Corneal Opacities in the Neonate

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Education Gaps

1. Congenital corneal opacities often can be an early sign of an underlying systemic condition.

2. The visual prognosis for a newborn with a congenital corneal opacity can be significantly affected by delays in diagnosis and treatment.

Abstract

A congenital corneal opacity is a rare occurrence but can cause significant visual compromise to the affected infant. Corneal opacities can arise from infectious, metabolic, genetic, developmental, and idiopathic causes. Early diagnosis is imperative so that an appropriate treatment plan can be initiated as soon as possible to obtain the best visual potential. An early diagnosis can facilitate the recognition of an underlying systemic disorder that may also be affecting the infant. Management strategies include amblyopia treatments, refractive error correction, and surgery. Despite aggressive treatment, visual potential may still be limited in many cases.

Objectives After completing this article, readers should be able to:

1. Derive a thorough differential diagnosis for a patient with a congenital corneal opacity.

2. Recognize the signs of common causes of congenital corneal opacities.

3. Recognize the challenges associated with the treatment and management of infants born with corneal opacities.

4. Describe common components of treatment for congenital corneal opacities.

INTRODUCTION

Congenital corneal opacification is a rare condition, occurring in 6 in 100,000 newborns globally. However infrequent, corneal opacities can have devastating consequences for a child’s long-term visual potential, especially if not recognized and treated promptly. Congenital clouded cornea has various etiologic factors:
genetic, metabolic, developmental, and idiopathic. A quick and accurate diagnosis by the treating neonatal team can aid a child’s visual prognosis and may also help diagnose a systemic condition or syndrome that may be affecting the infant.

**CLINICAL APPROACH**

When trying to decipher the cause of a congenital corneal opacification, clinicians should obtain a thorough and accurate history from the infant’s parents and obstetrical staff. Many infectious processes, including herpes simplex virus (HSV), can cause a keratitis. Therefore, it is important to find out if the infant’s mother either tested positive or was symptomatic for HSV, rubella, or other pertinent infections during her pregnancy or delivery. Clinicians should obtain information about the infant’s delivery because birth trauma, particularly the use of forceps to assist with delivery, can cause corneal lacerations, corneal edema, and clouded corneas. Care providers should review the family’s detailed pedigree, which may reveal a genetic or familial inheritance pattern for the corneal clouding, which can help establish a metabolic or genetic diagnosis. Finally, physicians should conduct a thorough review of systems to identify any other coexisting congenital systemic anomalies that may provide clues to a syndrome unifying the ocular and systemic abnormalities.

When examining a newborn eye, it is important for the clinician to identify all the major structures of the anterior segment to recognize any potential abnormalities. In a normal eye (Fig 1), the cornea is clear and allows visualization of the structures posterior to it, namely, the iris and lens. Peripheral to the cornea is the white, opaque sclera which is covered by the conjunctiva. The limbus is the region where the sclera and cornea meet. Often, abnormalities in 1 segment of the eye occur in conjunction with abnormalities elsewhere in the eye. Therefore, it is critical to examine all the structures of the eye to identify all potential pathologies. The eyelids are particularly important when considering a corneal opacification. If a neonate has a defect in the eyelid, such as an eyelid coloboma, or a lagophthalmos, in which the eyelids cannot close fully, the infant is at risk for exposure keratopathy. In this situation, the infant’s cornea can develop abrasions and ulcerations because the eyelid is no longer providing complete protection. The clinician should also note any lesions on the face and eyelid because this could assist with diagnosis. For instance, vesicles on the eyelids could signify a herpetic infection.

