Review Article

Taiwan J Ophthalmol 2024;14:190-196

Access this article online

Quick Response Code:

Website: http://journals.lww.com/TJOP

DOI: 10.4103/tjo.TJO-D-22-00096

Primary congenital glaucoma: We are always on the way

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Abstract:

Primary congenital glaucoma (PCG), a developmental glaucoma occurring due to angle anomaly, earns growing concerns among ophthalmologists for its vision-damaging attribute. The incidence of PCG varies among races and geographic regions and is mostly genetically associated. Theories have been posed in attempt to address the etiology of this congenital maldevelopment and in the meanwhile providing evidence for feasibility of PCG surgeries. In regard to the clinical aspects of this entity, both the clinical characteristics and general principals of management are introduced, with angle surgeries highlighted for clarifying details including their success rates, key points for a successful surgical intervention, postoperative management, and follow-up strategies. Taking patients' vision-associated quality of life into consideration, we stressed that further perceptual learning and low vision rehabilitation are momentous. However, much has yet to be elucidated in respect of the truly comprehensive pathogenesis underneath as well as means by which clinical outcomes of PCG can be further improved. We are now looking forward to innovative therapeutic approaches like gene therapy in specific genes in the future, with the hope of improving their life-long visual quality in those young patients.

Keywords:

Angle dysgenesis, angle surgeries, postoperative follow-up, primary congenital glaucoma

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Submission: 29-07-2022
Accepted: 24-08-2022
Published: 12-12-2022

Introduction

Primary congenital glaucoma (PCG), one of the major causes of childhood visual dysfunction, is a developmental glaucoma occurring due to maldevelopment of the trabecular meshwork (TM) and anterior chamber (AC) angle that precludes aqueous humor drainage.[1] It is typically recognized at birth or in early childhood without other associated ocular or systemic abnormalities.[2] Its early onset and devastating effect on patients' future quality of life urge for more concerns on this childhood anomaly.

The prevalence of PCG varies among races, geographic regions, and the frequency of consanguinity. It lies in 1 per 10,000 live births in Western countries, 1:3300 at Andhra Pradesh in India, 1:2500 in Middle East countries, and the highest of 1:1250 in Gypsy of Slovakia.[3] As for Chinese, the prevalence among the Han population is about 1:5000–1:25,000.[4] More large epidemiological studies and updated results are expected.

For better understanding of PCG, more insights into the etiology, pathogenesis, clinical characteristics, and treatment are essential, aiming to deal with this congenital abnormality promptly and properly.

Etiology and Pathogenesis of Primary Congenital Glaucoma

Genetic involvement of primary congenital glaucoma

As a primary congenital disorder, it is estimated that 10%–40% of PCG patients are familial and show autosomal recessive inheritance patterns.[5] Several genes at different loci have been reported, among which the three most well-known

How to cite this article: Yang H, Lu W, Sun X. Primary congenital glaucoma: We are always on the way. Taiwan J Ophthalmol 2024;14:190-6.

implicated genes are cytochrome P450 family I subfamily B polypeptide 1 (*CYP1B1*) located in the 2p21 (GLC3A), latent transforming growth factor β-binding protein 2 (*LTBP2*) located at 14q24 (GLC3D), and myocilin (*MYOC*).[5] Another recently reported protein product was angioprotein receptor tunica interna endothelial cell kinase (TEK) encoded by *TEK* gene.[6] Given that the functions of protein products vary, the underlying genetic mechanisms involved in PCG could, to some extent, be explained by the dysfunctional proteins that interfering either the outflow pathway[7] (specifically the TM[8] or the Schlemm's Canal[9]) or ciliary zonule formation and thereafter lens structure.[10]

