Developmental Glaucoma & Ocular Hypertension

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Learning Objectives

- Distinguish between congenital, infantile, and juvenile glaucoma
- Differentiate between primary and secondary developmental glaucomas
- Discuss the pathophysiology of developmental glaucoma
- Review the optimal treatment and prognosis of developmental glaucoma
- Define ocular hypertension
- Review major points from the Ocular Hypertension Treatment Study (OHTS)
- Identify key clinical pearls from OHTS

Introduction

- Glaucoma is much less common in children than adults
  - 1 in 10,000 live US births
- Consequence of glaucoma is much more severe in children
- Glaucoma surgery has drastically improved visual prognosis for congenital glaucoma
- IOP control is a lifelong goal requiring perseverance by patients, their parents, and doctors

Congenital Glaucomas

- Group of diverse disorders in which abnormal high intraocular pressure results from developmental abnormalities of the anterior chamber angle
  - May or may not be associated with systemic anomaly
  - Hereditary with variable incidence in different populations
  - M>F

Terminology

- Congenital glaucoma
  - Birth to 3 months
- Infantile glaucoma
  - 3 months to 3 years
- Juvenile glaucoma
  - 3 years to16 years

Pathophysiology

- Exact mechanism of primary congenital and infantile glaucoma unknown
  - Clinical and histopathologic observations of anterior chamber show that anatomic relationship between iris, trabecular meshwork, and ciliary body is immature
  - Principal defect: failure of one or more steps in the normal development of the anterior chamber angle, leading to goniodysgenesis at the level of the TM
- Secondary glaucomas of childhood display profound developmental abnormality of the anterior chamber angle
  - Iridodysgenesis
  - Corneodysgenesis

Prognosis

- Glaucoma present at birth
  - Difficult to treat
  - 50% of eyes become legally blind
- Corneal diameter > 14: poor prognosis
- Infantile glaucoma presenting between 3-12 months of age
  - Favorable prognosis
  - 80-90% have good IOP control after angle surgery
- Vision loss is multifactorial
  - High myopia
  - Corneal scarring
  - Lens subluxation

Epidemiology

- Primary congenital glaucoma
  - 50-70% of the congenital glaucomas
  - 1 in 10,000 births
  - Bilateral in 65-80%
  - 90% are sporadic, 10% are familial
    - Autosomal recessive with incomplete or variable penetrance
  - 20% diagnosed as newborn
  - 60% diagnosed by 6 months
  - 80% diagnosed within 1st year of life
  - Results in blindness in 10% of cases
  - Results in reduced vision in 50% of cases

Presentation

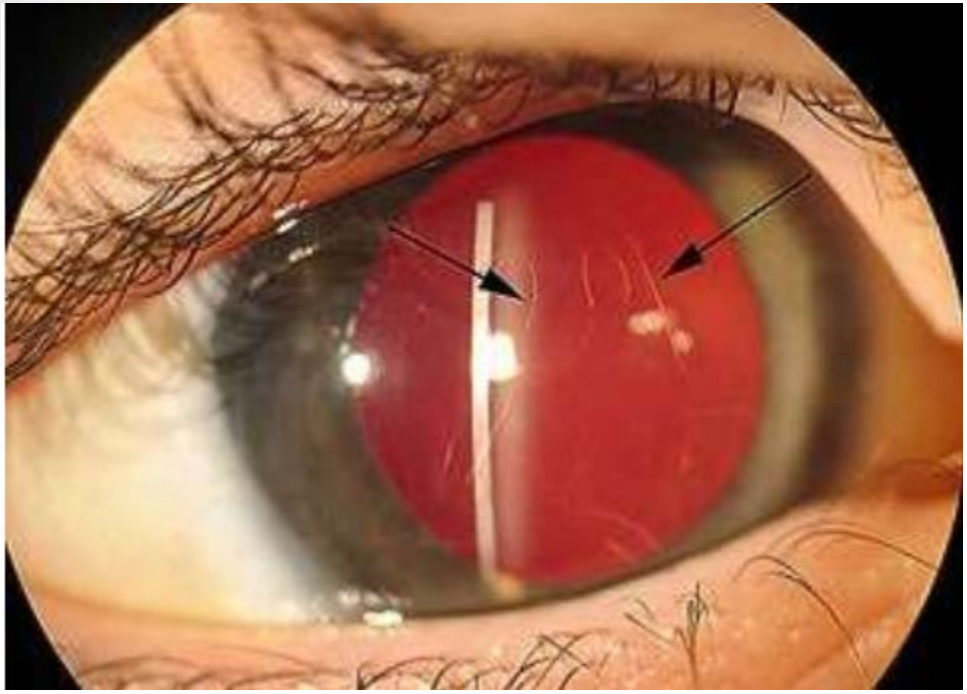
- Signs and symptoms variable depending on child's age, severity of glaucoma, and secondary corneal abnormalities
- Clinical triad
  - Epiphora
  - Blepharospasm
  - Photophobia
- Other findings
  - Myopia
  - Rapid cupping – may be reversible in infants with IOP normalization due to relative immaturity and elasticity of lamina cribrosa

