Update on Congenital Cataract

11

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11.1 Introduction

Vision 2020: The Right to Sight has identified the control of congenital cataract and blindness in children as a priority in its global initiative to reduce the burden of avoidable blindness [1]. Congenital cataract (CC) (Fig. 11.1), which refers to the opacity of the lens detected at birth or in early childhood [2] is a leading cause, along with retinopathy of prematurity (ROP), of treatable childhood blindness worldwide [3].

The epidemiological impact is often confused in the literature [4–6] but it is estimated that the prevalence of children worldwide that are bilaterally blind from cataracts is about 190,000, and an additional number suffer from partial or unilateral cataracts that cause differing levels of visual impairment [1, 7]. Of 1.4 million children worldwide who are blind, cataract is responsible for an estimated 14% [8]. A blind child is more likely to live in socioeconomic deprivation, to be more frequently hospitalized during childhood, and to die in childhood than a child not living with blindness.

Since Dr. Gregg Norman published the observation that CC is associated with material Rubella infection in 1941, a great deal of progress has been made in the epidemiology, etiology, diagnosis, and management of CC. This update on congenital cataract and the related burden of visual impairment focuses on emerging knowledge and therapies for children with severe visual disabilities. Much of this progress has been in recent years, and the goal of this chapter is to provide an update.

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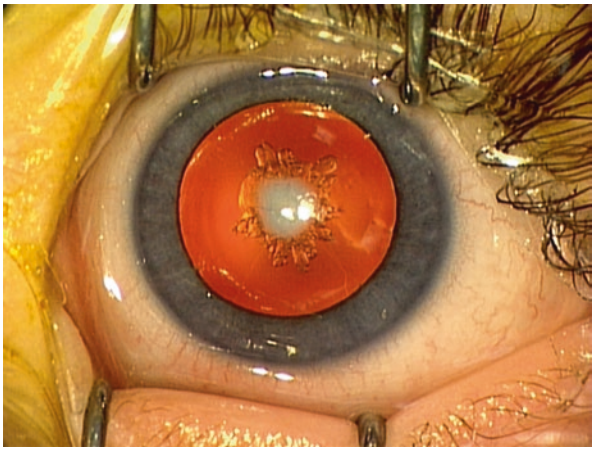

Fig. 11.1 Central congenital cataract with clear peripheral lens

11.2 Epidemiology

In most studies, cerebral visual impairment and optic nerve anomalies remain the most common causes of childhood severe vision impairment and blindness, while retinopathy of prematurity (ROP) and cataract is now the most common avoidable causes [9–11]. The constellation of causes of childhood blindness in lower income settings is shifting from infective and nutritional corneal opacities and congenital anomalies to more resemble the patterns seen in higher income settings.

In a study of 231,000 children (aged under 16 years) examined in a population-based study, 8 per 10,000 had vision worse than 3/60; almost half of the blind children had retinal disorders, the most common being retinopathy of prematurity. Cataract (28%) and globe anomaly (11%) were the next most common blinding disorders [10, 12]. These findings have been reproduced with minor variations in the incidence of etiology in multiple studies [12].

In a meta-analysis of the epidemiology of CC, the prevalence was estimated to be 4.2/10,000 children worldwide, which makes it a rare disease based on WHO (<6.5/10,000) and European (<5/10,000) standards. In contrast with common disorders, rare diseases have a much lower population prevalence, resulting in greater demands for documenting disease data and a greater reliance on accurate and comprehensive epidemiological information [13].

The incidence, or the number of new cases that develop over a specific time period (typically 1 year), is a harder figure to obtain. Estimates suggest an incidence of bilateral CC between 2.2 and 3.2/10,000 births per year worldwide, or about 20–30,000 new cases globally per year [14, 15].

Although relatively rare compared with age-related cataracts, CC tends to alter the quality of sensory information available to the child during sensitive periods of visual system development and causes irreversible visual defects [16, 17]. Children who are born blind and are not effectively treated have a lifetime of irreversible

blindness. The resulting loss, expressed in blindness years, has a dramatic impact on the socioeconomics of the child, family, and community.

Genetic, metabolic, traumatic, and infectious factors can all lead to childhood cataracts.

