Childhood Glaucoma

Current Trends and Future Prospects

Yasmine M. El Sayed
Abdelrahman M. Elhusseiny
Editors

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Foreword

Childhood glaucoma is a devastating and frequent cause of childhood blindness worldwide, and it is an important cause of social and occupational disability in adolescence and adult years.

Childhood Glaucoma: Current Trends and Future Prospects is a timely addition and will become an important resource for clinicians and all others caring for childhood glaucoma patients and who are studying the many primary and secondary causes and consequences of this disease. Over the past 80 years, treasured textbooks and chapters have been published and authored by single clinicians, including works by Anderson (1939), van der Helm (1963), Shaffer (1970), Kwitko (1973), Mandel (2006), and Sampaolesi (2009). The authors, Drs. El Sayed and Elhusseiny, have drawn on a distinguished faculty of recognized international contributors to focus on 28 chapters of importance in understanding and caring for childhood glaucoma patients. The combined work of these authors will make this textbook an essential resource for many specialists.

A widely accepted classification of childhood glaucoma is presented, which emphasizes the importance of recognizing the primary and secondary glaucoma etiologies and the frequent association of glaucoma with certain systemic diseases. The book includes an excellent chapter updating the importance of genetic studies, which have aided patient care as well as helped to redefine the classification of many primary glaucomas, especially those associated with systemic diseases. The importance of older and proven glaucoma procedures is considered relative to the choice of promising new surgical alternatives. An important consideration relative to surgical decisions is the highly varied glaucoma mechanisms responsible for childhood glaucomas, which is actively discussed.

I congratulate the authors and contributing chapter authors for the success of their work and look forward to witnessing frequent references to this textbook, for which they should collectively be very proud.

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Preface

Childhood glaucoma is a rare yet serious condition, presenting a myriad of challenges in its management. Beyond the expertise of a childhood glaucoma specialist, a multidisciplinary approach is imperative to ensure optimal care for these young patients, thereby enhancing their outcomes and overall quality of life. Central to this approach is the treating physician, who assumes a pivotal role in the lifelong journey of these cases. Their responsibility encompasses delivering tailored, evidence-based care to each child while also navigating the emotional struggles caregivers may endure. The physician shoulders the weight of burnout resulting from the demanding treatment regimen, frequent examinations under anesthesia, potential surgical interventions, financial strains, and the unpredictable path ahead.

The purpose of this book is to provide a comprehensive guide to childhood glaucoma, grounded in the latest empirical evidence and enriched by the wisdom and insights of experts in the field. Our aim was to cover the full spectrum of childhood glaucoma within these 28 chapters, spanning not only epidemiology and genetics but also embracing clinical and surgical management. Beyond that, we shed the light on the psychosocial and socioeconomic dimensions of this disease. Recognizing the nuanced challenges associated with ocular comorbidities in these patients, we included chapters tailored for non-glaucoma specialists, including cornea, strabismus, cataract, and retina specialists, who share in caring for these children.

Our surgical chapters lay out a stepwise methodology for the glaucoma procedures these patients may require, coupled with pearls of wisdom from seasoned surgeons in these specific procedures. Our aspiration is to provide a learning resource for both novice surgeons seeking to acquire skills in these intricate procedures and for experienced surgeons looking to refine their techniques. The chapter dedicated to minimally invasive glaucoma surgery (MIGS) casts a thought-provoking light on the potential of these tools in managing childhood glaucoma—both in the present and with an eye toward the future.

Presenting this textbook on childhood glaucoma brings us immense joy and pride as we anticipate its pivotal role as a reference for physicians dedicated to caring for this vulnerable patient population. We extend our unending gratitude to the global cohort of experts who generously shared their invaluable knowledge and experiences. Each contribution was enlightening and facilitated a harmonious editing process that minimized redundancy and contradictions. Our heartfelt appreciation goes to all the 62 authors who lent

their expertise to this endeavor. We are equally indebted to the dedicated Springer team, whose professionalism and diligence expedited the publication process, making our shared vision a reality.

Cairo, Egypt — Yasmine M. El Sayed
Little Rock, AR, USA — Abdelrahman M. Elhusseiny

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Embarking on this endeavor to publish this book on childhood glaucoma has been a rewarding and challenging journey for me. I could not have done it without the help and support of many people. I want to express my sincere gratitude and profound appreciation to them.