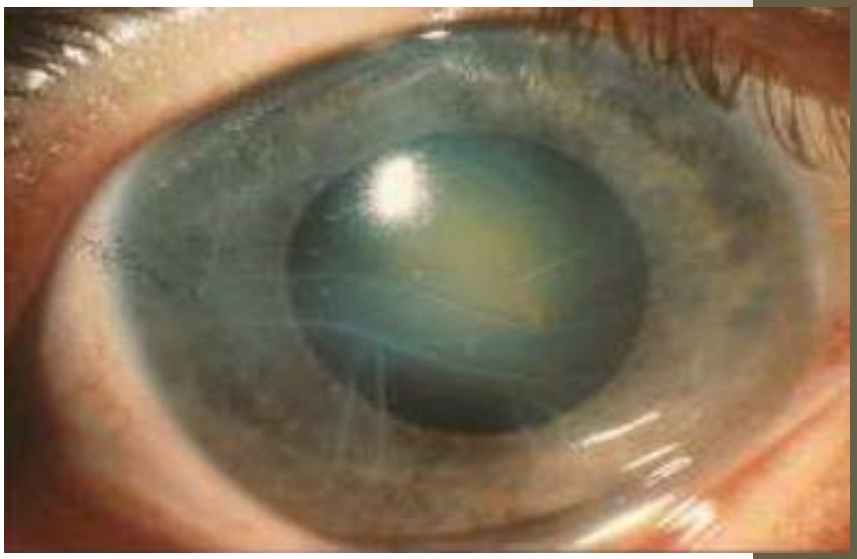
Clinical features

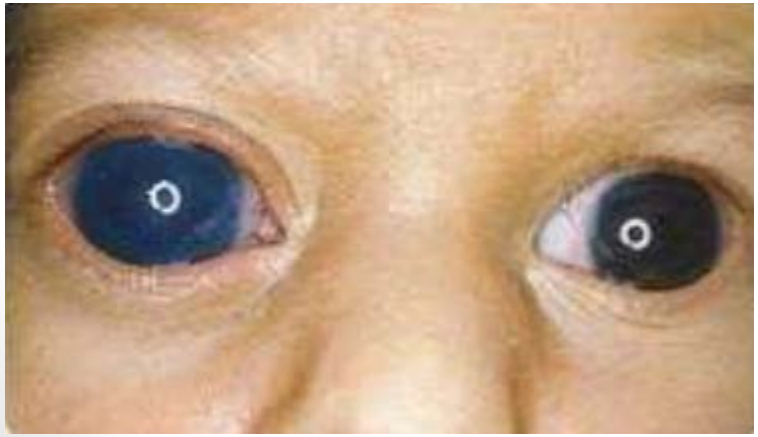
- Corneal edema
- Corneal enlargement
- Descemet's breaks – Haab's striae
- Sclera becomes thin and appears blue due to underlying uveal tissue
- Anterior chamber becomes deep
- Iris may show iridonesis
- Lens becomes flat due to stretching of zonules, and may subluxate
- Axial myopia

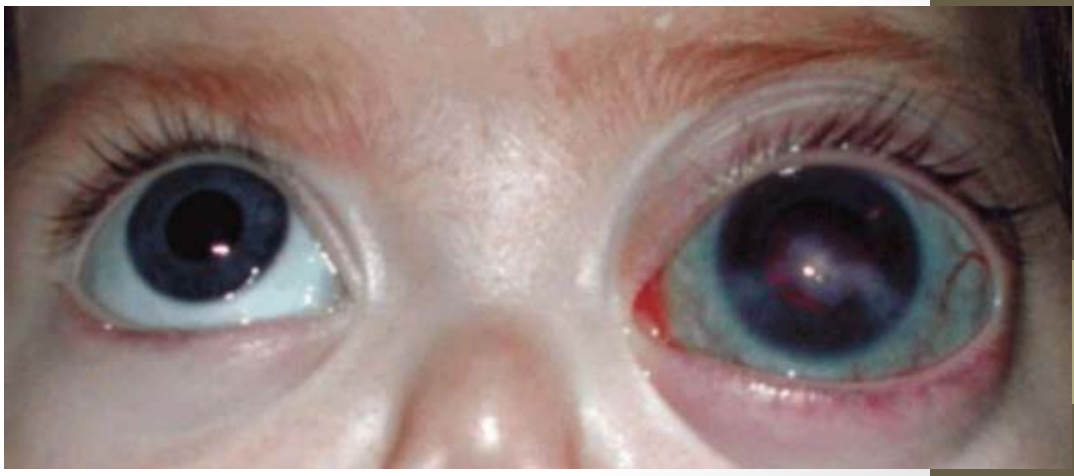
Corneal enlargement

Age	Normal	Suspicious
Birth – 6 months	9.5-11.5 mm	>12 mm
1-2 years	10-12 mm	> 12.5 mm
> 2 years	< 12 mm	> 13 mm









Evaluation

- Typically done under general anesthesia if glaucoma is suspected
  - Caution: most anesthetic agents and sedatives have IOP lowering effects
  - Normal IOP under anesthesia: 10-15 mmHg
- Evaluation must include
  - Corneal diameter measurement
  - IOP measurement
  - Gonioscopy
  - Optic nerve assessment

Differential diagnosis

- **Tearing & conjunctival injection**
  - Nasolacrimal duct obstruction
- **Cloudy cornea & Haab's striae**
  - Corneal dystrophy
  - Forcep trauma
  - Infectious keratitis
- **Enlarged cornea**
  - Primary megalocornea
  - Unilateral high myopia
- **Photophobia & blepharospasm**
  - Uveitis
  - Keratitis
  - Corneal abrasion
  - Cone dystrophy

Secondary developmental glaucomas

- **Anterior segment dysgenesis**
  - Axenfeld Rieger's anomaly
  - Peter's anomaly
  - Aniridia
- **Phacomatoses**
  - Neurofibromatosis
  - Sturge-Weber syndrome
- **Ocular tumors**
- **Inflammatory/infective**
  - Congenital rubella, syphilis
  - CMV
- **Ocular disease**
  - PHPV
  - ROP

Chromosomal/systemic disease

Down's

Turner's

Rubinstein-Taybi

Pierre Robin

Metabolic disease

Lowe's syndrome

Homocystinuria

Mucopolysaccharidoses

Connective tissue disorders

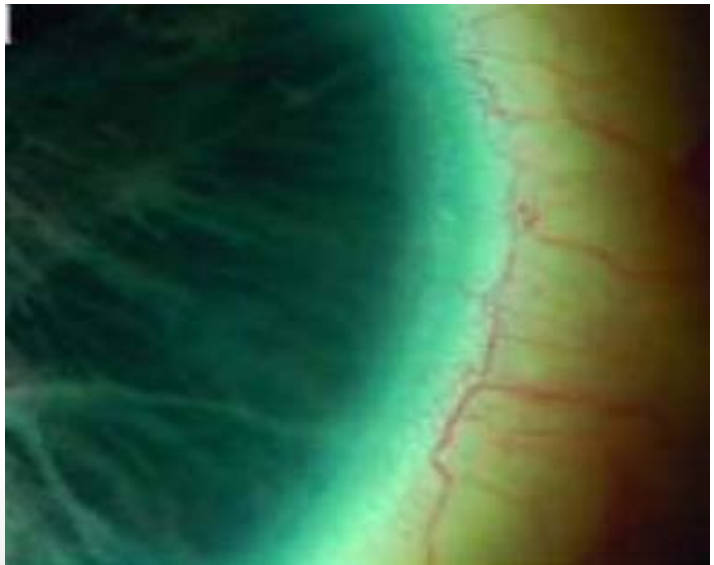
Marfan's

Weil-Marchesani

Ehler-Danlos

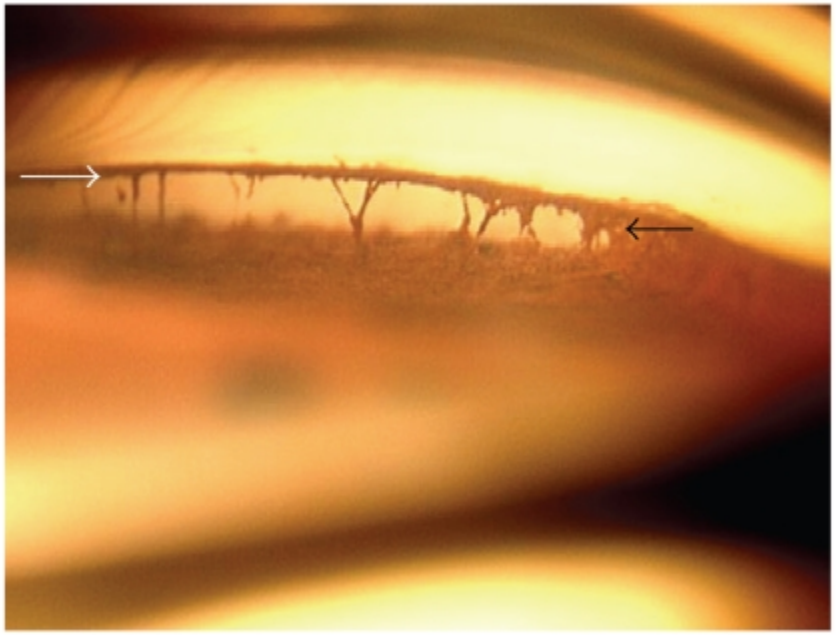
Axenfeld-Rieger Syndrome

- Axenfeld anomaly
  - Anteriorly displaced Schwalbe's line
- Rieger anomaly
  - Anteriorly displaced Schwalbe's line with iris adhesion
- Rieger syndrome
  - Ocular anomalies with systemic developmental defects



