Chapter 4
Bilateral Congenital Cataracts

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Congenital cataract is the leading cause of preventable childhood blindness [1]. The incidence of congenital cataract is 1–6 cases per 10,000 live births in developed countries [2] and 5–15 cases per 10,000 in the developing countries [3]. Globally, an estimated 200,000 children are bilaterally blind from cataracts [4]. Due to the visual deprivation associated with complete or central opacities, successful management requires early detection and treatment, since the critical period of visual development lasts until about 4 months of age for bilateral cataracts and 2 months of age for unilateral cataracts [5]. For bilateral congenital cataracts, the best visual acuity results are typically associated with surgery prior to 14 weeks, during which time there is a trend for better visual acuity with earlier surgery [6]. With regard to classification and management, pediatric cataracts are typically categorized as bilateral or unilateral and into the following groups:

1. Isolated congenital cataracts (hereditary or sporadic)
2. Cataracts associated with ocular developmental anomalies
3. Cataracts that are part of multisystem genetic or metabolic disease [7]

Examination

Prior to examination, a detailed prenatal, birth, medical, and family history should be obtained. A thorough ocular examination is an important part of the workup of congenital cataracts. Visual acuity testing is typically not possible in young infants, who may only demonstrate light responses. Older infants should be able to fix and

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follow with each eye, in a central, steady, maintained fashion, with no nystagmus. External features should be noted as typical or dysmorphic. A portable slit lamp can be used in infants to assess any corneal opacities, iris vascular anomalies, undilated pupil size and shape, and cataract morphology. The red reflex and view to the fundus should be assessed prior to dilation. Indirect ophthalmoscopy should be used to evaluate the fundus, with special attention to persistent fetal vasculature, optic nerve, and other retinal anomalies. If the cataract is too dense to obtain a view to the posterior pole, a B-scan ultrasound can be performed. Finally, review of family photos in an older infant may help elicit the timing of cataract onset. Examination of family members may assist in determining familial etiology. Central cataracts >3 mm in diameter are generally visually significant.

Classification of cataract morphology can sometimes help suggest an identifiable hereditary or genetic cause. Central cataracts include nuclear, lamellar, cortical, sutural, pulverulent, and cerulean. A detailed summary of morphologies can be found in Trumler and Krishnamurthy's reviews [8, 9]. Polar cataracts can be either anterior (anterior polar, anterior pyramidal, and anterior subcapsular) or posterior (posterior subcapsular, posterior lenticonus, posterior fetal vascular [PFV]) [10]. Nuclear cataracts are bilateral in up to 80% of cases, and many affected eyes are microphthalmic [11]. Bilateral nuclear cataracts represent the most frequent morphology for autosomal dominant inherited cataracts. Phenotype alone can occasionally suggest a specific genetic cause; however, in most cases, cataract structure is insufficient to predict a specific gene mutation, since mutations at different loci within a gene can result in different phenotypes, and different gene mutations can result in similar phenotypes [12].

Inherited Bilateral Cataracts

Hereditary cataracts are typically isolated and inherited in an autosomal dominant pattern with a high degree of penetrance [10]. History is very important to determine any family history of congenital cataract, as there will often be several family members with a similar condition, and parents and/or siblings of the affected infant can be examined. Most mutations are in genes for lens crystallins and connexins [13]. Autosomal recessive and X-linked inheritance patterns have been described, but these are less common. Hereditary cataracts account for 12–30% of all congenital cataracts [14, 15–17]. Gene panel testing can also be offered to identify not only mutations in a particular family but also pathogenic mutations in genes that cause cataract for sporadic bilateral cases, some of which may be passed on to future generations.

Non-inherited Bilateral Cataracts

In patients where there is no known family history, it is important to establish whether the cataracts are isolated and, if not, determine an identifiable cause. Isolated cataracts could be due to a sporadic gene mutation but can also be associated with other ocular abnormalities or systemic or metabolic syndromes. In an

infant with bilateral cataracts, note in the history any prior retinopathy of prematurity treated with laser, radiation exposure, steroid use, or trauma, which are each secondary causes of cataract. Cataracts should only be considered "idiopathic" if other causes are ruled out. Older studies have estimated that idiopathic cataracts comprise about 50% of congenital/infantile cataracts [14, 15].