Unfortunately, few large-scale epidemiological studies have provided a complete synthesis of the population, disease etiology, heritability of the evidence, and epidemiological traits. The common understanding for many years has been that roughly one-third of CC cases are inherited, one-third are associated with environmental risk factors and the remaining one-third are idiopathic [18]. However, more recent examination of the data suggests that idiopathic CC accounts for as much as two-thirds (62%) of all CC cases, while hereditary (22%) and nonhereditary (11%) are substantially less [13]. These older studies did not have the benefit of newer genetic testing. At the time of this writing, mutation screening of inherited congenital cataracts has identified nearly 200 locus and more than 100 causative genes, which are well summarized in the "Cat-Map" website (http://cat-map.wustl.edu/) (Messina-Baas and Cuevas-Covarrubias, 2017; Shiels et al., 2010). Newer genetic analysis would predict that, in the isolated bilateral CC category, 75% of cases have a genetic etiology [19]. Evaluation of the idiopathic aspects of this condition leave room for progress in this area of research in terms of both cataractogenesis and clinical considerations.

At this point, it may be beneficial for the reader to segregate bilateral and unilateral CC into separate categories of CC. The heritability, etiology, and visual consequences roughly separate along this distinction. Bilateral CC constituted only a slightly higher pooled proportion (54%) than unilateral CC. However, the proportions were quite different in subsets formed according to hereditary factors. Unilateral CC constitutes 56% of idiopathic CC but just 6% of hereditary CC [14, 20].

Bilateral congenital cataracts are often associated with monogenetic gene defects, systemic diseases, and infectious factors. Unilateral cataracts are more often related to local anomaly, such as persistent fetal vasculature (PFV). PFV is a congenital ocular dysgenesis in which the hyaloid embryonal vasculature is unable to regress completely [21, 22]. PFV was found in 22–46.5% of unilateral congenital cataract patients undergoing surgery [20, 23, 24]. A number of pathogenic gene mutations have been identified in animal models with bilateral PFV, including CRYBA3/A1, TSPAN12, and FZD5, but no genetic basis has been identified for unilateral PFV [25–27].

In regard to comorbidity associated with CC, isolated CC accounted for the highest percentage (62%), followed by CC associated with ocular disorder (23%), and CC associated with systemic disorders (17%) [13].

While the amassed knowledge on the genetics of congenital cataracts and associated systemic diseases has expanded dramatically in the last two decades; [4, 28] there is limited knowledge on the prevalence of systemic disorders in patients with unilateral congenital cataracts.

In the infantile aphakia treatment study (IATS), a very low percentage 8/217 (3.7%) of patients with a significant unilateral cataract had a significant associated

systemic disorder. Including two patients with Down's syndrome, one with cerebral atrophy and delayed maturation, and one with Conradi–Hunermann syndrome, one patient with a mitochondrial disorder, another with autism, and one with Stickler syndrome. Finally, one adopted patient was found to have a profound hearing impairment and the cataract was presumed to be the result of congenital rubella [23].

Of the infectious causes of CC, Rubella and Herpes simplex virus (HSV) are the most common etiology [29, 30]. Congenital Rubella Syndrome (CRS), is the most important worldwide preventable cause of CC. In many countries, Rubella (German measles) has been virtually eliminated through childhood vaccination programs. The Rubella infection in adults is generally mild; however, if infected in the first trimester the rate of fetal infection is 90% with severe fetal detrimental effects. It is estimated that more than 100,000 infants worldwide are born each year with CRS [31]. According to a survey of the member countries in the World Health Organization (WHO), the number of countries that have incorporated rubella-containing vaccines into their routine national immunization programs increased from 83 in 1996 to 148 (76%) of countries in 2016. As of December 2016, the WHO Region of the Americas and the European Region have established rubella elimination goals, verified by the Region of the Americas in 2015 [32]. The South-East Asia region has rubella/CRS reduction goal (95%) by 2020; [33] the Western Pacific Region has established a rubella elimination target without a specific date, and the Eastern Mediterranean and African Regions do not currently have elimination targets (https://www.cdc.gov/vaccines/pubs/surv-manual/chpt15-crs.html).

Despite the great efforts made to improve the management of CC and a giant leap in surgical techniques, CC treatment is among the most difficult and cost-intensive interventions in ophthalmology, and the etiology of this condition remains largely unknown [34].