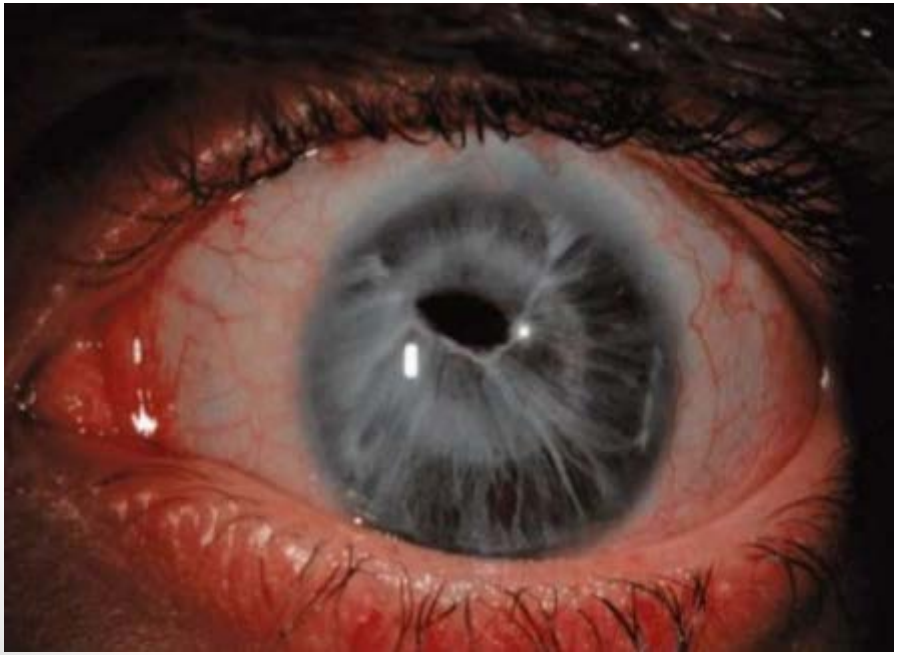
Anterior chamber angle

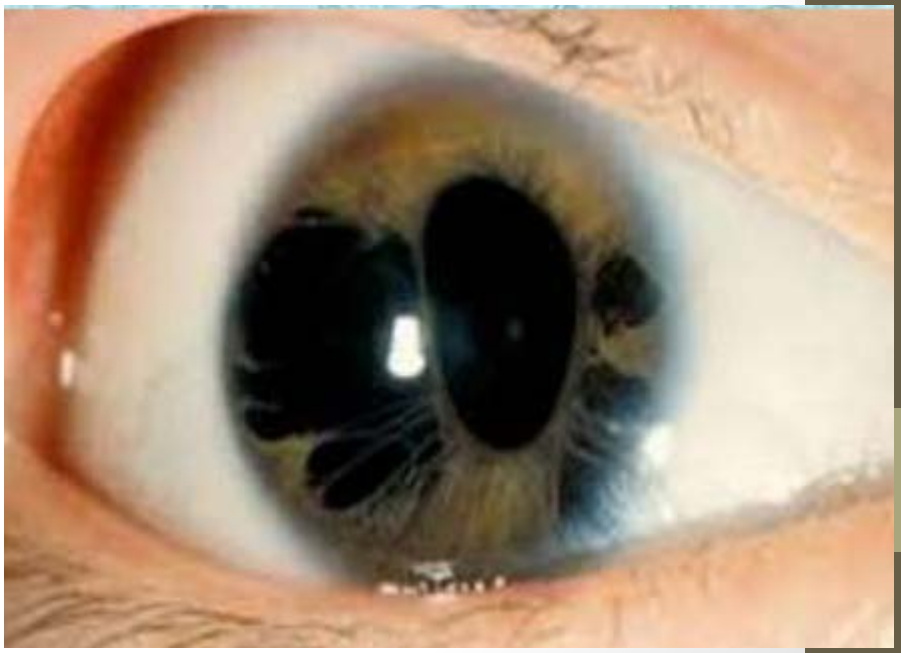
- Prominent Schwalbe's line
- Iridocorneal adhesions
- Anterior chamber angle is open and TM is visible, but SS usually obscured by peripheral iris that inserts into SL