Cataracts associated with ocular abnormalities can be seen in microcornea or microphthalmos, aniridia (evaluate for Wilms tumor, especially in sporadic aniridia), Peters anomaly, or other types of anterior segment dysgenesis. It is also crucial to rule out intraocular tumors. These abnormalities should be apparent during the ophthalmologic evaluation, and ultrasound testing should be done if there is no view of the posterior segment. Some forms of anterior segment dysgenesis with cataract are associated with genetic causes (e.g., *PAX6* mutations) with most findings limited to the eye. However, others may have systemic implications (e.g., *B3GLCT* gene mutation, Peters plus syndrome with cleft lip/palate, short stature, abnormal ears, and mental retardation) [18, 19].

Careful physical examination of the child will provide clues into any genetic or systemic conditions associated with congenital cataracts, as well as tailor the systemic workup. Abnormal facial and orbital features, as well as dermatologic/hair, skeletal, genitourinary, and gastrointestinal (failure to thrive or vomiting), may have a correlation and are worth noting. With assistance from the pediatrician or geneticist, noting the head circumference (presence of hydrocephalus or encephalocele), ear appearance, presence of hearing loss, syndactyly/polydactyly, nasal appearance, presence of cleft lip/palate, or dental abnormalities is valuable when seen in conjunction with cataracts. A highly extensive list of multisystemic associations with syndromic cataract can be found in Trumler's 2011 review [9]. A large Danish observational study showed cataracts with systemic abnormalities are bilateral in 89% of cases [14]. Down syndrome comprised almost a third of cases, the majority of which (72.2% [13/18]) had bilateral cataracts. Patau syndrome (trisomy 13) and Edwards syndrome (trisomy 18) also commonly have the feature of cataract [5]. These syndromes are typically diagnosed by characteristic phenotypical features and confirmed by karyotype testing.

Extensive systemic evaluations cannot feasibly be performed on every child with non-hereditary bilateral cataracts, and assessments are highly unlikely to yield abnormal results in a well, non-dysmorphic infant [20]. In a retrospective study of 421 cases of pediatric cataract in Australia, no child who was otherwise well and had cataract was found to have an associated syndrome on further investigations [21]. However, it is prudent to enlist the assistance of the pediatrician when considering a need for further metabolic and genetic testing, tailored to the medical and developmental history of the child. In the United States, routine newborn screening often includes evaluation for infectious exposures and some metabolic conditions. The US Department of Health and Human Services provides recommendations of core conditions that each state may include in newborn screening panels, and this information is available online or can be confirmed in the child's health record [22].

In the case where newborn laboratory testing has not been performed, it is crucial to elicit any history of intrauterine infections or exposures in utero. Routine testing of all bilateral cataracts for TORCHS (toxoplasmosis, rubella, cytomegalovirus, herpes simplex, and syphilis) infection should be performed. A history of maternal fever/rash during pregnancy or systemic clinical indicators in the child such as

microcephaly, hearing loss, developmental delay, thrombocytopenia, hepatosplenomegaly, or skin abnormalities should alert the clinician to possible infectious etiology [9]. Maternal and fetal rubella infection usually occurs in the first trimester and can manifest with growth deficiency, microcephaly, cardiac abnormalities, deafness, and ocular manifestations (cataract, glaucoma, retinopathy) [5].

