A Neonate with Bilateral Corneal Opacities and Glaucoma

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A term male neonate born via normal delivery to an African-American woman at 39 weeks gestation presented with bilateral corneal clouding. The anthropometric measurements were all < 10% for gestational age (birth weight of 2239 g, head circumference of 31 cm, and length of 46 cm). A cephalhematoma measuring approximately 3 cm × 3 cm was present on right parietal area.

Laboratory studies revealed a white blood cell count of 13,300/mm³ with 74% neutrophils, 3% bands, 14% lymphocytes, hematocrit of 52.2%, and platelet count of 115,000/mm³. Total bilirubin at 24 hours of age was 6.2 mg/dL with a direct component of 3.8 mg/dL. MRI of the brain revealed moderate dilatation of both lateral ventricles. The third and fourth ventricles appeared normal without any calcifications. Abdominal ultrasound was unremarkable.

Examination of the cornea using an indirect ophthalmoscope and 20-diopter lens revealed bilateral central corneal opacities measuring 6 mm in diameter and completely obstructing the visual axis (Figure 1). Intraocular pressure (IOP) ranged from 30 mm Hg to 40 mm Hg bilaterally. The infant was started on IOP-lowering medication (topical levobunolol 0.25% and oral acetazolamide 10 mg/kg, divided 3 times daily) as well as topical mydriatic agents in an attempt to enlarge the pupil margin beyond the opacity to prevent amblyopia (atropine 1%, cyclopentolate 0.2%, phenylephrine 1%). Further testing revealed the diagnosis.

Figure 1. Corneal opacities at birth.

Editor’s note: Each month, this department features a discussion of an unusual diagnosis in genetics, radiology, or dermatology. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at pedann@Healio.com.
The differential diagnosis in this case includes anterior segment dysgenesis (ie, Peters anomaly, which is a central defect in the corneal basement membrane with adhesion of the iris and lens capsule to the central cornea) and infectious etiologies, including congenital cytomegalovirus (CMV) infection. Urine culture at birth and at 1 week grew CMV, so oral valgancyclovir 30 mg/kg in two divided doses was started. At 3 weeks, an anterior chamber paracentesis was performed and aqueous fluid was sent for polymerase chain reaction testing. Results were positive for CMV DNA.

Follow-up examination 2 weeks later demonstrated substantial corneal clearing of the right eye with minor improvement in the left eye. During the course of the following 2 weeks, the IOP increased from the mid 20s mm Hg bilaterally to 38 mm Hg and 42 mm Hg in the right and left eyes, respectively. Additional topical steroid drops and IOP-lowering medications were initiated. The patient underwent bilateral Ahmed Glaucoma Valve (New World Medical Inc., Rancho Cucamonga, CA) implantation at 5 months of age for elevated IOP in the 30s mm Hg in the right eye and the 50s mm Hg in the left eye. The pressures remained elevated so he underwent bilateral Baerveldt Glaucoma implantation (Abbott Medical Optics, Abbott Park, IL) at 7 months of age. He was on oral valgancyclovir for 6 months. The corneal opacities showed substantial improvement (Figures 2-3), and IOPs are currently in the range of 20s mm Hg at 9 months of age.

The features in this case that led us to classify the baby as congenital symptomatic CMV are as follows: 1) CMV cultures from two urine specimens; 2) small for gestational age (birth weight < 3%); 3) microcephaly (head circumference < 3%); 4) bilateral corneal opacities; 5) CMV DNA detected in aqueous humor fluid of left eye; 6) cholestatic jaundice peaking on day 2 of life, with total bilirubin of 9.7 mg/dL and the direct component being 5.4 mg/dL; and 7) significant improvement in the corneal opacity with valganciclovir treatment.

**DISCUSSION**

CMV infection is the most common intrauterine infection, affecting 1% of all infants born in the United States. Of those infected, 10% are symptomatic as neonates and the majority survive the initial infection. However, more than 90% of these survivors develop long-term neurological sequelae, including sensorineural hearing loss, mental retardation, cerebral palsy, and impaired vision. Of the remaining 90% of congenital CMV infections that are
asymptomatic, approximately 10% to 15% will later develop long-term neurological sequelae.\textsuperscript{2,3} The classical manifestations of CMV have been widely described and include microcephaly, chorioretinitis, hepatosplenomegaly, petechial rash, deafness, and periventricular calcification. We report a rare manifestation of cytomegalovirus infection in a neonate: bilateral corneal opacities with glaucoma.

Corneal opacities with glaucoma secondary to CMV infection rarely have been described in neonates. The pathophysiology behind these corneal opacities in neonates has not been described in any of the published case reports.\textsuperscript{4,5} Corneal endothelitis resulting from the destruction of endothelium by CMV is a probable explanation for the opacities seen in our patient. The role of an infectious virus as the cause of the endothelial infection is supported first by detection of viral antigen, viral DNA, or viral particles in the corneal endothelial cells.\textsuperscript{7,8} Secondly, endothelial lesions can rapidly resolve with the addition of systemic antiviral treatment.\textsuperscript{7,9} The elevated IOP can result from anterior uveitis, which is not uncommon in CMV infection.\textsuperscript{10,11}

The clinical observation that corneal endothelial lesions always start from the periphery and move toward the center of the cornea implies that tissues surrounding the cornea, such as the trabecular meshwork or ciliary body, may be the reservoir for CMV.\textsuperscript{7} CMV infects the CD34+ myeloid progenitor cells of the bone marrow, in which specific human cellular DNA binding proteins in the nucleus bind to the CMV immediate-early promoter and inhibit transcription. Therefore, the production of infectious particles is blocked and the virus becomes latent.\textsuperscript{12} It has been shown in the murine model that bone marrow-derived cells migrate to the cornea.\textsuperscript{13} and intraperitoneally inoculated CMV reaches the cornea of nude mice via the bloodstream.\textsuperscript{14}

Although the exact pathogenesis of CMV corneal endothelitis is not yet understood, anterior chamber-associated immune deviation, first described by Streilein et al.,\textsuperscript{15} offers a potential explanation. In this condition, transforming growth factor-beta alters the intraocular presenting cells such that cell-mediated immunity becomes impaired while humoral immunity remains intact or even enhanced. These antibodies may neutralize the extracellular virus, thus preventing the spread of the virus into other cells and tissues within the anterior chamber and limiting the damage to corneal endothelial cells.\textsuperscript{8}

CMV DNA in the anterior chamber along with partial resolution of corneal clouding with the antiviral agent supports the contention that CMV is the causative agent of corneal clouding, with elevated IOP being a contributing factor. Early diagnosis and institution of treatment offer the possibility of preserving vision in such patients. Currently, a clinical trial of 6 weeks versus 6 months of valgancyclovir is being performed by the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. The patient discussed in this case is currently 9 months old. He received oral valgancyclovir for 6 months, the corneal opacities have shown substantial improvement, and IOPs are currently in the range of 20s mm Hg.

REFERENCES