First and foremost, I would like to express my deepest thanks to my father, *Mohamed,* my mother, *Arwa*, and my brother, *Ayman*, for their unconditional love, encouragement, and sacrifice. They have always been there for me, generously cheering me on, listening to me, and inspiring me. They have taught me the values of hard work, perseverance, and compassion. I owe them a debt of gratitude that no words can express.

I am immensely grateful for my mentor, *Hala Elhilali*, Professor of Ophthalmology at Cairo University, for her invaluable guidance, support, and friendship. Her generosity, perseverance, kindness, and dedication to her field have always been a great inspiration and motivation. She has been and will always be a role model for me. I would like to dedicate this book to my dear husband, *Mohamed Awadalla*, who has been my rock, my soulmate, and my best friend. He has constantly shared his passion and wisdom with me. He has supported me in every way, from the emotional to the practical. Thank you, Mohamed, for your unwavering encouragement to pursue my dreams and for being my partner in everything in life.

—Yasmine M. El Sayed

Working on this book has been a journey filled with countless moments of inspiration, support, and guidance. I am genuinely grateful to everyone who has contributed to bringing this project to fruition.

At the forefront, I want to express my heartfelt gratitude to my wife, *Reem*. Your unwavering belief in me and constant encouragement have been my driving force throughout this endeavor. Your patience, love, and understanding have been my pillars of strength, allowing me to dedicate the time and effort needed to see this book through. To my precious daughters, *Farida* and *Kenzy*, always remember that hard work is the key for success. Your Mom and I believe in you and will always be your biggest supporters. Dream big!

I am also deeply indebted to my parents, *Fatma and Mahmoud*, and my sister, *Ola*, for their endless support and sacrifice. Your guidance and belief in my abilities have been instrumental in shaping the person I am today. I am fortunate to have been guided by remarkable mentors at Abu ElReesh Children's Hospital, Boston Children's Hospital, and the University of Illinois. They generously shared their knowledge and expertise, which have

expanded my horizons and helped me navigate my pathway in the pediatric anterior segment field.

I owe a special debt of gratitude to *David Hunter* and *Linda Dagi*. Your impact on my professional growth is immeasurable, and I am deeply appreciative for your presence in my journey.

I extend my heartfelt appreciation to everyone who has played a role, whether big or small, in shaping this book. I hope this book brings you as much insight and enjoyment as it has brought me in editing it.

—**Abdelrahman M. Elhusseiny**

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Part I

Epidemiology and Types of Childhood Glaucoma

Epidemiology and Classification of Childhood Glaucoma

Elena Bitrian, Rachel H. Lee, and Alana L. Grajewski

Epidemiology of Childhood Glaucoma

Epidemiology of Blindness Due to Childhood Glaucoma

Over one million children under the age of 15 years are estimated to be blind worldwide, three-quarters of whom reside in low-income countries [1, 2]. Nearly 500,000 children become blind yearly, and almost half of these children die within two years due to the underlying systemic conditions associated with blindness [3].

Primary causes of childhood blindness include congenital cataract, corneal abnormalities, retinal dystrophies, and glaucoma [1]. Importantly, an estimated 40% of childhood blindness is thought to be the result of treatable or preventable ophthalmologic conditions [4].

Although childhood glaucoma accounts for roughly 6% of treatable causes of childhood blindness in low- and middle-income countries [3], a disproportionate number of cases are in lower-income countries. In the Western world, blindness due to glaucoma is uncommon. Childhood glaucoma is associated with 2–3% of childhood blindness in the USA and less than 1% in the Netherlands [5, 6]. By contrast, childhood glaucoma is tied to over 20% of cases of childhood blindness in Nigeria and over 40% of cases in India, depending on the study [6–8].

These significant regional variations in the prevalence of blindness due to glaucoma may reflect disparities in access to specialty care for rare diseases. Previous studies estimated that an ophthalmologist in the Western world may encounter one case of childhood glaucoma every 5 years [9]. Due to its relative infrequency, proper diagnosis and treatment may be delayed. Early diagnosis of childhood glaucoma is essential to preventing blindness. Thus, delays could lead to vision loss due to optic nerve atrophy, corneal clouding, and amblyopia [10].

Additionally, differences in cultures or beliefs on the origins of childhood blindness and the accessibility of specialty care may affect families' decisions to seek treatment. For instance, beliefs that childhood blindness is incurable or the result of divine punishment could cause some families to forgo obtaining medical care. For families with limited financial resources, deciding to travel long distances to obtain medical care and invest time and income into diagnosing and

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possibly treating children with blindness may not be feasible [11].