Metabolic disorders that have not yet manifested systemic symptoms can be found in infants with bilateral cataract. Urine amino acids and serum electrolytes can be checked especially in males with cataracts, hypotonia, poor weight gain, and mental retardation with concern for Lowe oculocerebrorenal syndrome [10]. Lowe syndrome is an X-linked recessive syndrome, which is also frequently associated with glaucoma and corneal keloids [7]. Galactosemia is an autosomal recessive condition caused by mutations in galactokinase (*GALK1*), galactose-1-phosphate uridylyltransferase (*GALT*), or uridine disphosphate galactose-4-epimerase *(GALE)*, which result in high-serum galactose (which can be measured with urine galactitol). In the more common transferase deficiency, symptoms may become apparent when the child starts drinking whole milk and can present with vomiting, failure to thrive, liver disease, and lethargy [23, 9, 5]. Generally, these patients are diagnosed by systemic symptoms prior to development of cataract. These patients should be screened for urine-reducing substances. Erythrocyte galactokinase can also identify the less common *GALK1* deficiency [5]. Sengers syndrome is a metabolic disorder associated with cardiomyopathy (mutation in the *acylglycerol kinase* gene, chromosome 7q34); asymptomatic and undiagnosed cases can be detected by cardiomegaly on chest X-ray. Spoke-like cortical cataracts can also be seen in lysosomal storage diseases (alpha-mannosidosis and the X-linked Fabry disease), though these are typically not seen in infants.

Cat-Map (http://cat-map.wustl.edu/) is an online chromosome map and reference database for inherited and age-related forms of cataracts in humans and other selected animals [24]. Hejtmancik also summarizes the different types of genes in detail associated with congenital cataracts [13]. In the future, it may be possible to find the genetic cause for more sporadic cataracts using next-generation sequencing [20].

Case 1

An 11-day-old full-term baby girl presented to the pediatric ophthalmologist after referral from the pediatrician for an abnormal red reflex in both eyes on newborn screening. Her sister, father, and paternal grandmother had a history of congenital cataracts, for which they underwent surgery at young ages. On examination, she was a well-appearing full-term baby, who opened her eyes spontaneously and blinked to light in both eyes. Anterior segment exam with portable slit lamp showed a central 4 mm nuclear cataract in each eye (Fig. 4.1), with a clear peripheral lens. The corneas were clear and estimated to be of normal diameter (about 10 mm). The conjunctiva was white and quiet bilaterally. The pupils were normally reactive without afferent pupillary defect. The iris was blue, and the pupils were round without any synechiae or persistent iris fetal vasculature. Intraocular pressures were soft to tactile palpation bilaterally. The dilated fundus exam showed normal optic nerve without evidence of persistent stalk, normal macula, vessels, and periphery in each eye.

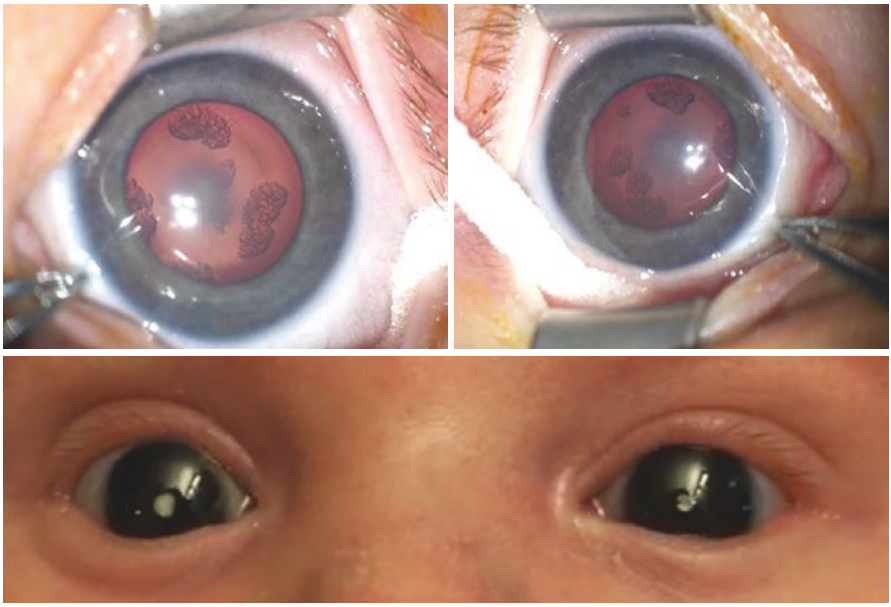

Fig. 4.1 Intraoperative photos of bilateral hereditary cataracts of Case 1, the right eye and the left eye, demonstrating central nuclear opacities with peripheral vacuoles

No additional workup was done due to the strong family ocular history of hereditary cataract in a well child. The patient underwent bilateral (immediate sequential) 23-gauge cataract extraction with primary posterior capsulectomy and anterior mechanical vitrectomy at week 4 of life. Surgery was uneventful and the patient was left aphakic. She was fitted with aphakic soft contact lenses at postoperative day 5 (Silsoft base curve 7.5, diameter 11.3, power +29.00 diopters in each eye).