Among all the genes mentioned above, *CYP1B1* turned out to be the most frequent cause of PCG worldwide, as 20%–90% of familial PCG cases and up to 27% of sporadic cases map to this gene. 17.2% of Chinese PCG patients carry *CYP1B1* mutation.[4] To date, there are nearly 200 pathogenic variants in *CYP1B1* listed in the Human Gene Mutation Database, while discovery of more novel mutations is on the way,[4] accompanied by growing evidence on the relationship between different genetic patterns and clinical manifestations. Just as our statistical analysis revealed, patients with *CYP1B1* mutations tended to have earlier onset age and higher corneal opacity score.[4] However, controversy remains in regard to intraocular pressure (IOP),[11,12] corneal diameter, cup/disc (C/D) ratio, number of surgery required, bilateral incidence,[12] and disease severity[13] between mutation-positive and mutation-negative patients. In other words, the heterogeneity of gene mutation patterns, even within the same locus, tended to result in variations of the phenotype.

The clinical significance in recognizing the role of these genes paves the way for the early diagnosis and future development of gene therapies in PCG, yet to date, there is rarely any specific gene therapy developed for this multifactorial group of diseases. Nevertheless, as a major trend for the treatment of most genetic diseases, gene therapy is likely to occupy a place in the future management of PCG, e.g., through stem cells expressing wild-type *CYP1B1* to rectify specific mutant.[14]

Pathogenesis of primary congenital glaucoma: Theories and hypotheses

Although widely acknowledged that angle structure malformation and congenital AC angle dysplasia were culprits for PCG,[15,16] the exact pathogenesis of PCG remains unclear.

With the observation of the shiny appearance at the angle and subsequent falling back of the peripheral iris postgoniotomy, Barkan proposed that an anatomical abnormal "pseudo-membrane" masked the TM with a high iris insertion, obstructing the aqueous outflow.[16] Based on this theory, he introduced goniotomy in 1938, dramatically changing the poor prognosis of PCG.[17] However, detailed histologic studies have failed to confirm this "impermeable membrane." In this regard, other researchers advocated that the so-called membrane observed is actually compacted trabecular sheets that prevents the visualization of normal posterior recess of ciliary body and iris.[18]

Compared with the membrane theory from the perspective of histomorphology, the role of neural crest cells has been highly appreciated. Angle structures mainly derive from neural crest cells,[19] upon which the hypothesis was hold that the immature angle appearance and drainage angle anomaly of PCG was likely due to development arrest of neural crest cells in the third trimester.[20] Others suggested that defects in neural crest cells gene expression also matter.[16,21]

In addition, there are other inconspicuous theories including contraction or separation of angle and ciliary body pushing the TM.[22,23] The latter is supported indirectly by the angle surgeries that work through changing the relationship between the ciliary muscle and the TM. Note that all of the aforementioned theories come down to a matter of trabeculodysgenesis ultimately, corresponding to the type 1 in Hoskins classification system with regard to pathophysiology.[24]

Clinical Characteristics of Primary Congenital Glaucoma

According to the European Glaucoma Society Terminology and Guidelines for Glaucoma (5th edition), PCG can be divided into the following three subtypes depending on the age of onset: (1) true congenital glaucoma (newborn glaucoma), with IOP raised in the intrauterine life and thereafter diagnosed within 1 month of life; (2) Infantile glaucoma, manifesting between 1 and 24 months after birth; and (3) late onset glaucoma, with IOP raised in the absence of IOP-driven ocular anatomic changes presenting at above the age of 2 to puberty.[25] For those spontaneously nonprogressing cases with normal IOP but typical signs of PCG, self-healed PCG was defined.[26] This classification became basis of clinical diagnosis, management decision, and later-on disease prognosis of PCG.