11.3 Genetics

Over the last 10 years, the progress and integration of diverse genetic approaches have accelerated the research of inherited cataracts to try to identify genetic defects that are associated with a specific phenotype. The molecular basis of congenital cataract is generally considered monogenetic, with causative mutations identified in genes encoding many different proteins.

Monogenic CC is of particular importance, as it is associated with high recurrence risk in affected families. It has been estimated that approximately 22–40% of CC are caused by single-gene mutations [13, 35, 36]. Monogenic CC is a genetically heterogeneous disorder, as mutations in over 100 genes have been associated with isolated pediatric cataract (Cat-Map; https://cat-map.wustl.edu/). Notably, mutations in a particular CC gene can result in different lens phenotypes even among subjects from the same family, this clinical heterogeneity precludes a genotype–phenotype correlation which could facilitate molecular diagnosis [37, 38].

The clinical phenotypes of childhood cataract are complex and diverse, categorized under a variety of classifications according to the lesion location and

morphology, with a significant disparity in clinical outcome and visual compromise. Morphologic subtypes include anterior lenticonus, anterior polar, anterior pyramidal, anterior subcapsular, posterior polar, posterior lentiglobus, posterior lenticonus, posterior subcapsular, nuclear, cortical, lamellar, zonular, pulverulent, cerulean, sutural, polymorphic, membranous, and total cataracts [39, 40]. The main phenotypes of CC epidemiologically are (1) total (37%), (2) nuclear (27%), and (3) posterior subcapsular (27%) [13].

Morphology of cataract can help to reveal the cataractogenesis mechanisms in different stages of lens development, and, hence, help with diagnosing the cause and treating the disease properly. However, hereditary cataracts have significant clinical heterogeneity, both genetically and phenotypically, and reveal considerable changes among family members [37].

A great many pathogenic genes and mutations of congenital cataract have been successfully characterized by linkage analysis, DNA probe microarray, gene sequencing, and other screening strategies [35, 41]. Genes responsible for distinct isolated cataract can be divided into five main groups based on the encoded proteins: (1) *Crystallins*: including intracellular lens proteins, (2) *Connexins:* membrane gap junction proteins, (3) *Major Intrinsic Protein (MIP) or Aquaporins:* membrane water channel proteins, (4) *Cytoskeletal proteins:* (e.g., BFSP1 (filensin), BFSP2 (phakinin) and vimentin), and (5) *Transcription factors:* (TFs) (e.g., FOXE3, PAX6, PITX3, and MAFA) [6] see Fig. 11.2.

First-generation sequencing is based on the Sanger chain termination method, while Next Generation Sequencing (NGS), also known as High-throughput

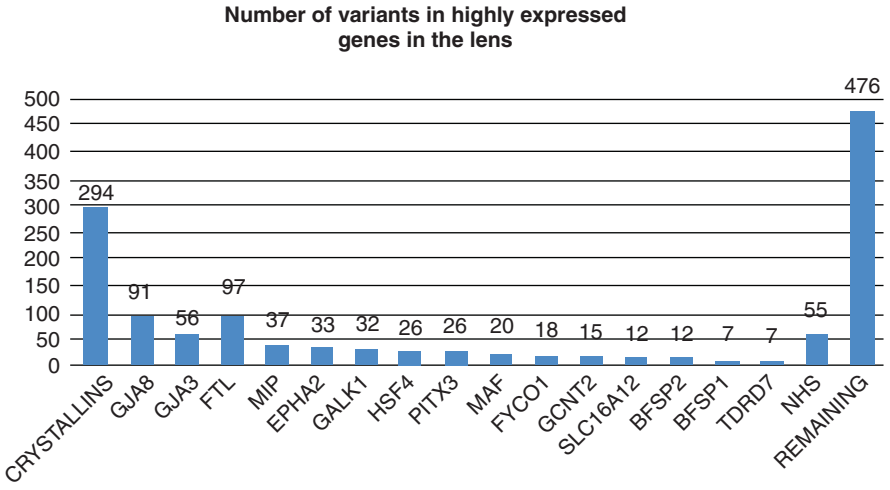

Fig. 11.2 Cataract-causing variants by gene. Total number of 1314 disease-causing variants (novel and recurrent) are shown in various highly expressed genes to date (http://cat-map.wustl.edu/), including crystallins, gap junction proteins, membrane proteins, developmental and cytoskeletal proteins in the lens; the remaining 476 variants are found in various other genes important for the normal function of the crystalline lens