Comment In this case, the strong family history likely contributed to the early identification of bilateral cataracts by the child's pediatrician and prompt referral. Workup was not necessary with such a strong family history, but genetic testing could be offered if desired.

Case 2

A 13-day-old full-term baby girl was seen after ophthalmology was consulted to evaluate for leukocoria. Her parents reported "white pupils" in both eyes since birth but stated that she responds to light. There is no family history of childhood cataracts.

Her pregnancy was uncomplicated with no history of intrauterine infections. She was born at an outside hospital by spontaneous vaginal delivery, with heart rate deceleration and cooling protocol initiation given concern for hypoxic encephalopathy. She completed a sepsis rule out and was monitored for supraventricular tachycardia (SVT) by cardiology. An echocardiogram done on day 4 of life showed a patent foramen ovale with normal anatomy and systolic function. The SVT was successfully treated with Sotalol. On examination, she had a non-dysmorphic and symmetric

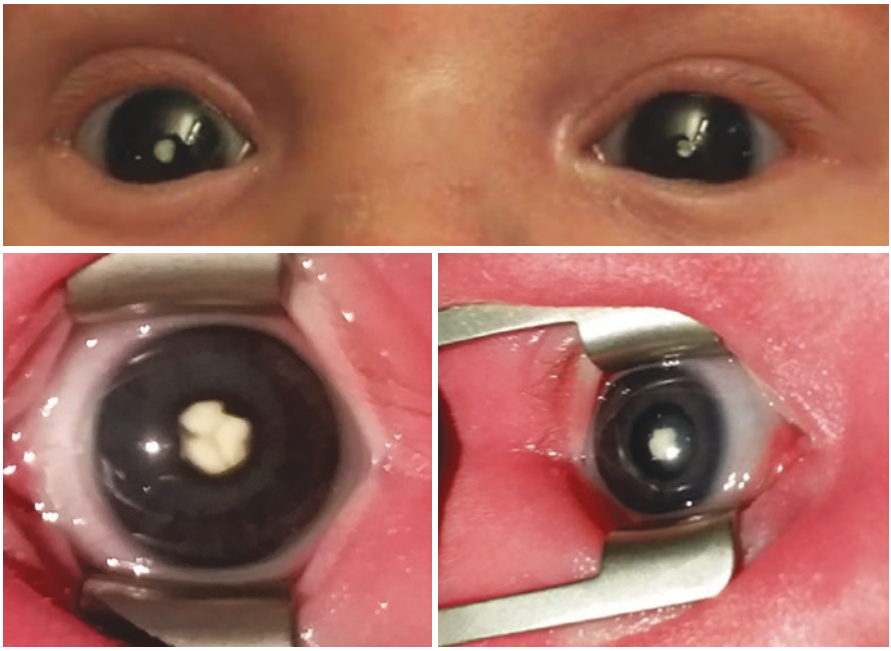

Fig. 4.2 Top photo shows preoperative miotic pupils with dense white central cataracts of patient no. 2. Bottom photos of the same patient show intraoperative dense white chalky cataracts, the left greater than the right, with poor pupillary dilation

facial appearance. On ocular exam, she unreliably blinked to light in both eyes, pupils were very small and poorly reactive, and there was no red reflex bilaterally. Hand light examination showed clear corneas (9 mm) and normal anterior segments, with central dense chalky white cataracts and poor dilation bilaterally (Fig. 4.2). There was no view to the posterior pole; B-scan ultrasound showed attached retina, clear vitreous, and no masses. Given the lack of family history for childhood cataracts, a systemic infectious, metabolic, and genetic workup was performed.