In clinical scenarios, it is accepted that PCG usually occurs within 3 years after birth, and 80% occur in the 1st year of life.[1] The age at first visit ranges from 2 months to 12 years old and averaged at 22.63 months in our previous report.[27] The gender ratio of PCG showed

a male preponderance.[28-30] The manifestation can be unilateral or asymmetrically bilateral, yet bilateral cases dominate with a proportion of 65%~75%, especially among those with *CYP1B1* mutation.[16,29]

PCG occurring in infancy commonly present with one or more of the classic triad of photophobia, epiphora, and blepharospasm,[16] though they commonly give a first impression of enlarged eyeball (buphthalmos) or hydrophthalmos.[23,31] Other signs of PCG include corneal opacity, increased corneal diameter, horizontal or sometimes circumferential breaks of Descemet membrane (Haab's striae, as distinguished from the vertical corneal splits caused by forceps delivery), elevated IOP and optic disc excavation.[32-35]

Primary Congenital Glaucoma: Toward Standard Managements

General principals

Once diagnosed, urgent care should be provided for PCG patients, with surgical intervention being the mainstay strategy. Medical therapy is only arranged as a complement,[16] with β-blockers and carbonic anhydrase inhibitors generally preferred followed by prostaglandin analogues due to their acceptable IOP-lowering effect and limited adverse reactions.[16,36,37] Nevertheless, the alpha-2 adrenergic receptor agonists is contraindicated in infants and must be used with caution in children under 9 years of age, as it may depress central nervous system in young patients.[38,39]

Surgical intervention

In this part, we would discuss briefly various aspects of surgical intervention for PCG patients, giving insight into the means for better clinical outcomes.

Preoperative examinations

When PCG is suspected, it is mandatory to perform the following examination with the help of sedation or general anesthesia in uncooperative young patients.

For IOP measurement, a handheld applanation tonometer is preferred, e.g., Schiötz tonometer, Tonopen tonometer, Icare[1] since regularly used tonometer is unavailable in the supine position. Mind that measurement under prolonged general anesthesia tends to underestimate IOP by around 30%–35%, with a possible exception of ketamine.[40] Therefore, it is suggested to finish the IOP measurement as soon as possible after intubation.

As corneal diameter varies among patients according to disease severity, its measurement is of necessity.[23] A corneal diameter >12 mm in the 1st year of life is highly suggestive of PCG.[39] Both compasses ruler and caliper are universally used for horizontal corneal diameter measurement, and it should also be noted that corneal opacity and other corneal signs (e.g., Haab's striae) should not be missed.

Ultrasonography shows clinical superiority when examining PCG patients with opaque cornea as being able to reveal in-depth structures. A-scan gives details about the axial length (AL), which is also indicative of eyeball enlargement under high IOP.[41] B-Scan confirmed structurally normal posterior segment except for glaucomatous optic excavation. Nevertheless, it is still essential as to rule out posterior neoplasm and other posterior segment pathologies. Ultrasound biomicroscopy (UBM) noninvasively reveals the anterior-segment structures in PCG. Common findings include the anterior insertion of the iris masking the TM, iris atrophy, and anomalously deep AC, while elongation of ciliary process and zonules were also reported,[22] all of which are instructive for further surgical intervention and indicative of PCG prognosis.

Further evaluation with gonioscope under surgical microscope is required if corneal status permits. It not only verifies the high iris insertion and invisible scleral spur-TM with or without mesodermal tissue/pectinate ligaments at the angle hinted by UBM,[39] but is also conducive to the selection of surgical modalities and predicting the surgical effect.

Overview of surgical treatment

Here, we present briefly these widely acknowledged surgical treatments with recent update on both the efficacy and limitations.

Angle surgeries

"Angle surgeries" are those designed to reduce the resistance located between Schlemm's canal and AC through either internal or external approach. Regarding that AC angle structures complete major morphogenesis at birth but continue to develop postnatally, especially during infancy,[42] some advocated that early angle surgeries before the age of 4, particularly during the infancy, would likely stimulate angle re-development and confer them another chance of restoring physiologic aqueous drainage pathway and IOP homeostasis.

Goniotomy

As the earliest practice of angle surgery, it is performed through an internal way under gonioscope. Goniotomy was reported most successful in patients with early recognized and treated PCG,[39] though the success depends greatly on the corneal transparency. In cases with severe corneal opacity, trabeculotomy or microcatheter-assisted trabeculotomy (MAT) is suggested.