The size of the eye is also important. A small eye (ie, microphthalmos), particularly one with many obvious ocular anomalies, could indicate a developmental problem with the eye in utero. In contrast, a large eye (ie, buphthalmos), with a larger than normal cornea, may suggest a diagnosis of congenital glaucoma. When examining the conjunctiva, the presence of conjunctival injection might suggest an inflammatory or traumatic component to the condition. In evaluating the newborn cornea, any opacification of the cornea is considered abnormal. Detailing the location of the opacification (central vs peripheral, anterior vs posterior) can help the clinician determine the diagnosis because various conditions can manifest in stereotypic patterns. Fluorescein staining at the bedside can be helpful if a corneal epithelial defect or herpetic infection is suspected. If it is possible to visualize the anterior segment despite the cloudy cornea, the clinician can inspect the iris to identify any iridocorneal adhesions, ectopic pupils, iris colobomas, or other structural abnormalities. Finally, the clinician can use a direct ophthalmoscope to evaluate the red reflex of the newborn eye to detect potential lens abnormalities such as cataracts as well as retinal abnormalities.

**DIFFERENTIAL DIAGNOSIS**

As mentioned before, there are various potential causes for congenital clouding of the cornea. The following is a mnemonic for the most common causes of congenital corneal opacification:

- **S** – Sclerocornea
- **T** – Tears in the Descemet membrane (from birth trauma or congenital glaucoma)
- **U** – Ulcers
- **M** – Metabolic
- **P** – Peters anomaly
- **E** – Edema (congenital hereditary endothelial dystrophy [CHED])
- **D** – Dermoid

![Figure 1. Anatomic structures of a normal eye.](image-url)
Congenital clouding of the cornea has many other rare causes, including cornea plana, corneal keloids, congenital hereditary stromal dystrophy, and oculoauriculovertebral dysplasia. For the purpose of this review, only the most common causes will be discussed further.

Sclerocornea
Sclerocornea is a rare congenital developmental abnormality of the eye. In this condition, intrauterine mesenchymal dysgenesis causes the cornea to become opaque, vascularized, and quite similar in appearance to the sclera, making the limbus indistinct (Fig 2). This disorder can have a spectrum of clinical findings, with milder cases having a clear central cornea. However, infants with severe manifestations can have near-total corneal involvement, though the central cornea is often still clearer than the periphery. This is in contrast to Peters anomaly wherein the central cornea is more opaque than the periphery. The corneal clouding found in infants with sclerocornea is full thickness through the stroma and will limit visualization of the intraocular structures.

Although sclerocornea is typically bilateral in occurrence, it can be unilateral in 10% of cases. It tends to occur sporadically but can have a familial or autosomal dominant inheritance pattern. Systemic associations include spina bifida occulta, cranial and cerebellar abnormalities, decreased hearing, limb deformities, cryptorchidism, Hallermann-Streiff syndrome, Smith-Lemli-Opitz syndrome, Mietens syndrome, osteogenesis imperfecta, and hereditary osteoonychodysplasias. The prognosis for severe cases of sclerocornea is guarded. Affected infants should be referred promptly for consideration of early corneal transplantation but often have quite limited visual potential despite surgical intervention.

Tears of the Descemet Membrane
The most posterior or innermost layer of the cornea is the endothelial cell layer (Fig 3). The Descemet membrane is a specialized basement membrane of the corneal endothelial cells that separates the posterior corneal stroma from the endothelial cell layer. The endothelial cells are responsible for actively pumping water out of the cornea and keeping it in a relatively desiccated state. If there is a tear in the Descemet membrane, the endothelial cell function declines and the cornea becomes edematous and thereby loses its clarity.

Traumatic injuries to the Descemet membrane are most commonly caused by forceps trauma to the eye during delivery. These tears are often vertical and linear in configuration. The rupture of the Descemet membrane leads to stromal, and occasionally, corneal epithelial edema, which in extreme cases can cause bullae or blisters on the surface of the cornea. Even after the corneal edema regresses, the edges of the torn Descemet membrane can persist and be visualized as ridges protruding from the posterior corneal surface. Often, other signs of trauma are apparent on the child’s face and head as well. Infants may have periorbital soft tissue swelling or concurrent eyelid lacerations.