sequencing, has been gradually applied in congenital cataract detection [19], such as genome sequencing, whole exome sequencing [42], sure select target enrichment [19, 43], and targeted exome sequencing [44]. NGS improves the yield in diagnosis of small deletions beyond the resolution of microarray and improves the detection of defects in genomically complex regions. NGS, which has gained acceptance as the testing method of choice, has demonstrated the efficiency of gene panel NGS testing in CC diagnosis with impressive mutation pick-up rates, ranging from 70 to 85% for isolated cataract [4, 28, 45], and 63% for syndromic CC [4, 19]. However, this still leaves approximately 25% of bilateral isolated CC of unknown etiology (Fig. 11.3). Moreover, these studies have highlighted the enormous clinical utility of ascertaining the precise cause of CC. Examples of this include where genetic diagnosis has (1): altered the clinical hypothesis regarding predicted mode of inheritance thereby redefining recurrence risk and informing genetic counseling (2); directed clinical management and patient care via presymptomatic diagnosis of significant multisystemic disease (3); diagnosed an unsuspected metabolic disease that is amenable to treatment where early treatment significantly reduces morbidity [46]. Furthermore, a study of 50 patients by CC panel testing found that over 15% of cases were due to mutations in genes associated with inborn errors of metabolism [19].

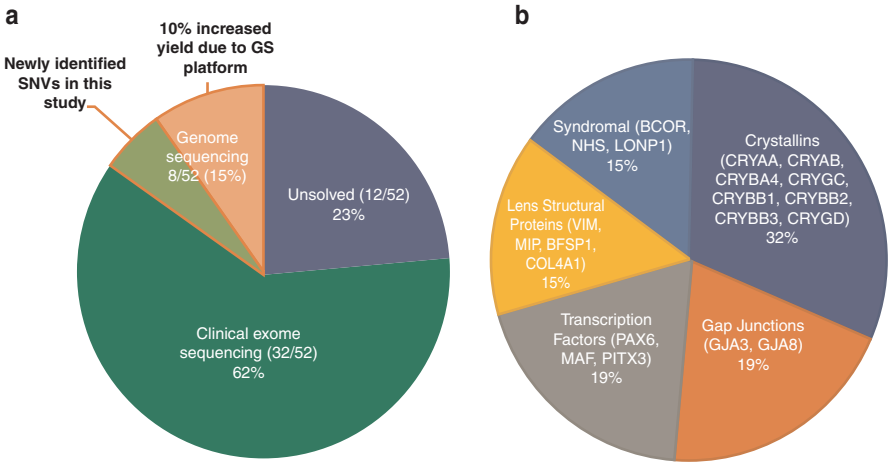

Fig. 11.3 Overall yield and gene breakdown in combined cataract cohort of 52 patients. (**a**) The overall yield in the congenital cataract cohort studied in this and our previous publication. In 52 patients, pathogenic variants were found in an additional 10% of cases using the genome sequencing (GS) platform due to detection of small copy number variants (CNVs) (2), indels in repetitive regions (2), and single-nucleotide variants (SNVs) in GC-rich regions (1). Additional SNVs were identified in this study due to the use of an extended gene list (2) and identification of an SNV in a known disease gene in a previously uninvestigated case (1). In total, 62% were identified previously on clinical ES. (**b**) The chart demonstrates the overall breakdown, by gene category, in the entire cataract cohort. Over half the responsible variants are still in the frequently reported crystallin and gap junction genes. However, an increasing role of rarely reported genes such as the transcription factors and lens structural proteins has been found. Also, syndromal genes are increasingly reported, even in cases referred initially as nonsyndromal cataracts. (From Ma [47])

The Cat-Map and iSyTE (integrated Systems Tool for Eye gene discovery) databases are effective tools for exploring the molecular genetics and mechanism of inherited cataracts. The Cat-Map, a web-based database and chromosome map, summarizes the spectrum of mutations associated with hereditary and age-related cataract and updates the data in real-time [48] (Cat-Map, http://cat-map.wustl.edu/). Further, the eye gene expression database iSyTE uses a microarray data set of the mouse embryonic lens to identify genes associated with lens growth and cataract, and to indicate the potential regulatory pathways of these genes [49, 50].