Iris

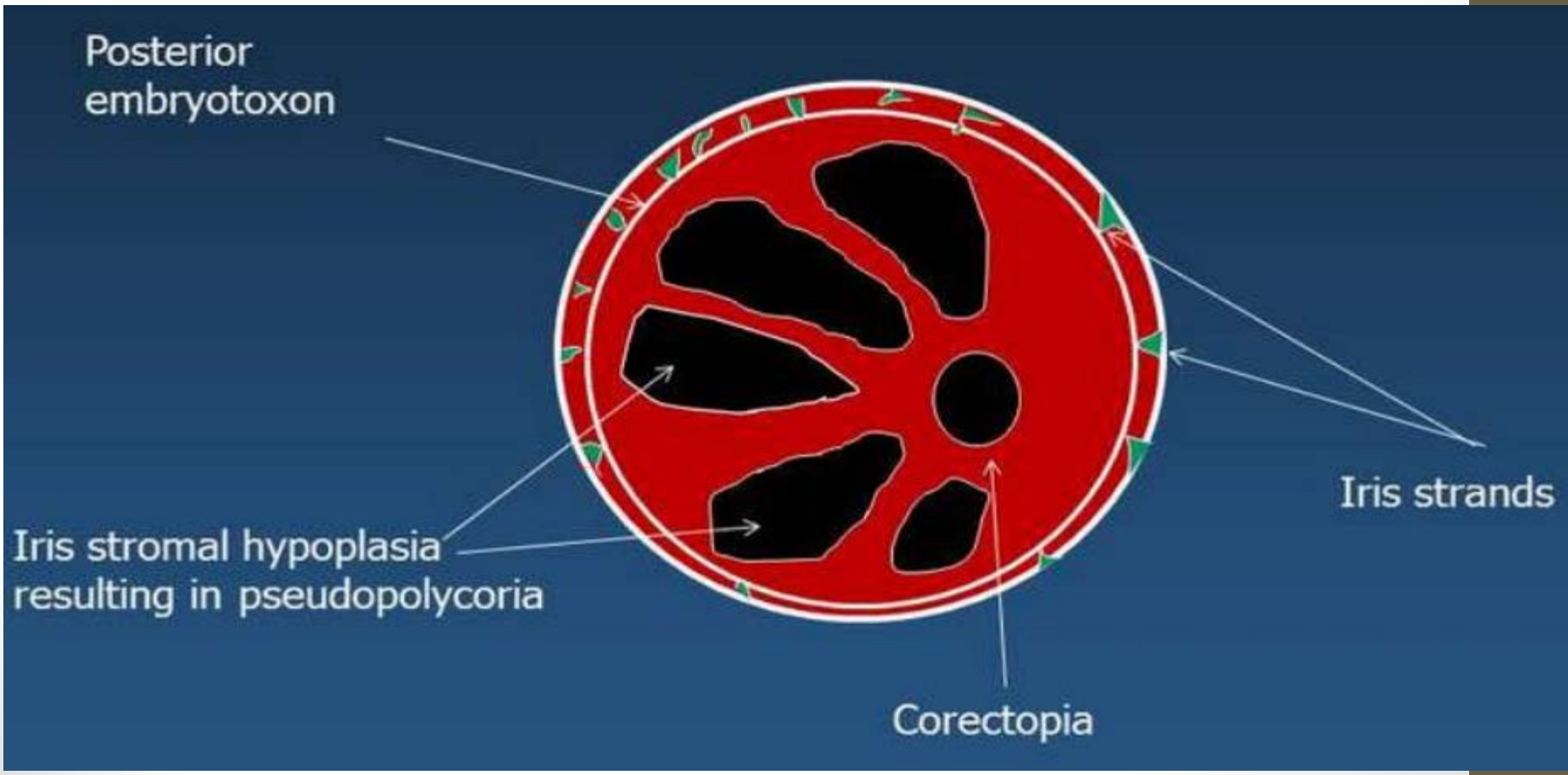
- Mild stromal thinning to marked atrophy
- Corectopia
- Ectropion uveae





Axenfeld-Rieger Syndrome

- 50% will develop glaucoma, typically in childhood or early adolescence

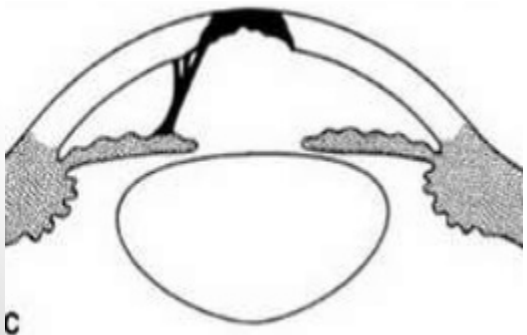


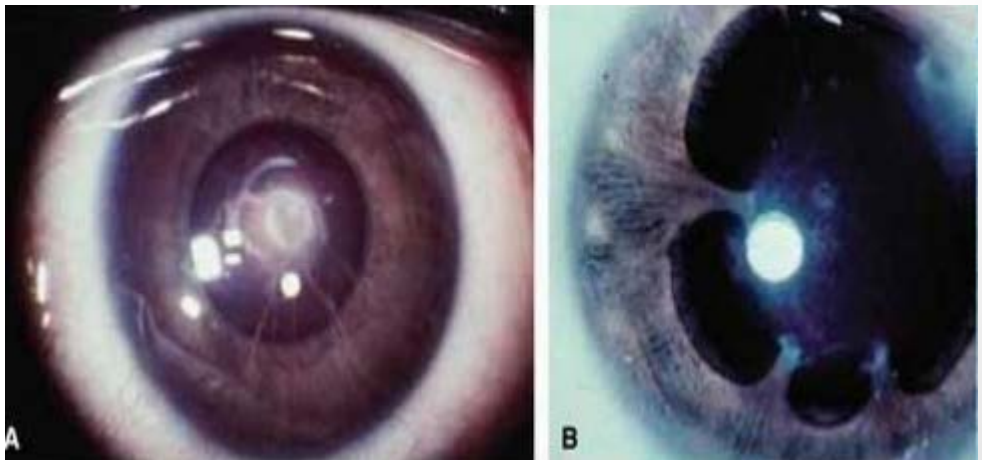
Systemic anomalies

- Dental anomalies
  - Microdontia
  - Hypodentia
- Facial anomalies
  - Hypertelorism
  - Maxillary hypoplasia with midface flattening
  - Telecanthus
  - Broad flat nose

Peters anomaly

- Present at birth
- Usually bilateral
- Most cases are sporadic or AR
- Defects of ear, auditory system, heart, genitourinary system, spine, and musculoskeletal system
- Central corneal abnormality
  - Defect in Descemet's membrane and corneal endothelium
  - Thinning and opacification of corresponding corneal stroma
  - Iris adhesions





Peter's anomaly

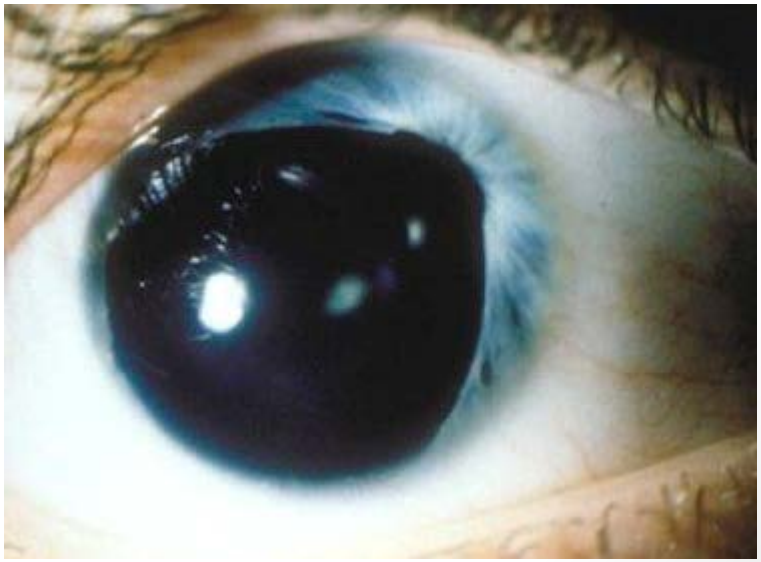
- May be associated with Axenfeld-Rieger syndrome
- May be associated with kerato-lenticular contact
- 50-70% of patients will develop infantile glaucoma

Peter's anomaly

- Systemic association
  - Craniofacial anomalies
  - CNS anomalies
  - Peter plus syndrome
    - Short-limbed dwarfism
    - Cleft lip/palate
    - Learning difficulties

Aniridia

- Bilateral developmental disorder
- Absence of normal iris due to abnormal neuroectodermal development
- Classification
  - AD: 2/3
  - Sporadic: 1/3
  - AR: rare (1%)
- Variable severity