Trabeculotomy ab externo

As the name indicates, it reduces TM resistance via an external approach, not only independent of cornea clarity but demonstrating a higher success rate. Nonetheless, creation of a false passage with a probe deviating from the target position will possibly misdirect the trabeculotome into the suprachoroidal space and cause severe complications. Therefore, precisely locating the Schlemm's canal is one of the key points during the surgery.

Gonioscopy-assisted transluminal trabeculotomy and microcatheter-assisted trabeculotomy

Inspired by the higher accumulative success rate of multiple angle operations in PCG, there has been a shift away from conventional angle surgeries to 360° opening of trabeculum as a primary intervention modality either through internal or external pathway, namely gonioscopy-assisted transluminal trabeculotomy and MAT, respectively. By threading 5-0 or 6-0 prolene suture or illuminated microcatheter into the Schlemm's canal and incising circumferentially,[43,44] these new modified procedures raised the surgical success rate to more than 90%.[45-49] In addition, other alterations such as viscotrabeculotomy arose, aiming to increase the success rate and reduce bleeding intra- and postoperatively.[50-52] However, their history is still too short to conclude the long-term efficacy and complications versus conventional angle surgeries in PCG.

Trabeculectomy

As a filtration surgery, trabeculectomy with intraoperative antimetabolites (mitomycin C, MMC) cannot avoid high complication rate and dissatisfactory success rate caused by sclera thinning, robust healing properties, and more difficult bleb managing in the pediatric population.[34,39,53] Compared with trabeculotomy based on our more than 2-year follow-up, the IOP control rate in PCG patients undergoing trabeculectomy was much lower (62.9% vs. 80%~87.5%).[54] Trabeculotomy combined with trabeculectomy is advocated in cases at advanced stages, either for the greater risk of failure from angle surgery alone or to achieve long-term IOP control in refractory patients with neonatal onset. However, there is no direct evidence demonstrating its superiority.[55]

Drainage devices implantation

Although commonly performed in adult glaucoma, glaucoma drainage devices are not preferred in PCG management in respect of children's strong proliferative response postprocedure. However, it has recently been proposed as a better choice for late-onset PCG.

Cyclodestruction

It is traditionally the last resort for both adult and children with absolute glaucoma or refractory PCG for its severe postoperative reaction. Nevertheless, what's encouraging is that newly introduced micropulse transscleral cyclophotocoagulation and endoscopic cyclophotocoagulation have been described as promising alternatives with higher safety, less postoperative inflammation, and thereby less pain or phthisis.

Highlights on traditional angle surgeries

Clinically means to elevate success rate of angle surgeries has long been discussed. Either postoperative topical administration of 1% pilocarpine for 3 months to keep the trabecular incision dehiscence through ciliary muscle and pupil constriction during the healing phase, or steroid applied immediately and for 1 month postoperation to reduce the anterior uveal reaction, is important to maintain a sufficient range of trabecular incision opening. With this, our follow-up data showed a complete success (IOP <21 mmHg without medication) rate of 86.4% and a qualified success (with the application of pilocarpine and timolol) rate of 97% at 1 year posttrabeculotomy, and 80.9% and 87.2%, respectively, at 5 years after surgery.[27,56]

Even so, variations of success rates still exist,[51,57] urging for discovery of underlying factors. The development of Schlemm's canal and disease severity correlates; therefore, factors including patients' age and corneal diameter that imply Schlemm's canal morphogenesis may be good breakthrough points. Quigley has proposed that this success rate seemed to depend more upon the patient characteristics, and the main predictors are the timing of diagnosis and ensuing surgical intervention, with 3-year-old or cases between 1 and 24 months after birth being preferred.[40,58] Our previous studies also confirmed the distinction in success rates between infantile and juvenile surgeries, as a follow-up at 15.2 months showed the rate of 78.2% and of 40% in the two age groups, respectively; and another follow-up lasting a mean of 6.83 years showed the corresponding percentages being 87.2% and 50% (data not published).