Incidence and Prevalence of Childhood Glaucoma

Large-scale epidemiologic studies on the incidence and prevalence of childhood glaucoma remain challenging because it is a rare condition. These studies are also difficult to compare due to variations in definitions and the ages of individuals included in analyses.

Primary Congenital Glaucoma

Primary congenital glaucoma (PCG) is the most common form of childhood glaucoma [12–14]. Of the sparse epidemiologic studies on childhood glaucoma, the majority estimated the incidence of PCG.

In the British Infantile and Childhood Glaucoma (BIG) Eye Study, investigators estimated that the incidence of PCG to range from 5.4 in every 100,000 live births in Great Britain, 3.3 in every 100,000 live births in Ireland, to 11.7 in every 100,000 live births in Scotland. The incidence of PCG did not vary by gender. Interestingly, the incidence of PCG was higher among infants of Pakistani and Chinese descent (relative risk: 8.8 and 12.7 times, respectively) than among Caucasian infants [14].

Other studies around the world echo similarly low rates of childhood glaucoma. In Australia, PCG may be encountered in an estimated 1 in every 30,000 live births [15]. The majority of these patients were diagnosed at around 18 weeks of age, 70% of whom received glaucoma surgery upon diagnosis. According to a big data study based in South Korea, less than 1% of infants were diagnosed with glaucoma within an 11-year timeframe [16]. These diagnoses occurred after the age of 5 years. In Germany, the total prevalence of all childhood glaucomas remained below 0.2% among patients under the age of 18 years [17].

Given the strong genetic component of the disease, it is unsurprising that the incidence of PCG is higher within populations with consanguineous marriages. For instance, the Slovakian gypsy population has the highest reported incidence of PCG (1 in 1250) [18]. Similarly, in Saudi Arabia, the estimated incidence of PCG is up to 1 in every 2500 [19–21].

Thus, while a rare disease, reported rates of PCG are variable worldwide and increase among populations with higher consanguinity.

Secondary Glaucoma

Secondary childhood glaucomas include a broad spectrum of diseases that are associated with other ocular and systemic diseases or are acquired after birth. These conditions may range from trauma, uveitis, retinopathy of prematurity, to post-surgery (i.e., cataract). While PCG is the most common among non-white infants and children, studies have shown that secondary glaucoma is more common among Caucasian children [22, 23].

Multiple studies based in the USA suggest that secondary glaucoma remains a major cause of childhood glaucoma at tertiary referral centers. In a regional study based in Olmstead County, Minnesota, in the USA, an estimated 2.3 out of 100,000 individuals under the age of 21 had glaucoma. The majority of these were due to secondary glaucoma (1.46 out of 100,000 individuals under the age of 21) related to prior trauma, surgery, drug-induced, or uveitic etiologies [24]. Similarly, studies based in Dallas, Texas, Akron, Ohio, and Miami, Florida, found that secondary glaucoma was the most common type of childhood glaucoma, accounting for up to half of all glaucoma and glaucoma suspect cases [25–27].

Outside of the USA, secondary glaucoma is reported to be a substantial cause of childhood glaucoma in the developed world, accounting for over 40–78% of referrals in tertiary care centers in Brazil [28], Germany [29, 30], and Hong Kong [31].

Thus, while PCG remains the most common type of childhood glaucoma, secondary glaucoma is the most common subtype among children in developed countries.

Definition and Classification of Childhood Glaucoma

The Childhood Glaucoma Research Network (CGRN) created a classification for childhood glaucoma with the aim of unifying the nomenclature in childhood glaucoma through a logical and systematic approach. The classification system was discussed among a group of experts that met at the World Glaucoma meeting in Vancouver in 2013, and a consensus on the classification was achieved [32]. Clinical test cases were used to validate the classification. The CGRN classification is also endorsed by the American Board of Ophthalmology [33].

The CGRN classification starts with the definition of childhood glaucoma and childhood glaucoma suspect. A number of requirements are listed, and if the child meets two or more of those requirements, the diagnosis of glaucoma is made. If only one requirement is met, the diagnosis made is glaucoma suspect.