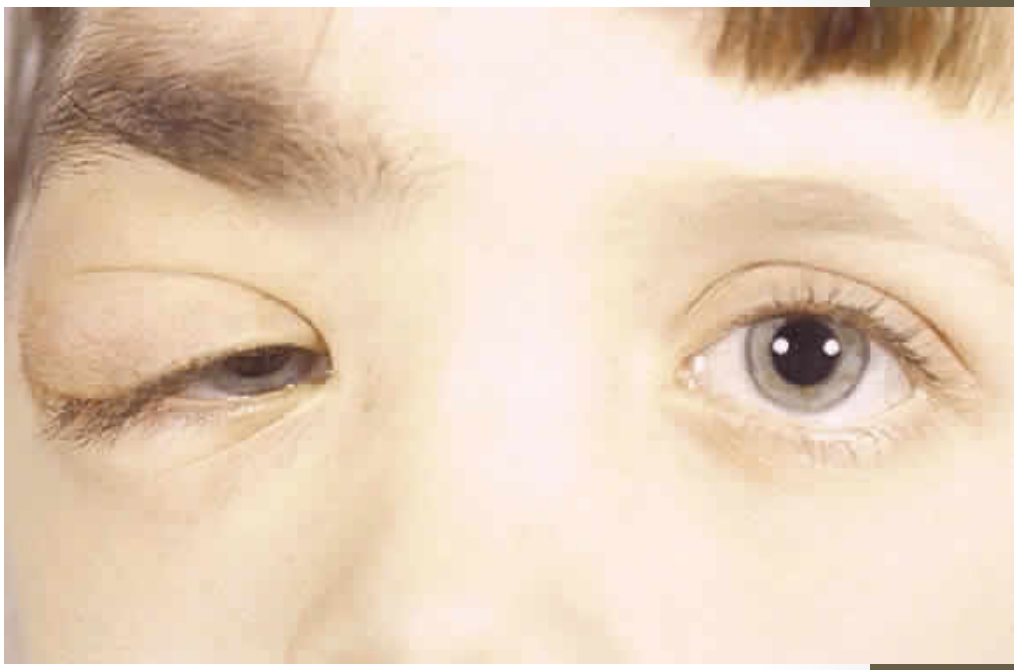


Aniridia: associated ocular findings

- Subluxation of lens or aphakia
- Foveal hypoplasia
- Nystagmus
- Choroidal coloboma
- Optic nerve hypoplasia
- 75% develop glaucoma in late childhood and adolescence
  - Synechial angle closure due to pulling of rudimentary iris tissue by contraction of pre-existing fibers

Phacomatoses

- **Sturge-Weber Syndrome**
  - Glaucoma develops in 30% of patients, ipsilateral to facial hemangioma
  - Facial hemangioma (nevus flammeus), choroidal hemangioma, and intracranial meningeal angiomas
  - No gender or race predilection
- **Neurofibromatosis**
  - AD inheritance
  - Neurofibromas form in CNS, nerves, skin, and mucus membranes
  - Glaucoma uncommon
    - Unilateral
    - If plexiform neuroma present, 50% develop glaucoma
    - Surgical success rate much lower than for primary congenital glaucoma



Management of developmental glaucoma

- Surgery: definitive treatment
- Medical therapy provides supportive role to reduce IOP and clear cornea to facilitate surgery
- Laser therapy has very limited role
- Goniotomy and trabeculectomy first line treatments
- Refractory congenital glaucomas
  - Trabeculectomy with anti-fibrosis drugs
  - Glaucoma drainage implants
  - Cyclodestructive procedures

Medical therapy

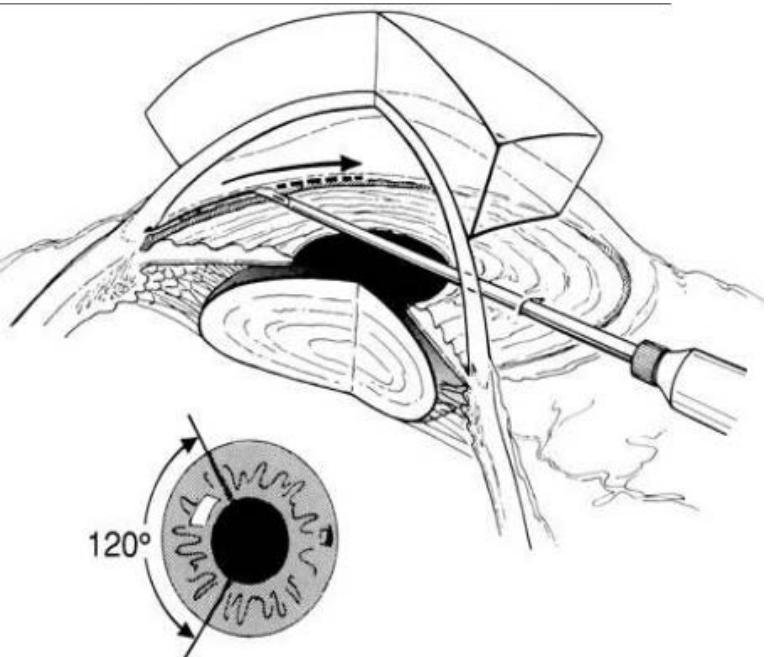
- Beta blockers
  - Used with extreme caution in neonates due to possibility of bronchospasm, apnea, and bradycardia
  - Must rule out cardiac abnormalities and bronchial asthma before initiation
  - Use of 0.25% recommended in children

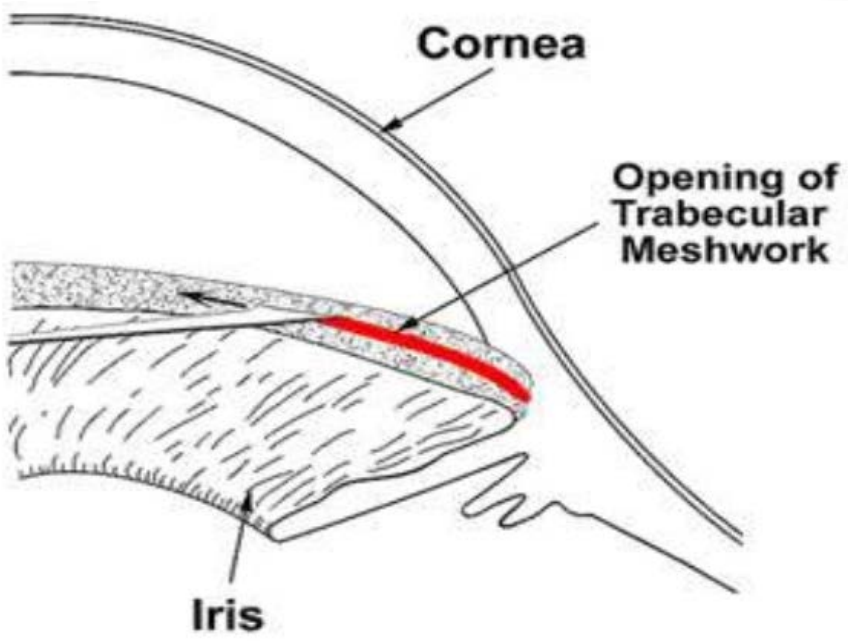
Medical therapy

- Alpha agonists
  - Limited use in children due to CNS depression
- Carbonic anhydrase inhibitors
  - Orals are more effective in IOP reduction, but produce more side-effects, including diarrhea, lethargy, poor appetite, and metabolic acidosis
- Prostaglandin analogs
  - Little effect on IOP in congenital glaucoma
- Miotics
  - Ineffective for primary congenital glaucoma

