depigmentation in the peripheral temporal retina. It was observed in children as young as 5 weeks, 2 and several series have reported the presence of retinopathy in almost 100% of patients after 7 to 10 years. 7,18,21 Maculopathy has often been noted in the second decade of life, 7,14,18 with poor visual acuity and flattening on electroretinogram. 7,23 By contrast, we observed 14 of 29 patients without retinopathy and only 3 cases of maculopathy and 3 instances of impairment on electroretinogram. This mildness of retinal infiltration is illustrated by the case of a patient who received a corneal transplant at 21 years of age for severe corneal infiltration and in whom visual acuity was 20/20 postoperatively.

In previous series without treatment with oral cysteamine, more than 50% of patients had a visual acuity of 20/40 or worse in the second decade of life; 7,14; this was the case for 25% of our patients. Furthermore, visual acuity was better in patients without retinopathy. The only series with mild ocular manifestations described a French–Canadian population with a different evolution presumably related to genetic homogeneity. It can be hypothesized that our patients had a milder retinal involve-