Definition of Childhood Glaucoma

Childhood glaucoma is defined as two or more of the following:

- Intraocular pressure >21 mmHg.
- Axial length and refractive power: progressive myopia or myopic shift with increasing ocular dimensions that outpace normal growth.
- Cornea: findings including Haab striae, corneal diameter ≥11 mm in newborns, >12 mm in children younger than 1-year-old, and >13 mm in children of any age
- Optic nerve: progressive increase in cup-disc ratio or cup-disc asymmetry of ≥0.2.
- Visual fields: reproducible visual field defect that is consistent with glaucomatous optic neuropathy with no other observable reason for the visual field defect.

Definition of Glaucoma Suspect

Glaucoma suspect is defined as at least one of the following:

- Intraocular pressure >21 mmHg on two separate occasions.
- Axial length: increase axial length in the setting of normal IOP.
- Cornea: increase corneal diameter in the setting of normal IOP.
- Optic nerve: suspicious optic disc appearance for glaucoma.
- Visual fields: suspicious visual field defect for glaucoma.

The Classification Algorithm

Childhood glaucoma is divided into primary childhood glaucoma and secondary childhood glaucoma and includes the following seven categories:

Glaucoma

Primary Childhood Glaucoma
Primary congenital glaucoma (PCG)
Juvenile open angle glaucoma (JOAG)

Secondary Childhood Glaucoma
Glaucoma associated with non-acquired ocular anomalies
Glaucoma associated with non-acquired systemic disease or syndrome
Glaucoma associated with acquired condition
Glaucoma following cataract surgery

Glaucoma Suspect

The algorithm provides a systematic approach or flow chart to be able to achieve the correct classification (Fig. 1). The flow chart starts in the upper left corner with the items that define childhood glaucoma. If two or more of those items are met, the eye is diagnosed as having childhood glaucoma. If less than two items are present, the eye will be considered a glaucoma suspect.

Once the diagnosis of glaucoma has been made, the algorithm offers guidance to classify the types of glaucoma with five questions:

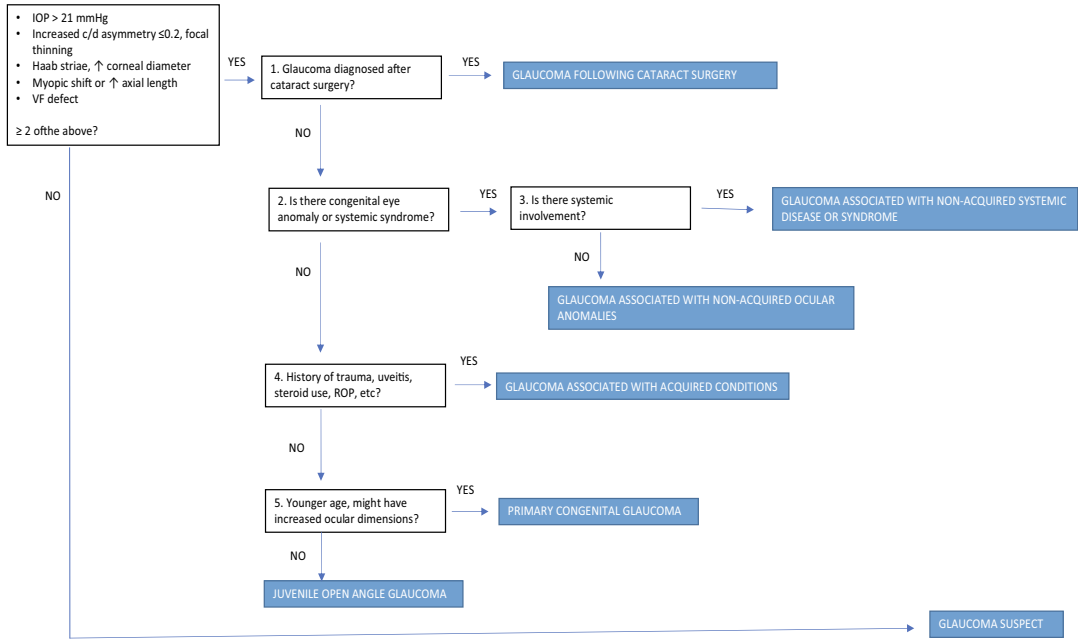

Fig. 1 The Childhood Glaucoma Research Network Classification System Flowchart, adapted from the World Glaucoma Consensus Series-9: Childhood Glaucoma. *c/d* cup-to-disc ratio, *VF* visual field

1. Did glaucoma develop after cataract surgery?
2. Are there congenital ocular or systemic anomalies present?
3. Is there systemic involvement?
4. Is there a history of uveitis, trauma, steroid use, tumor, or retinopathy of prematurity?
5. Is buphthalmos present?