Surgical treatment

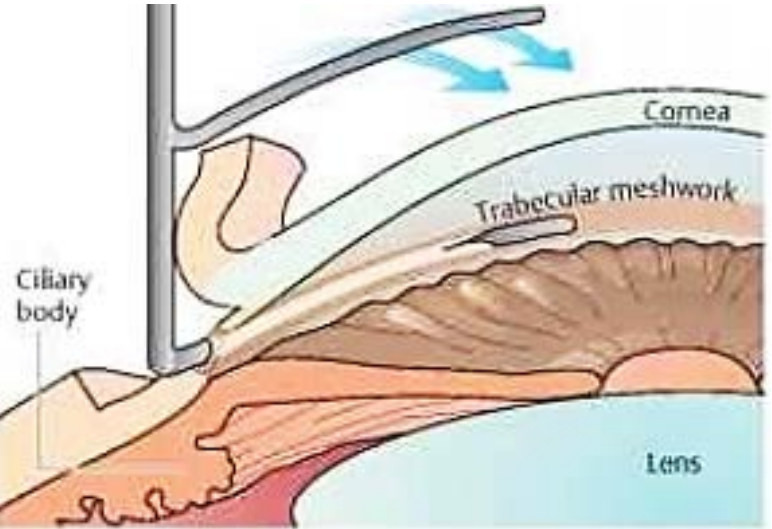
- **Goniotomy**
  - Blade is inserted through peripheral cornea and used to make a linear incision through the TM 1/3 the circumference of the eye
  - Corneas must be relatively clear
  - Reported rate of success: 80%

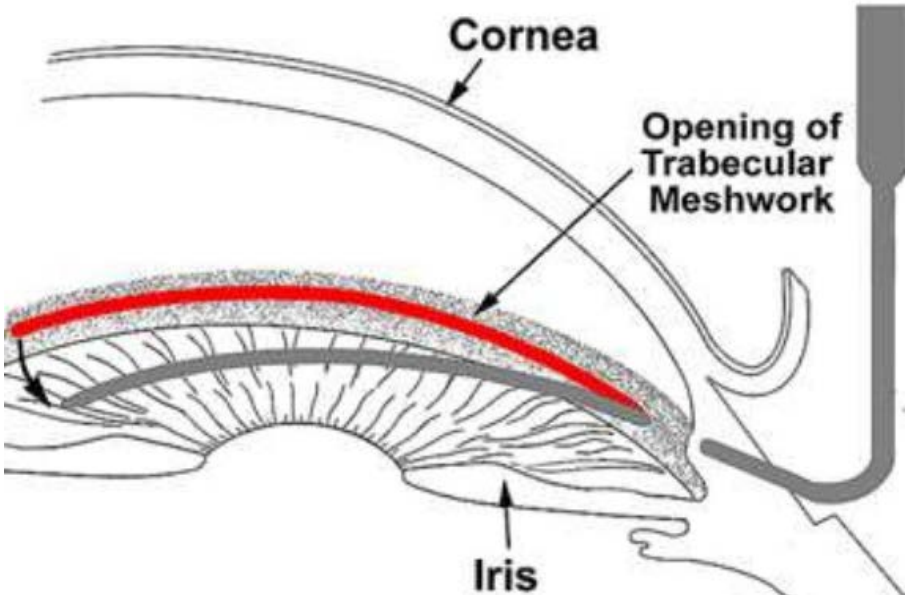




Surgical treatment

- **Trabeculotomy**
  - If corneal clouding prevents visualization of the angle, or goniotomy has failed
  - Scleral flap created, dissection into Schlemm's canal is made, and tabeculotome is used to open the TM
  - Usually 120-140 degrees of the TM can be treated
  - Success rate: 90%