Descemet membrane tears are also common in congenital glaucoma. In this scenario, these tears are termed “Haab striae” and can be differentiated from traumatic Descemet membrane tears by typically being more horizontal and curvilinear in appearance. In addition, the eyes of affected infants will demonstrate higher intraocular pressures and often will have corneal enlargement and abnormally deep anterior chambers. It is critical to identify eyes at risk of having congenital glaucoma as early as possible because optic nerve damage from sustained ocular hypertension can cause permanent vision loss. These patients require surgery to address the glaucoma as soon as possible.
Ulcers
Viral keratitis, such as rubella or herpetic keratitis, can also produce a clouded cornea in a newborn. Herpes simplex infections most commonly occur in infants of women with active genital HSV infections. The risk of transmission is higher with a primary genital herpes infection than with recurrent activations of the virus. While most infants are infected during parturition, some may acquire the infection in an ascending manner after premature rupture of the amniotic membranes. Ocular involvement in congenital HSV infections most commonly consists of a blepharoconjunctivitis with vesicular eruptions on the eyelids and/or a keratitis with epithelial dendrites (branching treelike pattern of fluorescein staining on the corneal surface) that can be identified with fluorescein staining. It is important to perform a well-dilated funduscopic examination in these patients because some may have a chorioretinitis with vitritis and optic atrophy, particularly those with central nervous system involvement. Any infant who is suspected of having a herpetic keratitis should be promptly treated with systemic and topical antiviral medications because ocular disease often occurs in association with central nervous system involvement. The diagnosis can be confirmed by isolating the virus from vesicles or corneal scrapings if needed, using polymerase chain reaction and/or viral culture.

Corneal clouding associated with congenital rubella syndrome has dramatically decreased in incidence subsequent to the development and widespread usage of the attenuated rubella virus vaccine. However, the possibility of rubella should be considered in infants born to women who have not been vaccinated or who originate from developing countries where widespread rubella vaccination may not have been implemented. The corneal clouding in rubella syndrome can result from a true keratitis, or less commonly, an elevation of the intraocular pressure that leads to corneal edema. The associated keratitis often clears in weeks to a few months but residual scarring may persist. The most common associated ocular abnormalities in congenital rubella infection are cataracts and pigmentary retinopathy. Other systemic signs include sensorineural hearing loss, intellectual disability, hepatosplenomegaly, microcephaly, thrombocytopenic purpura, osteopathy, lymphadenopathy, and diabetes.

Metabolic Causes
Mucopolysaccharidoses. Mucopolysaccharidoses (MPSs) are lysosomal disorders that cause accumulation of glycosaminoglycans in various tissues. Affected children can present with corneal clouding as early as a few months of age that typically worsens with time. Corneal opacification is a prominent feature in all MPS I subgroups (Hurler, Scheie, Hurler-Scheie), MPS IV Morquio syndrome, and MPS VI Maroteaux-Lamy syndrome. Corneal clouding is not present in Hunter syndrome (MPS II) or Sanfilippo syndrome (MPS III). Although retinopathy can be found in patients with MPS, it is not often evident until children are at least several years of age, and may be obscured by the clouded cornea.

Sphingolipidoses. Typically, most sphingolipidoses affect the retina and spare the cornea except in Fabry disease. Fabry disease is inherited in an X-linked recessive pattern and can cause whorl-like opacities termed “verticillata” in the cornea epithelium. Other systemic signs of Fabry disease include skin lesions, peripheral neuropathy, and renal failure.

Mucolipidoses. Mucolipidoses, particularly GM gangliosidosis type 1 and mucolipidoses types I and III can manifest with corneal clouding as well.

Peters Anomaly
Peters anomaly is a central corneal stromal opacity, or leukoma, that results from a corneal defect affecting the posterior corneal stroma, Descemet membrane, and endothelium (Fig 4). Eighty percent of cases are bilateral, and 50% to 70% of affected infants also have glaucoma. One key distinguishing factor between the leukoma in Peters anomaly and other corneal clouding disorders, such as sclerokeratome, is the lack of vascularization and the presence of a clear peripheral cornea. The defect may be accompanied by adherent iris strands (Peters anomaly type 1) or adherence of the lens (Peters anomaly type 2). The size and density of the corneal opacification can vary. In many cases, the central stromal leukoma can decrease in opacity with time. Peters

