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Primary Congenital Glaucoma: A Comprehensive Review of Epidemiology, Pathogenesis, Diagnosis, and Surgical Management.

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Introduction and Classification

Primary congenital glaucoma (PCG) is a non-syndromic, potentially blinding ocular disease manifesting in early childhood. It is characterized by elevated intraocular pressure (IOP) and progressive expansion of the globe (buphthalmos) due to isolated goniodysgenesis. By definition, PCG occurs in the absence of other ocular or systemic anomalies and is not secondary to previous ocular surgery. Clinical classification is traditionally based on the age of onset:[1,2]

- Neonatal-onset: Manifesting within the first month of life (0–4 weeks).
- Infantile-onset: Presenting between 1 and 24 months of age.
- Late-onset: Developing between 2 and 18 years of age.From a pathological standpoint, the Hoskins classification remains the clinical gold standard for academic specialists, categorizing the severity of the anatomical malformation.

Epidemiology and Geographical Distribution

The incidence of PCG exhibits profound geographical and ethnic variation, heavily influenced by the prevalence of consanguinity.

Global Incidence and Prevalence

In Western cohorts, the incidence is approximately 1:10,000 to 1:30,000 live births. However, in regions with high rates of cousin-cousin unions, the burden is significantly higher. Saudi Arabia reports an incidence of 1:2,500, while the Slovakian Roma population reaches a peak of 1:1,250.[3]

Regional Data and Demographics

- Egypt: Prevalence is estimated at 1:4,237 live births in the Dakahlia Governorate. Consanguinity increases the risk five- to six-fold.[4]
- China: PCG accounts for 46.07% of all childhood glaucoma cases, with a male-to-female ratio of 2:1.[5]
- Korea: The incidence is approximately 11.0 per 100,000 births.[6]
- Clinical Presentation: In high-prevalence regions (India, Saudi Arabia), the mean age of presentation is 3–4 months, significantly earlier than the 11-month average observed in Western countries.[7]

Genetic Basis of PCG

While often sporadic, PCG follows an autosomal recessive inheritance pattern in over 90% of familial cases. Several genetic loci have been identified as drivers of trabeculodysgenesis.[8]

Pathogenesis: The Arrested Posterior Recession Theory

The primary mechanism of elevated IOP in PCG is a failure of embryological "recession" of the angle structures.[9]

Embryological Context

Normal development involves the posterior migration of the ciliary body and iris root. By the 7th month of gestation, intercellular fenestrations form in the TM, and Schlemm's canal (SC) develops fluid vacuoles signifying active filtration. By term, the iris root should reside at the level of the scleral spur.

Histological Insights (Anderson's Findings)

Anderson's electron microscopy studies demonstrate that in PCG, the ciliary muscle and iris fail to migrate, remaining anteriorly inserted and overlapping the posterior TM. The angle appears similar to that of a 7th or 8th-month fetus.

- The "Barkan's Membrane" Fallacy: Histology has largely debunked the existence of a distinct, imperforate membrane. Instead, the "membrane" seen clinically is a misinterpretation of the innermost trabecular sheet being separated from the underlying disorganized layers.
- Trabecular/SC Changes: The TM beams are thickened with abnormal amorphous collagenous substances. The inner wall of SC is often present but lacks the necessary vacuoles for aqueous passage.[9]

Clinical Evaluation and Diagnostic Criteria

PCG presents with the classic triad of epiphora, photophobia, and blepharospasm.

Diagnostic Thresholds

A definitive diagnosis requires at least two of the following:

- IOP: >21 mmHg (assessed via Tono-pen, Icare, or GAT).
- Corneal Diameter (WTW): >11mm at birth, >12mm under age 1, or >13mm over age 1.
- Axial Length: Progressive myopia or growth exceeding normal age-adjusted parameters.
- Optic Nerve: Progressive increase in cup-disc ratio (CDR), CDR >0.3 in infants <1 year, or CDR asymmetry >0.2.[10]

Examination Under Anesthesia (EUA)

Clinicians must consider the IOP-altering effects of anesthetic agents. Ketamine provides a stable IOP window for the first 8 minutes of induction. Alternatively, Chloral Hydrate is a safe, non-inhalational option for outpatient assessment.[11,12]

Structural and Functional Monitoring

Modern literacy requires the assessment of Bruch's Membrane Opening (BMO) and peripapillary RNFL . Successful treatment often results in the "reversal of cupping" due to the high elasticity of the infant lamina cribrosa. However, even with normalized IOP, amblyopia (secondary to anisometropia or corneal opacities) remains a leading cause of functional vision loss, necessitating aggressive refractive correction and occlusion therapy.

Differential Diagnosis

It is mandatory to distinguish PCG from secondary causes of pediatric glaucoma and non-glaucomatous corneal opacities.[13]

Advanced Ocular Imaging

Imaging is vital when corneal clouding precludes direct visualization.

Ultrasound Biomicroscopy (UBM)

UBM parameters help quantify the severity of goniodysgenesis. Notably, PCG eyes often show reduced Lens Thickness (LT) due to meridional stretching of the globe.[14]

Handheld AS-OCT

AS-OCT reveals a characteristic "flat iris" pattern. Diagnostic cutoff values for PCG include:

- Iris Thickness: Nasal <180 μm; Temporal <231 μm.
- Angle Width: Nasal >33°; Temporal >35°.[15]

Traditional Surgical Management

Surgery is the definitive treatment for PCG. Angle-based procedures are preferred as they target the site of resistance while sparing the conjunctiva.

Goniotomy (Ab-Interno)

This involves an internal 90–120° incision of the TM.