If the patient had cataract surgery and glaucoma was diagnosed only after cataract surgery, this is considered glaucoma following cataract surgery. This category includes congenital idiopathic cataracts, congenital cataracts associated with ocular anomalies or systemic disease, and acquired cataracts. On examination, those eyes might have open-angle glaucoma (>50% angle is open) or angle-closure glaucoma (less than 50% of the angle open).

If the patient has not had cataract surgery, then the presence of congenital eye anomalies or systemic syndromes is considered. If there is systemic involvement, it is called glaucoma associated with non-acquired systemic disease or syndrome. If there is no systemic involvement, it is called glaucoma associated with non-acquired ocular anomalies. Examples of glaucoma associated with non-acquired systemic disease or syndrome are trisomy 21, Marfan syndrome, Stickler syndrome, Homocystinuria, neurofibromatosis, Sturge-Weber syndrome, etc. (Table 1). Examples of glaucoma associated with non-acquired ocular anomalies are Axenfeld-Rieger anomaly, aniridia, Peters anomaly, ectopia lentis, etc. (Table 2).

If there is a history of trauma, uveitis, steroid use, tumor, retinopathy of prematurity, etc., the

Table 1 Glaucoma associated with non-acquired systemic disease or syndrome. CGRN Childhood Glaucoma Research Network, adopted from the World Glaucoma Consensus Series-9: Childhood Glaucoma

Examples of glaucoma associated with non-acquired systemic disease or syndrome
Trisomy 21
Connective disorders: Marfan, Weill-Marchesani, Stickler syndrome
Metabolic: homocystinuria, Lowe syndrome, mucopolysaccharidoses
Phacomatoses: neurofibromatoses, Sturge-Weber syndrome
Rubinstein-Taybi
Congenital rubella

Table 2 Glaucoma associated with non-acquired ocular anomalies. CGRN Childhood Glaucoma Research Network, adapted from the World Glaucoma Consensus Series-9: Childhood Glaucoma

Examples of glaucoma associated with non-acquired ocular anomalies
Aniridia
Axenfeld-Rieger
Peters
Congenital ectropion uveae
Iris hypoplasia
Microphthalmia
Oculodermal melanocytosis
Persistent fetal vasculature
Posterior polymorphous dystrophy
Ectopia lentis

category is called glaucoma associated with acquired conditions.

The absence of the above anomalies with buphthalmos present is PCG. If there is no buphthalmos and glaucoma developed in an older child, the category is JOAG.

Use of the CGRN Classification

Since the consensus on the CGRN classification in 2013, this nomenclature has become widely accepted by organizations of clinicians and researchers, including the American Academy of Ophthalmology. Language unification allows a more precise, descriptive, and non-overlapping classification for the different categories of childhood glaucoma. Hoguet et al. retrospectively reviewed the charts of children diagnosed with congenital glaucoma and reassigned the 26 different diagnoses initially given into the 7 categories of the CGRN classification [34]. This helped to avoid overlapping categories and implemented a system that is easy to use and unifies the previous older nomenclature. Lopes et al. performed a similar study in a Brazilian tertiary hospital and found that 48% of the diagnoses were reclassified into the 7 CGRN categories. Currently, recent publications on pediatric glaucoma research use the classification, and it has become widely accepted [35–37].

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Primary Congenital Glaucoma

Daniel M. Vu, Sylvia L. Groth, and Ta Chen Chang

Introduction

Primary congenital glaucoma (PCG) can be a devastating condition that typically presents in the neonatal period or early childhood (before age 2). PCG is attributed to dysfunction of the trabecular drainage system and often needs urgent, repeat surgical intervention. According to the Childhood Glaucoma Research Network (CGRN) consensus statement, PCG diagnosis is given when exam signs meet the definition of glaucoma (optic nerve damage, high intraocular pressure [IOP], buphthalmos, etc.) and there are isolated angle anomalies and no other systemic or ocular entities are deemed responsible for the elevated IOP effects on the eye [1].

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Epidemiology

PCG is the most common type of pediatric glaucoma. It has variable incidence based on geographic region but is seen roughly in one of 10,000–20,000 live births in Western countries [2]. This increases to 1 in every 2500 or 8000 births in Saudi Arabia and the Middle East, respectively [2]. High consanguinity leads to a higher incidence in regions such as Saudi Arabia [3]. Roughly 65–80% of cases are bilateral, and there is a 3:2 ratio in male-to-female cases in the USA and Europe [4, 5].