The genetics and metabolism teams examined the baby. She underwent evaluation for metabolic causes of cataract not included in her state newborn screening, such as galactosemia (urine galactitol) and Lowe syndrome (urine and plasma amino acids, serum electrolytes). There are 32 disorders included in required newborn screening in Massachusetts, which can be found in detail through the New England Newborn Screening Program [25]. The genetics team did not find any additional dysmorphisms and ordered genetic testing using a Cataract Panel (GeneDx, https://www.genedx.com/test-catalog/available-tests/cataract-panel/). The methods utilized by this panel are expected to detect over 99% of sequencing variants present in the covered regions of the majority of genes known to be associated with cataract. This patient had a heterogeneous mutation in the major intrinsic protein (*MIP*) gene, which was reported as a "likely pathogenic variant – most likely consistent with diagnosis of autosomal dominant MIP-related cataract." The *MIP* gene encodes the major intrinsic protein of the ocular lens fiber membrane, also

referred to as aquaporin-0. MIP belongs to the aquaporin family of water channels. It is involved with water transport across lens cortical fiber cell membranes and may be involved in fiber-fiber adhesions, functions which are important in keeping the lens transparent [26]. The genetics team determined that this mutation was the most likely etiology of her cataracts, but not as a cohesive unifying diagnosis for her history of SVT and perinatal stress requiring protocol cooling. They recommended monitoring head circumference, and if there were out of proportion growth or craniosynostosis, they would re-evaluate for other genetic causes of her constellation of symptoms.

At 34 days of life, this patient underwent bilateral (immediate sequential) and uncomplicated 20-gauge cataract extraction with primary posterior capsulectomy and anterior vitrectomy. She was left aphakic and fitted for aphakic contact lenses in each eye the following week (Silsoft base curve 7.5, diameter 11.3 mm, power +32.00 diopters in each eye).

Comment Once an infant has been diagnosed with bilateral cataract that is nonfamilial, prior to proceeding with surgery, we recommend confirmation from the

Table 4.1 Stepwise approach to ancillary testing for bilateral infantile cataracts

History	Inquire about pre- or postnatal exposures, infections, trauma	
	Examine parents and siblings to determine hereditary etiology	
	Communicate with pediatrician regarding what testing was done in newborn screen and if any concerns for associated medical conditions	
Physical exam and systemic associations	Dysmorphic facies or other organ systems	
	Failure to thrive	
	Developmental delay	
Laboratory testing[a]	Infectious	Titers for toxoplasmosis, rubella, cytomegalovirus, herpes simplex, syphilis (VDRL)
	Metabolic	Galactosemia: urine-reducing substances; erythrocyte galactokinase (less common *GALK1* deficiency)
		Lowe syndrome: urine and plasma amino acids; serum electrolytes
		Others: glucose, calcium, phosphorus
		Chest X-ray: cardiomyopathy (Sengers syndrome)
Genetic testing	Next-generation sequencing[b] or	
	GeneDX Cataract Panel	

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[a]When not included in newborn screening
[b]Musleh et al. [20]

pediatrician that the child is well and non-dysmorphic. If there is any concern for a syndromic or metabolic diagnosis, referral to a geneticist is recommended and further workup tailored to the findings. If the child is well, confirmation that the newborn screening tests have ruled out conditions that may require intervention or add risk to the anesthetic or surgical exposure should also be performed. Table 4.1 lists the classic and more common conditions that can be identified in these patients.

Pediatric cataracts occur in 1–15 per 10,000 births, with 60% being bilateral [9]. A detailed family history (possibly with examination of family members) and a prenatal history and current health history are important. Collaboration with the pediatrician to determine whether further testing for metabolic, genetic, or syndromic disease is needed is paramount to successful management. Completion of a thorough ocular and physical examination can provide helpful clues in identifying cataract cause and targeting the workup. Care is required to identify and treat underlying systemic conditions, when present. Genetic testing is available and may help identify causes for "idiopathic" cases.

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