The crystallin proteins constitute 90% of the proteins in lens fibers [51], and were discovered and named nearly 125 years ago by Morner as the main structural proteins of the ocular lens [52]. The lens fibers are a long-lived, ever-growing avascular capsulated organ and the crystallin protein is essential for maintaining transparency [53–56]. To maintain its life-long transparency and optical function crystallin organization in the lens is critically important. Mutations in the crystallin genes may affect the stability, solubility, and oligomerize feature of these proteins, disrupt the ordered arrangement, and result in lens opacity [57].

Crystallin proteins are divided into Alpha α, Beta β, and Gamma γ proteins. The α-crystallins constitute approximately 35% of the lens. They are heat shock proteins that contribute to the refractive power of the lens and act as a molecular chaperone [52, 56]. α-crystallins are the most abundant water-soluble proteins in the lens and their specific, closely packed arrangements play an important role in maintaining the lens transparency [56]. β and γ crystallins are very similar in structure, and together form a superfamily, called βγ-crystallins that share a common polypeptide chain fold [58].

Major intrinsic protein (MIP) is also known as aquaporin-0 due to its function as a voltage-dependent water channel and adhesion molecule [59]. It is only expressed in terminally differentiated fiber cells and is the most abundant integral membrane protein in the lens. They provide nutrients to central fiber cells and maintain homeostasis [60]. Genetic studies reveal mutations inherited in an autosomal dominant fashion.

Connexins also known as hemichannel are hydrophilic gap junctions that provide the transfer of small molecules and maintain lens transparency [61]. Three connexins have been identified in the lens: connexin 43,46, and 50. They are also critical in eye development and the lens growth process and have been identified in nuclear CC and CC with microcornea [62, 63].

Cytoskeleton proteins interact with crystallins in the lens cells to define the structural framework of the cell [64]. Cytoskeletal proteins include actin filaments, microtubules, and intermediate filaments and provide the structure for lens fiber cells [65]. Beaded filament structural protein interacts with crystallin α and currently 14 mutations have been described contributing to inherited cataract [5].

Transcription factors regulate embryonic lens development. Mutations in the *HSF4, PITX3, MAF, and FOXE3* genes lead to cataracts, anterior chamber dysgenesis, and developmental ocular anomalies. Currently, mutations in transcription factors are associated with 19% of CC [45, 47].

Congenital cataracts universally occur in an isolated pattern but can also be a part of syndromes affecting other systemic tissues. Genes responsible for major syndromic cataracts include GLA (Fabry's disease) [66], OCRL (Lowe syndrome) [67], GALK117q (galactosemia) [68], NHS (Nance–Horan cataract–dental syndrome) [69], and PAX6 (aniridia) [70, 71]. Besides, pediatric cataract may also be one component of syndromes related to chromosomal disorder or DNA repair defects, such as Down syndrome, WAGR syndrome, Cockayne Syndrome, and Prader-Willi syndrome [72–74].

11.4 Treatment

11.4.1 Goals

The principle of treatment for congenital cataract is to preserve and restore vision, prevent permanent vision loss or blindness, and reduce the incidence of amblyopia and maximize vision potential. It is well-established that there is a "critical period" for the development of vision and that without early treatment (in many cases 6 weeks of age) permanent damage begins to accrue to the developing visual system. This critical period requiring treatment before the onset of the beginning of permanent visual deprivation has been categorized as a bilinear/plateau model [75]. During the first 14 weeks after birth vision recovery is reduced by one line for every 3 weeks in delayed treatment, from 14 to 40 weeks of age, vision recovery reaches a plateau. It should be understood that delayed treatment may result in irreversible vision loss.

While complete CC requires emergent pediatric ophthalmologic care, some morphologic types of partial CC, that have less potential damage to the developing visual system, such as anterior polar, or punctate cataract, may not require immediate surgery [18, 76].