With the advances of the genetic perspectives, more was discovered on the relationship between genetic patterns and surgical outcomes. We have reported especially that the combination of preoperative corneal opacity score (adjusted with Haab's striae) and *CYP1B1* genotype can partially predict the outcome of postoperative IOP control.[4] The risk function proposed by our team indicated better surgical controlled IOP among patients with *CYP1B1* mutation and poorer corneal transparency rate.[4] Besides, other studies concluded that earlier onset of symptoms, larger corneal diameter (>14 mm), higher initial IOP, positive consanguinity, ocular axial elongation, and female gender were important predictors of worse probable final outcome in trabeculotomy.[40,59]

Postoperative Evaluation for Primary Congenital Glaucoma Patients

It should be minded that there are still a lot to be managed after surgical intervention.

Follow-up postoperation

PCG patients should be followed up regularly postoperatively, with attention not only to IOP, but to all relevant aspects including but not limited to corneal transparency and diameter, AL and the optic nerve head.

Corneal transparency is the most significant and reliable change at the early stage, and a cornea turning transparent indicates well-controlled IOP. Besides, it relieves form-deprivation in young patients, thereby reducing the risk of amblyopia, which is one of the leading causes of future visual acuity impairment. As for corneal diameter, it is recognized that for those receiving surgery in infancy, especially within 1 year old, the cornea would partly retract due to successful IOP control.[27,40,60] AL, another indicator of IOP at presentation, provides some reference for long-term IOP control, but is less sensitive than corneal diameter.[61]

Although IOP is typically used as an indicator for surgical success, it is not the most ideal parameter early after surgery. According to our study, the eyes with IOP higher shortly after surgery may be related to inflammatory response and surgical trauma.[27] However, the IOP fell back to normal spontaneously in the first 3 months postoperation. Postoperative IOP no more than 30 mmHg should not be judged as failure immediately, nor should it be considered in a hurry for reoperation. Instead, a close observation and follow-up is recommended.

In contrast to adult glaucoma, the papillary excavation or C/D ratio is reversible with IOP normalization after surgery in 40%–70% PCG children due to the elasticity of the scleral canal. This reversal is a helpful criterion for therapeutic success, but was observed exclusively in the 1st year of life. In this sense, time is vital for PCG patients for visual function perseverance before irreversible damage to the optic nerve takes place.

Factors that affect visual function

The visual prognosis of PCG patients depends greatly on the severity of disease at diagnosis and their response to surgery. The foremost mechanism underlying visual impairment would be ametropia, including severe myopia with an incidence at 67%~80% and a mean refractive error of −3.7D due to globe expansion, irregular astigmatism due to Habb's striae, anisometropia especially in unilateral cases, and amblyopia and strabismus happening in about 50% of all cases.[62,63] Definitely, corneal scarring and glaucomatous optic neuropathy also account for visual dysfunction.[64]

Perceptual learning and low vision rehabilitation

After regular follow-up, rehabilitation and perceptual learning are by any means the preferred way of exploiting the residual visual function to the utmost extent for PCG patients. Our team has spent years in the spatial discrimination and fixation stability training in advanced glaucoma. It is noteworthy that glaucoma specialists should be mindful of further improving visual function in controlled postoperative PCG patients, and only then can it be named a complete therapeutic strategy.

Conclusion

PCG, a developmental glaucoma occurring due to angle anomaly, is earning growing concerns on the etiology (especially genetic aspects), pathogenesis, clinical characteristics, and full-course management. Although there's still much to be elucidated, chances are that a more integral view of PCG would finally be formed, fulfilling the aim of receiving satisfactory life-long visual quality in those young patients who were supposed to have a clearer view of the world.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

This research project was supported by the Clinical Research Plan of SHDC (SHDC2020CR6029). The authors were also supported by grants from the State Key Program of National Natural Science Foundation of China (82030027) and the subject of major projects of National Natural Science Foundation of China (81790641).

Conflicts of interest

The authors declare that there are no conflicts of interest in this paper.

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