Figure 4. Central dense corneal opacity typical of Peters anomaly. The asterisk (*) symbol marks the limbus and the dagger (†) indicates the leukoma. (Adapted with permission, © 2015 American Academy of Ophthalmology, www.aao.org.)
anomaly can be caused by a multitude of diseases and genetic conditions such as Axenfeld-Rieger syndrome and congenital rubella. Unilateral cases are often isolated. However, bilateral cases can be associated with an underlying systemic disorder and should prompt a complete genetic evaluation. Systemic associations include craniofacial anomalies, congenital heart disease, pulmonary hypoplasia, syndactyly, ear abnormalities, genitourinary disorders, and central nervous system abnormalities. Peters plus syndrome is a rare autosomal recessive disorder with bilateral Peters anomaly, congenital brain defects, heart defects, and craniofacial abnormalities.

Edema (CHED)
CHED is a rare corneal dystrophy that manifests in infancy or early childhood with bilateral cloudy corneas, photophobia, tearing, and occasionally nystagmus. There are 2 types of CHED. In the type with an autosomal dominant inheritance pattern (CHED type I), the corneal haziness is progressive and often not detectible until the age of 2 years. However, in the type with an autosomal recessive inheritance pattern (CHED type II), the corneal clouding is present at birth and not progressive. Harboyan syndrome is a variant of CHED type II with the characteristic features of corneal opacification and edema at birth as well as sensorineural deafness.

Dermoids
Epibulbar or limbal dermoids are benign congenital tumors composed of choristomatous tissue (tissue derived from germ cell layers not normally found at that site). They often consist of fibrofatty tissue covered by keratinized epithelium and may contain hair follicles, sebaceous glands, or sweat glands (Fig 5). These tumors usually straddle the limbus and are most commonly found at the inferotemporal limbus. They can be very large, up to 10 mm in diameter, and can cause a lipoid infiltration of the corneal stroma at their leading edges. Large epibulbar dermoids can produce significant astigmatism with resultant amblyopia, and rarely, can cover the visual axis. Removal of these limbal dermoids is indicated if they cause amblyopia or ocular irritation, but residual scarring will be present. Epibulbar dermoids are most commonly isolated findings but 30% of cases are associated with Goldenhar syndrome (oculoauriculovertebral spectrum). Children with Goldenhar syndrome may have a myriad of other anomalies, including ear deformities and preauricular skin tags, eyelid colobomas, Duane retraction syndrome, maxillary or mandibular hypoplasia, and vertebral anomalies.

MANAGEMENT
The management of congenital corneal opacities in infants is challenging, and the approach must be tailored to the specific cause and child. Several factors must be considered when deciding on the best treatment strategy. First, the size and density of the corneal opacity is important in determining how much a patient’s vision is affected. A larger peripheral opacity may not affect vision as much as a smaller, denser, central one that is overlying the pupillary axis. If the opacity is small and central, it is possible that dilation eye drops may be used therapeutically to enlarge the pupil; this will allow the patient to see around the opacity, especially early in life, to aid visual development. Alternatively, an optical iridectomy can be created surgically wherein another or larger pupillary opening is created to allow some visual stimulation to occur.

Another factor to consider is refractive error. Any abnormalities in the corneal shape or makeup can affect a patient’s refractive error. As a result, even if a corneal opacity is peripheral and not in the visual axis, it can still cause significant visual compromise by inducing anisometropia (ie, a large difference in refractive error between the 2 eyes). Finally, amblyopia is also a serious concern. Visual deprivation amblyopia can occur from the opacity occluding the visual axis. Moreover, refractive amblyopia can occur from the anisometropia that develops. As a result, it is imperative that these patients be evaluated by a pediatric ophthalmologist quickly; delays in treatment can be detrimental to a patient’s end visual potential.