11.4.2 Early Detection

The most critical factor in the successful treatment of CC remains early detection and early treatment [77]. Untreated dense CC (Fig. 11.1) leads to irreversible neurophysiological changes and sensory deprivation amblyopia. Associated adverse outcomes such as nystagmus and strabismus commonly coexist [17]. Therefore, it is imperative that affected infants are referred promptly to centers able to manage them appropriately. Optimal surgical results require a very early referral and intervention. The best outcomes in dense unilateral CC follow surgery and optical correction before 6–8 weeks of age [16]. More recent studies of dense bilateral CC suggest that visual outcomes follow a linear model, correlating to the length of visual deprivation, but that best results occur in those infants operated on by 8 weeks of (corrected) age [78–80]. By 8–10 months of age a child with a complete CC may no longer be capable of recovery of visual function due to irreversible changes in brain development.

Delayed detection occurs in all communities; however, it is probably highest in the developing world. The mean delay to an appropriate treatment center, 39–49 months, is often far too late for effective treatment and restoration of vision [81–83].

Community education and training of primary health care providers may be the single most critical factor in reducing worldwide childhood blindness from CC. Effective screening should be performed within the first 72 h of birth and again prior to 6 weeks of age with a direct ophthalmoscope and the "red reflex test." [3, 77] It is important for health care providers to have resources for detection, recognize the urgency of treatment for CC, and be provided with tertiary centers capable of treatment. Additionally, community education is necessary for families to reduce educational barriers, cultural barriers, and provide access to care.

Finally, advances in 3D ultrasound have recently made it possible to diagnose CC in utero [84]. For families at risk, prenatal genetic testing of fetal DNA is possible to diagnose the likelihood of CC [85].

11.4.3 Evaluation

While identification and timely surgical intervention in infants and children are crucial for the preservation of sight, precise diagnosis is also important. CC is a highly heterogeneous disorder associated with a number of systemic diseases. Etiologies may include trauma, maternal infection, intrauterine chemical or drug exposure, biochemical disturbance, and genetic variation (chromosomal abnormalities or single-gene mutation-associated disorders). Pinpointing a diagnosis, even with the use of clinical algorithms, is complicated, and often protracted [17, 18].

A comprehensive history, including extended family history, is important. Examination of family members can be of critical importance because autosomal dominant cataract with significant phenotypic heterogeneity is responsible for a vast majority of inherited CC. Historically clinicians have pursued biochemical, genetic, clinical, and imaging tests either simultaneously or consecutively and iteratively [77]. Investigations performed will typically include chromosomal analysis and a "TORCH" screen to look for evidence of intrauterine infection with toxoplasmosis, rubella, cytomegalovirus, and herpes. Biochemical tests including urinary assays of amino acid profile, oligosaccharides, organic acids, and reducing substances together with blood tests for plasma amino acid profile, liver function tests, renal profile, and assay of Gal-1-P-uridyl transferase are often performed [4].

11.4.4 Morphology

In the management of CC, the morphology of the cataract is very useful because quantification of visual acuity in a preverbal child is often not possible and is associated with a significant overlay of amblyopia or associated neurodevelopmental impairment. The phenotypic classification is based on location of the opacity and

size and can be categorized into eight subtypes including (1) total, (2) anterior polar, (3) cortical lamellar, (4) Fetal nuclear, (5) posterior polar, (6) posterior lentiglobus/lenticonus, (7) subcapsular, and (8) persistent fetal vasculature (PFV) [18]. Many CC, if left untreated will slowly become diffuse, total cataracts.

In the Toddler Aphakia and Pseudophakia study (TAPS), the cataract morphologic characteristics for bilateral CC were classified as nuclear (43%), cortical and lamellar (32%), total white or mature (4%), posterior capsular or subcapsular (4%), posterior lenticonus (4%), anterior capsular or subcapsular (1%), ectopia lentis et pupillae (1%), and unknown (11%). Microphthalmia was detected in 117 eyes (50%). Microcornea was present in 19 eyes (11%), and other anterior segment abnormalities were present in 12 eyes (7%) [86].

Twenty-four children (25%) in this series demonstrated bilateral cataracts associated with chromosomal and neurodevelopmental anomalies. The IoLunder2 study reported a systemic disorder or neurodevelopmental impairment in 55% of children with bilateral cataracts [78]. These studies suggest a higher rate of ocular and systemic comorbidity than is present in the epidemiologic literature [13].