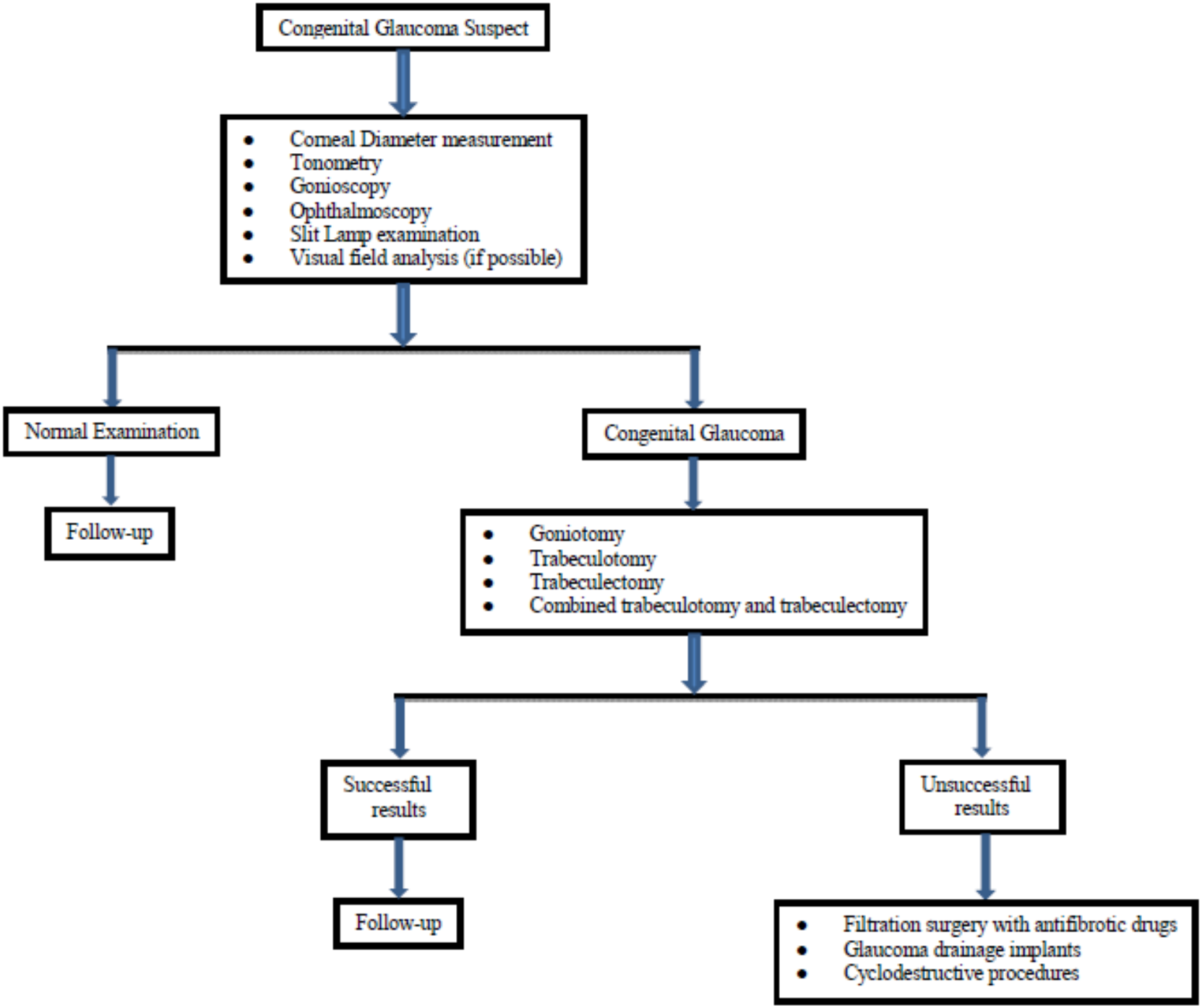


Surgical treatment

- Trabeculectomy
  - Full thickness opening made in the sclera for outflow of aqueous
  - A partial thickness scleral flap covers the opening and conjunctiva overlies the flap
  - Long-term success rate: 50%
    - Due to more aggressive wound healing response in infants and children

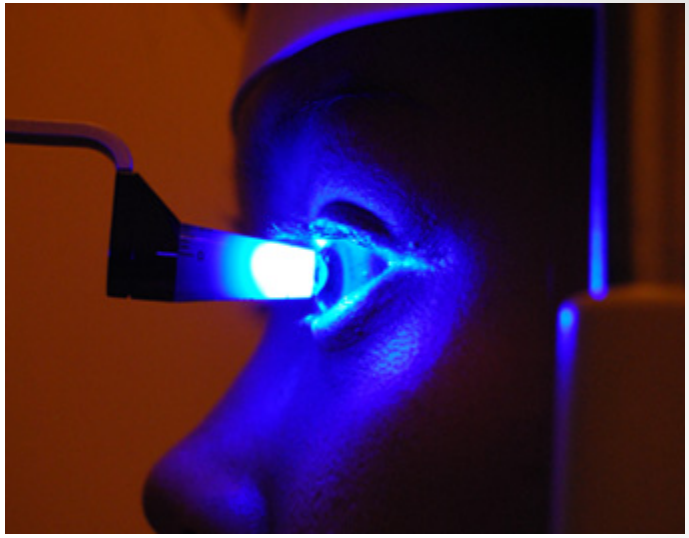
Refractory pediatric glaucomas

- **Trabeculectomy with anti-fibrotic agents**
  - Mitomycin-C and 5-Fluorouracil most commonly used
  - Decrease scarring of blebs
  - Increase risk of infection
- **Aqueous drainage implants**
- **Cyclodestructive procedures**
  - Selectively used for primary congenital glaucomas uncontrolled with conventional surgery and medical therapy
  - Ciliary epithelial ablation is produced by trans-scleral cyclophotocoagulation
  - Indications: blind painful eye, rapidly decompensating cornea


Congenital Glaucoma Suspect
Corneal Diameter measurement
Tonometry
Gonioscopy
Ophthalmoscopy
Slit Lamp examination
Visual field analysis (if possible)
Normal Examination
Follow-up
Congenital Glaucoma
Goniotomy
Trabeculotomy
Trabeculectomy
Combined trabeculotomy and trabeculectomy
Successful results
Follow-up
Unsuccessful results
Filtration surgery with antifibrotic drugs
Glaucoma drainage implants
Cyclodestructive procedures

Take-home

- Main goal in managing congenital glaucoma is early diagnosis and early surgical intervention
- Close life-long follow-up of these patients is critical
- Degree of ocular damage depends on length of period between appearance of the first ocular sign and surgery, or failure of surgery to regulate IOP



OCULAR HYPERTENSION

Ocular hypertension (OHTN)

- IOP $\geq$ 21 mmHg
- No detectable VF loss
- No detectable optic disc or RNFL damage
- Open anterior chamber angles
- No ocular or systemic cause of increased IOP

Epidemiology

- 119 million people in US over age 40
  - 4-8% have ocular hypertension
- Number will increase with aging population
- Considerations:
  - Managing a large group of people has substantial costs for examinations, tests, and treatment

OHTN - considerations

- Elevated IOP is the leading risk factor for development of POAG
- IOP is the only modifiable risk factor for POAG
- Patients can lose substantial proportion of RNFL before POAG is detected by standard clinical tests
- However –
  - does treatment of OHTN prevent POAG?