Genetics

Though most cases of PCG are sporadic, about 10% of cases are familial, with variable levels of penetrance and a recessive pattern of inheritance [6]. Though the discovery is ongoing, the best-described gene mutations in PCG patients are cytochrome P450 1B1 (*CYP1B1*), latent transforming growth factor beta binding protein 2 (*LTBP2*), and tunica interna endothelial cell kinase (*TEK*) [7].

The gene *CYP1B1* is the most widely identified genetic cause of PCG, specifically locus GLC3A [5, 8–11]. *CYP1B1* belongs to the cytochrome P450 family, which codes for membrane-bound oxidase enzymes involved in metabolism, among other functions. Though most cytochrome

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P450 is highly concentrated in the liver, CYP1B1 is commonly found in other tissues, including the lung, colon, kidney, and eye [12]. The mechanism by which PCG develops with this mutation is still uncertain, but recent studies indicate that the enzymes may be essential for developing the trabecular meshwork [13, 14]. Therefore, a mutation in this gene may lead to trabecular dysgenesis and result in elevated IOP. Migration of neural crest cells is necessary for angle development, and it occurs in the third trimester of pregnancy. Mutations in *CYP1B1* can produce arrest of this migration, likely contributing to the dysfunction in the outflow system [15].

In addition, *LTBP2* is adjacent to *CYP1B1* and has been linked to PCG [16]. *LTBP2* codes for extracellular matrix proteins, which are thought to be involved in cell adhesion and elastin microfibril assembly [7]. It is present in tissues throughout the body, including in the anterior chamber and zonules, which may be where the mutation impacts the eye structures and causes elevated IOP. Finally, *TEK* regulates angiogenesis and is most prevalent in blood vessels and lymphatic endothelia. It is also present in Schlemm's canal. Mutation in this gene may induce glaucoma by inhibiting the normal aqueous outflow pathway [17].

MYOC, which codes for the myocilin/trabecular meshwork-induced glucocorticoid response protein, also accounts for a small percentage (about 5%) of PCG cases [18, 19]. Though other genes and loci have been identified with links to PCG, additional work is needed to elucidate their involvement.

Pathogenesis

The pathogenesis of PCG is still uncertain but largely believed to be isolated to the trabecular outflow pathway. In the 1950s and 1960s, Barkan and Worst proposed the presence of a thin membrane overlying the outflow system [20, 21]. Despite extensive histologic examination, no membrane has been identified [4, 22]. Anderson's landmark work details the development of normal neonatal development and those with PCG. He tracked the movement of the ciliary process (CP) away from the underlying trabecular meshwork in development. The samples of children with PCG demonstrated an arrest of the normal posterior sliding of CP, resulting in CP overlapping part of the trabecular meshwork and inhibiting the function of the outflow pathway [23].

Diagnosis and Classification

The classic symptom triad of photophobia, epiphora, and blepharospasm may be the presenting symptoms of PCG. Children are also brought in for other complaints, such as the parents believing the eyes appear large, a white appearance of the cornea, or bluish discoloration of the sclera. All these signs can be an indication that the IOP is elevated. Though an early onset of PCG can portend a worse prognosis, a missed diagnosis can result in very poor outcomes.

PCG is a clinical diagnosis. Since examination in the clinic can be limited, patients are typically brought to the operating room for an examination under anesthesia (EUA) soon after presentation. Important data to collect include external examination, IOP, corneal diameter, axial length, anterior chamber abnormalities, gonioscopy, pachymetry, and a posterior segment exam if visible. If there is no view of the posterior segment, B-scan ultrasonography should be done. Ultrasound biomicroscopy (UBM) of the angle can also be helpful. More details on what to look for on the exam are discussed below.

Based on the CGRN classification, PCG is categorized based on the age of presentation. This is divided into neonatal or newborn onset (birth to 1 month), infantile (>1 to 24 months), and late-onset or late-recognition (>2 years). Infantile-onset describes the majority of PCG cases diagnosed, and the outcome is slightly better than those that are diagnosed within the first month of life. Late-onset or late-recognition is when the diagnosis is made after 2 years of age. Cases that have typical signs of PCG (buphthalmos, Haab's striae) but normal IOP, no secondary causes of possible prior IOP elevation, and no