11.4.5 Surgical Treatment

Assuming the CC is identified through early detection and appropriate timely referral is achieved, the successful management of CC is one of the most time-intensive and resource-demanding treatments. Currently, even though a high percentage of CC has a monogenetic etiology, there is no theoretical treatment paradigm that would allow for the restoration of lenticular clarity through gene replacement. Treatment for the foreseeable future relies on surgical management to (1) restore clarity to the optical media, (2) manage optical (refractive) rehabilitation, (3) Prevent and treat amblyopia, and (4) constant surveillance for secondary complications.

Age at surgery is a known determinant of successful visual outcome. Consensus in the literature recommends surgery at less than 6–8 weeks of age for unilateral cataract and 6–10 weeks of age for bilateral cataract surgery with less than 2 weeks between operations [18, 77, 87]. In an attempt to improve visual outcomes in this visually handicapping condition, the IOLunder2 study* and Infantile Aphakia Treatment Study (IATS) have confirmed and refined the management strategy for treatment of children with this condition [78, 88].

Modern surgical management relies on the vitrectomy machine to perform the major components of the surgical procedure. The vitrector can be used to perform the capsulorhexis (vitrectorhexis), lensectomy, posterior capsulotomy, and core vitrectomy of the anterior hyaloid face. Since secondary opacification of the capsule and anterior hyaloid occurs with a rate of essentially 100% in cases of congenital cataract, removal at the time of primary surgery is the standard of care [89, 90]. Standard vitrectomy instrumentation has relied on a 20-gauge system. Due to low scleral rigidity in children, surgical wounds tend to leak, creating an unstable anterior chamber during surgery. Advances in surgical vitrectomy intervention have

recently been refined to smaller gauge systems with recent addition of 23-, 25- and 27-gauge instrumentation [91, 92]. Smaller surgical wounds, accompanying the smaller instrumentation, have allowed for increased stability of surgical intervention.

Anterior capsulotomy is generally performed by curvilinear capsulorhexis using a 20- or 23-gauge microfixation forceps, or by vitrectorhexis [18]. Femtosecond laser-assisted capsulorhexis has been used in pediatric cataract surgery but is associated with the negative consequences of posttreatment enlargement of the capsule opening and the necessity for cantholysis to accommodate the laser equipment [93].

Determination of the use (or not) of an intraocular lens (IOL) has received considerable study. In children with a normal-sized eye under 7 months of age, the capsule measurement is approximately 7 mm in diameter [77]. Primary IOL implantation in children under 7 months of age is therefore not only challenging but did not confer any improvement in visual outcome and was associated with a higher rate of adverse events and need for additional surgery in the IATS [88, 94, 95]. These findings were supported by the IOLunder2 study [78]. However, IOL implantation in children over 7 months of age has been shown to confer a decreased risk of adverse events that is equivalent to IOL implantation in children over 2 years of age [96, 97].

Visual Axis obscuration (VAO) is a known common adverse event following pediatric cataract surgery, which increases in rate inverse to age at surgery. This effect is explained by a "scaffold effect" of the implanted IOL in the child's eye [77]. Thus, the use of primary IOL implantation in children under 2 should be accompanied by an informed consent process of the potential need for additional surgical intervention.

Determination of the power of the IOL implantation is additionally a more complex process. Growth of the eye and changes in the corneal curvature during childhood will change the refractive outcome as the child matures. The elements that are crucial in selecting the initial postoperative refractive goal are IOL calculation, amblyopia management, anisometropia management, and the logarithmic growth of the eye [98]. Biometry in CC is typically performed in the operating room. IOL calculations in children are of lesser accuracy than in adults, influenced by greater errors of biometry and the lack of an IOL formula for children. The IOL formulas shown to have the least error and greatest reproducibility in children have been the SRK/T and Holliday 2 formulas [99–101].

Anisometropia is of great concern in children who have unilateral cataract surgery. Optical correction with spectacles in this situation is generally not acceptable due to induced aniseikonia. Aphakic contact lenses are therefore relied on when IOL implantation is not advised. While there are several options for aphakic lens correction, many pediatric ophthalmologists rely on the extended wear "Silsoft" soft silicone lens (Bausch and Lomb) because of the high tolerance and oxygen permeability characteristics [102, 103].