- Prerequisite: Clear cornea for visualization.
- Success: Heavily dependent on the age of onset. For infantile PCG, success is 87.5% if performed after 1 year of age, but drops to 55.6% if performed before 1 year, reflecting the more severe dysgenesis in early-onset cases.[16]

Trabeculotomy (Ab-Externo)

The standard for cloudy corneas. It involves cannulating and severing the inner wall of SC.

- Circumferential Trabeculotomy: Uses a 6-0 Prolene suture or microcatheter for 360° disruption.[17]
- Viscotrabeculotomy: Dilation of SC with viscoelastic prior to incision to reduce resistance.[18]

Combined and Refractory Procedures

Combined Trabeculotomy-Trabeculectomy (CTT)

CTT is indicated for severe cases (WTW >13mm, neonatal onset) or where angle surgery has failed. It provides dual outflow pathways. Success is high initially (79–90%) but may decline to 55% over a ten-year horizon.[19]

Novel Surgical Variation: Saving the Conjunctiva

A modern academic approach involves a combination of nasal goniotomy and temporal trabeculotomy in a single session. This maximalist effort addresses 180–240° of the angle while specifically saving the superior conjunctiva for future filtering surgery or drainage implants, representing a paradigm shift in surgical planning.[20]

Refractory Management

- MMC-Trabeculectomy: Effective but carries risks of hypotony and bleb-related endophthalmitis.[21]
- Glaucoma Drainage Implants (GDI): Ahmed (valved) or Baerveldt/Paul/ClearPath (non-valved). The Paul Glaucoma Implant (PGI) uses a smaller tube to mitigate early hypotony, while the Ahmed ClearPath offers a larger surface area for long-term control.[22]

Modern Minimally Invasive Glaucoma Surgery (MIGS)

The paradigm shift in PCG management is the move toward ab-interno angle surgeries that maximize safety and preserve tissue.

- GATT (Gonioscopy-Assisted Transluminal Trabeculotomy): An ab-interno 360° procedure. It shows an 81% success rate in PCG.[23]

- Trab360 and OMNI: These systems allow for trabeculotomy and viscodilation (viscocanalostomy) to address post-trabecular resistance.[24]
- Kahook Dual Blade (KDB): Unlike incisional GATT, KDB performs an excisional trabeculectomy, removing a segment of TM. This scientific distinction is critical, as excision aims to prevent the closure of the goniotomy cleft, which often leads to late failure in simple incisional procedures.[25]
- Sub-conjunctival MIGS: The Preserflo Shunt (synthetic polymer) has shown a 75% success rate at 1 year in refractory cases.[26]

Conclusion

Primary Congenital Glaucoma requires a meticulous, multi-disciplinary approach. While traditional angle surgeries remain foundational, the shift toward 360-degree circumferential procedures and MIGS—particularly excisional techniques like KDB—represents the modern standard. Preserving the conjunctiva and managing amblyopia are as critical as the initial IOP reduction. Ultimately, the successful management of PCG is defined by the preservation of long-term visual function through timely, anatomically-focused intervention.

List of tables:

Table 1: Hoskins Pathological Classification of Congenital Glaucomas

Type	Pathological Name	Anatomical Anomaly
Type 1	Trabeculo-dysgenesis	Isolated abnormal development of the trabecular meshwork (Corresponds to PCG)
Type 2	Irido-trabeculo-dysgenesis	Abnormal TM development plus iris anomalies (hypoplasia, structural defects, or anomalous vessels)
Type 3	Corneo-trabeculo-dysgenesis	Complex malformations involving the cornea and angle structures (e.g., Peters anomaly)

Table 2: Genetic Loci Implicated in the Pathogenesis of PCG

Locus	Location	Gene Product	Function
GLC3A	2p22-21	CYP1B1	Steroid metabolism; TM collagen fiber development.
GLC3B	1p36	CDT6/ANGPTL7	Extracellular matrix (ECM) organization.
GLC3C	14q24.3-q31.1	Unknown	Pathogenesis currently under investigation.
GLC3D	14q24.2	LTBP2	Elastic fiber organization; ciliary muscle tone.
N/A	9p21.2	TEK/TIE2	Formation and homeostasis of Schlemm's canal.
N/A	1q24.3	MYOC	Myocilin; associated with anterior segment development.
N/A	6p25.3	FOXC1b	Transcription factor for anterior segment development.
N/A	16q24.1	FOXC2b	Mesenchymal development and ocular morphogenesis.
N/A	4q25	PITX2b	Critical for early eye development and angle formation

Table 3: UBM parameters and their changes in PCG eyes

Parameter	Definition	PCG Findings
TIA	Trabecular iris angle	Higher than normal
TMT	Trabecular meshwork thickness	Increased (thick/immature)
IT	Iris thickness at the root	Reduced
CPL	Ciliary process length	Increased
SC Dia	Diameter of Schlemm's canal	Often reduced/collapsed
CT	Corneal thickness	Variable
LT	Lens thickness	Reduced (Stretching)
ZL	Zonular length	Increased

Table 4: Common Causes of Secondary Childhood Glaucoma

Non-Acquired Ocular	Non-Acquired Non-Ocular	Acquired Ocular
Axenfeld-Rieger Anomaly	Down Syndrome (Trisomy 21)	Uveitis
Peters Anomaly	Marfan / Weil-Marchesani	Trauma (Hyphema/Recession)
Aniridia	Lowe Syndrome	Steroid-induced Glaucoma
Microphthalmos / Microcornea	Homocystinuria	Retinoblastoma
Ectropion Uvea	Mucopolysaccharidoses	Glaucoma after Cataract Surgery
Ectopia Lentis	Phacomatoses (SWS, NF-1, NF-2)	Retinopathy of Prematurity (ROP)
PFV / PPMD	Klippel-Trenaunay-Weber	Ocular/Orbital Tumor

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