In some disorders, such as Peters anomaly, observation may be the best course of action because many of these opacities will spontaneously improve with time. However, in large, dense central corneal opacities, the option of a corneal transplant, or penetrating keratoplasty, must be considered. Penetrating keratoplasties in neonates are technically demanding because of the reduced scleral rigidity and
increased elasticity in the newborn eye. The risk of intraoperative complications is high. In addition, children have higher rates of graft failure than adults and may require multiple repeat keratoplasties. These patients are also at risk of developing postoperative cataract and glaucoma. In addition, most of these patients carry a high risk for amblyopia from large refractive errors and require eyeglasses or contact lens treatment with prolonged patching regimens. As a result, if a patient has a unilateral corneal clouding, care providers must have an extensive discussion with the parents about the time and commitment involved in caring for an infant with a corneal transplant and the limited visual potential expected. If the involvement is bilateral, the decision to intervene and treat (at least 1 eye) is clearer, because it provides the infant with some level of visual function.

CONCLUSION

Corneal opacities in a neonate, while rare, can pose significant morbidity to a child’s visual function. In the immediate newborn period, it is essential that the neonatologist recognize the disorders that can cause rapid loss of vision if left untreated, such as congenital glaucoma, as well as those that can signify serious underlying systemic conditions, such as congenital HSV or rubella. The prognosis for many of these disorders is limited; however, early and prompt care coordinated by the neonatal team and ophthalmology can provide the infant with the best chance of obtaining good visual function.
1. You are performing a routine newborn physical examination and note a right eyelid coloboma. Which of the following concerns is most appropriate in the presence of this condition?
   A. Herpetic or adenoviral infection.
   B. Group B streptococcal sepsis.
   C. Exposure keratopathy with risk of abrasion.
   D. Congenital glaucoma.
   E. No concern at present with almost certain likelihood of spontaneous resolution.

2. You are called to examine a newborn infant due to concern for an eye abnormality. The infant appears to have bilateral partially opaque corneas. The central corneas appear clear, while the peripheral corneas appear opaque and similar in appearance to the sclera, making the limbus appear indistinct in both eyes. Which of the following is the most likely diagnosis?
   A. Sclerocornea.
   B. Secondary herpetic infection.
   C. Dermoid tumor.
   D. Syphilitic infiltration.
   E. Peters anomaly.

3. You are performing a physical examination on a newborn infant and note what appears to be a vertical, linear tear on the cornea. You suspect Descemet membrane tear. Which of the following is the most common cause of this condition?
   A. Herpes simplex infection.
   B. Ophthalmic antibiotic ointment adverse effect.
   C. Primary gonococcal infection.
   D. Traumatic injury associated with forceps use during delivery.
   E. Congenital abnormality associated with trisomy 18.

4. A male infant is noted to have abnormal-appearing, coarse facial features as well as abnormal neurologic findings. A congenital metabolic disorder is suspected and eventually diagnosed. Corneal opacification is noted at 2 months of age. Which of the following is the most likely diagnosis?
   A. Hunter syndrome (mucopolysaccharidosis type II).
   B. Sanfilippo syndrome (mucopolysaccharidosis type III).
   C. Noonan syndrome.
   D. Medium-chain acyl-coenzyme A dehydrogenase deficiency.
   E. Hurler syndrome (mucopolysaccharidosis type I).

5. An infant with corneal opacity is identified as having Peters anomaly and has bilateral occurrence of this condition. Which of the following aspects of management is appropriate for this patient?
   A. Because this condition is highly associated with the development of malignancy, it is considered a pediatric ophthalmic emergency, and surgery should be performed as soon as possible.
   B. Because this condition is most commonly associated with heavy maternal alcohol use, social work and child protective services should be involved early in this infant’s care.
   C. Depending on the degree of opacification, observation may be the best course of action because many of these opacities will spontaneously improve with time.
D. Approximately half of the cases of Peters anomaly can be treated and cured with intraocular injections of corticosteroids, as long as treatment is initiated within the first few weeks after birth.

E. If the corneal opacity is peripheral and not in the visual axis, it will not affect the patient’s refractive error and therefore, does not require further evaluation other than close follow-up.
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