From infancy, the growth of the eye follows a logarithmic curve [104]. This growth results in a myopic shift of the refraction over the first 20 years of life. Predicting the refractive trajectory of the eye is therefore troublesome, leading to the need in some children who undergo primary IOL placement in infancy, for IOL exchange later [88]. Another potential option is an investigational IOL which

involves a two-part IOL that includes an exchangeable optic for refractive management without the need to explant the entire lens [105]. A pediatric IOL selection computer program has been published that allows surgeons to calculate the relative myopic shift in a child who has IOL implantation [106].

11.4.6 Complications

The complications of visual deprivation and secondary amblyopia have been discussed, but despite the relative ability to treat these complications given timely referral, they remain the most visually disabling. Secondary visual axis opacification (VAO) has also been discussed and can occur with or without IOL implantation, but the rate is higher in CC with IOL implantation.

Postoperative open-angle glaucoma is emerging as potentially the most important visually disabling consequence of surgery for congenital or infantile cataract. It has been reported to occur in between 6% and 58.7% of children after cataract extraction, depending on the population studied and the length of follow-up [107–110]. It is insidious, can be difficult to detect, and may occur many years after surgery.

Many factors have been reported to increase the risk of postoperative glaucoma including age at detection of cataract, age at cataract surgery, primary intraocular lens implantation, significant postoperative uveitis, conspicuous family history, and associated ocular malformations, such as microphthalmos or persistent fetal vasculature (PFV) [86, 107, 108, 111, 112]. Despite speculation, IOL implantation has not conferred protection from the risk of secondary glaucoma, with multiple studies showing no associated risk or benefit [77, 113, 114].

Cataract surgery during early infancy is well-established to be the most important factor for the formation of postoperative secondary glaucoma. It should be considered that although younger age at the time of cataract removal can provide better prerequisites for prophylaxis of amblyopia, it also confers a higher risk of the development of glaucoma.

In one study, younger age at surgery and smaller (<9.5 mm) corneal diameter at surgery conferred an increased risk for glaucoma or glaucoma suspect designation (younger age: odds ratio [OR], 1.44; and smaller cornea: OR, 3.95). Multivariate analysis in this bilateral cohort also revealed that younger age at surgery conferred an increased risk of glaucoma. The OR analysis suggested that each month of reduced age increased the risk of glaucoma by approximately 40% [86].

The incidence of secondary glaucoma is unpredictable but constant, the risks include the age at the time of surgery, on the ocular anatomy, and on the follow-up duration. It is advisable that all children should be considered at risk for the remainder of their lives [114].

Strabismus is also a complication of CC. In the IATS trial, strabismus surgery was performed in approximately 50% (with or without IOL) of patients with strabismus by 5 years of age; esotropia surgery was twice as common as exotropia surgery [115]. Additionally, children without strabismus had better visual acuity

than those with strabismus. It has not been known whether better acuity in the treated eye is protective for the development of strabismus or whether straighter alignment improves amblyopia treatment after cataract surgery. In the present study, visual acuity was better in children who did not undergo strabismus surgery than in those who did (0.70/1.10 log MAR, $P = 0.097$).

Anisometropia is a constant postoperative challenge in the optical rehabilitation of children with unilateral CC. In the IATS study, infants that underwent unilateral IOL implantation at primary surgery were noted to have significant postoperative anisometropia, with the treated eye more myopic than the fellow eye in almost all cases. Anisometropia is likely one of the factors that contribute to both amblyopia and decreased binocular function in children with unilateral pseudophakia [116]. It is known that 2 diopters or more of spherical myopic anisometropia and 1 diopter or more of spherical hypermetropic anisometropia significantly increase the incidence of amblyopia and decreased binocular function [117].

Numerous encouraging advances in the recent science behind congenital cataract affords a new window into our management and understanding of this condition, with new insights into the risk factors, pathophysiology, and potential therapeutic strategies. Congenital cataract will remain a challenge for epidemiology, preventability, early diagnosis, heritable etiology, and technical therapeutic management.

The primary goal of preventing or reducing the incidence of congenital cataract development through congenital Rubella and Herpes reduction programs and genetic heritability studies is encouraging. The development of early detection, referral, and treatment programs are critical to the success of the elimination of blindness from CC. Finally, technical advances have made the goal to preserve and restore vision, prevent permanent vision loss or blindness, reduce the incidence of amblyopia, and maximize vision potential, achievable.

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