Ocular Hypertension Treatment Study (OHTS)
Primary Goals

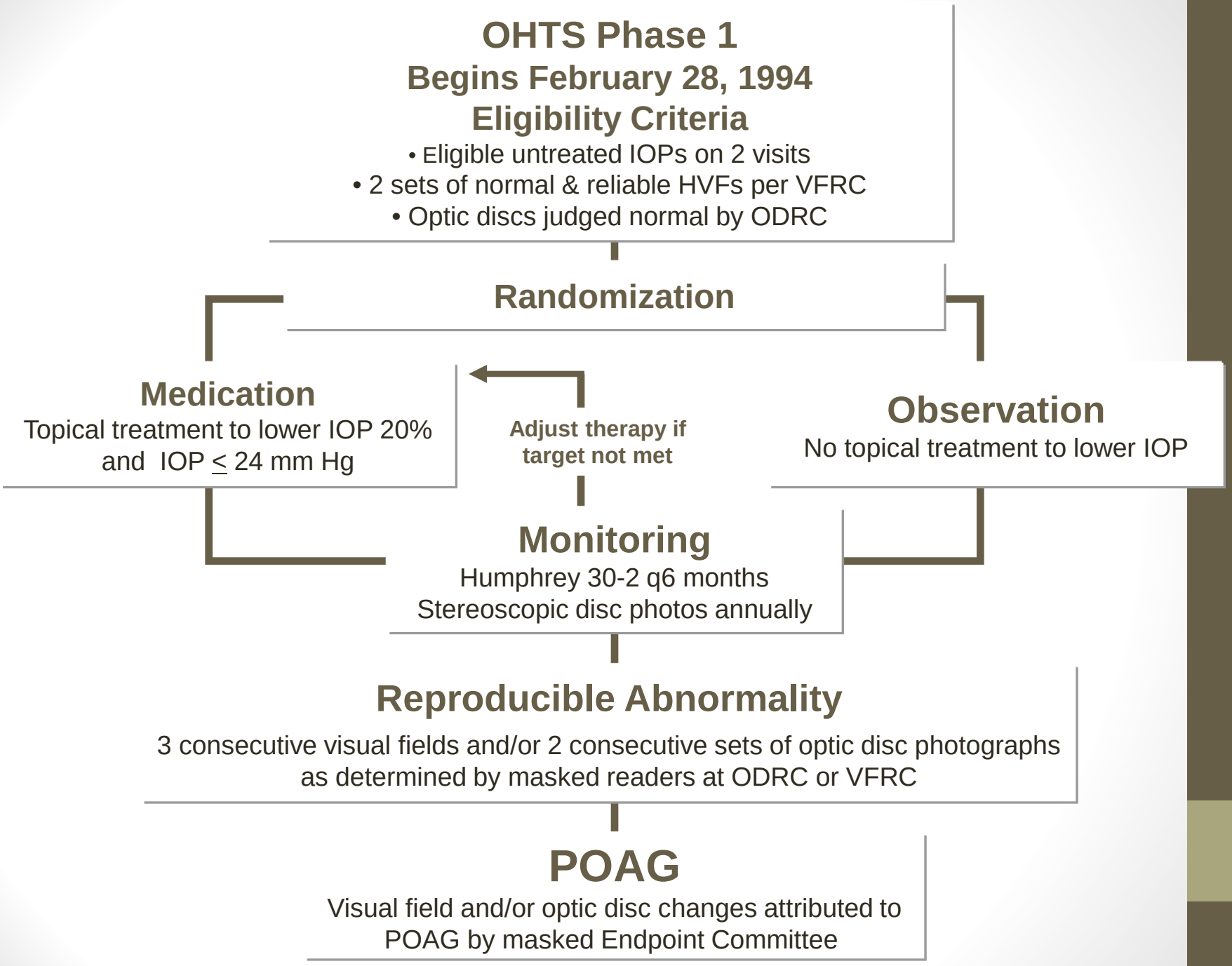
- Evaluate the safety and efficacy of topical ocular hypotensive medication in delaying or preventing development of POAG in individuals with elevated IOP
- Identify baseline demographic and clinical factors that predict which participants will develop POAG

OHTS entry criteria

- Age: 40-80
- Normal VF (Humphrey 30-2)
- Normal optic discs
- Untreated IOP
  - 24-32 mmHg in one eye
  - 21-32 mmHg in fellow eye

OHTS – POAG Outcome

- Development of reproducible VF abnormality on minimum of 3 VF's, or
- Reproducible optic disc deterioration attributed to POAG


OHTS Phase 1
Begins February 28, 1994
Eligibility Criteria
• Eligible untreated IOPs on 2 visits
• 2 sets of normal & reliable HVFs per VFRC
• Optic discs judged normal by ODRC
Randomization
Medication
Topical treatment to lower IOP 20%
and IOP ≤ 24 mm Hg
Adjust therapy if target not met
Observation
No topical treatment to lower IOP
Monitoring
Humphrey 30-2 q6 months
Stereoscopic disc photos annually
Reproducible Abnormality
3 consecutive visual fields and/or 2 consecutive sets of optic disc photographs as determined by masked readers at ODRC or VFRC
POAG
Visual field and/or optic disc changes attributed to POAG by masked Endpoint Committee

Baseline characteristics

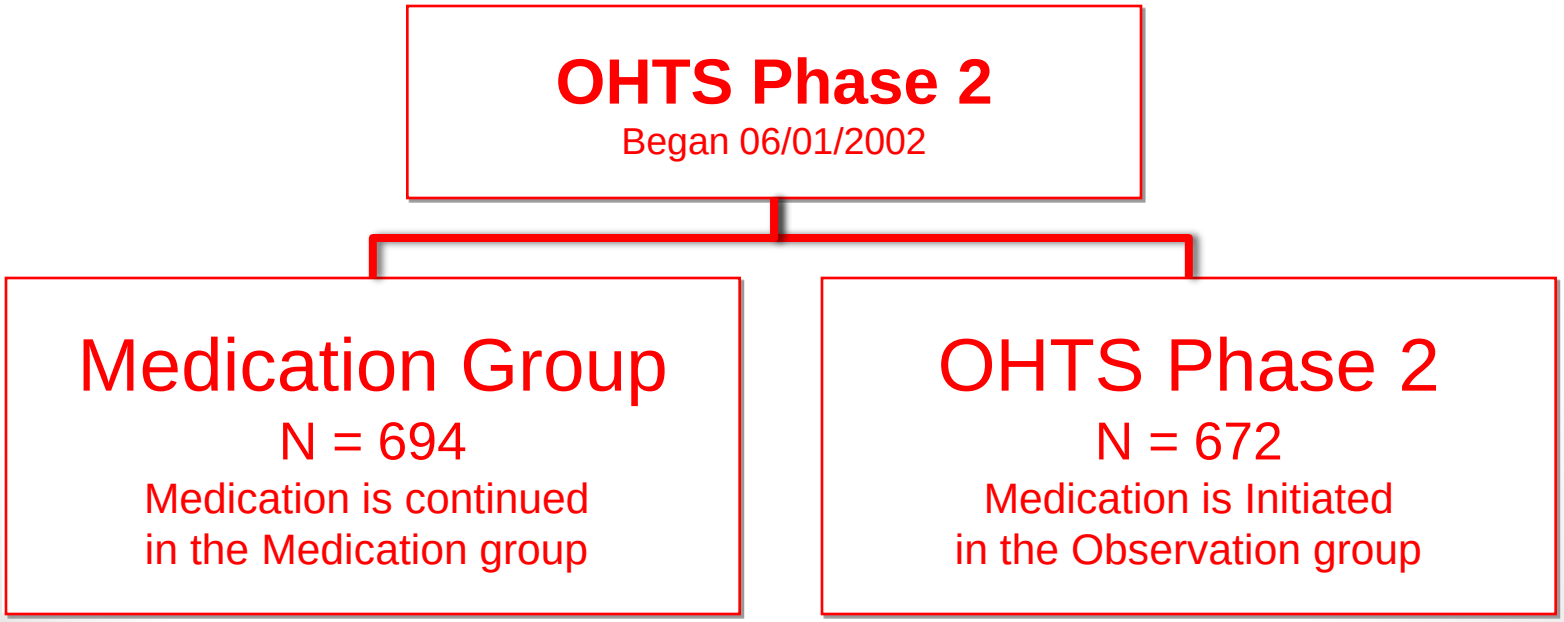
	Baseline Characteristics N=1,636
Age (mean ±SD)	55.4 ±9.6 SD
White	70%
African American	25%
Hispanic	4%
Other	1%
Sex	
Male	43%
Female	57%
IOP, mm Hg	24.9 ±2.7 SD
Vertical CD	0.39 ±0.2 SD
CCT	572 ±38.4 SD

OHTS Phase 1 summary

- Medication produced 20% reduction in IOP
- Medication reduced incidence of POAG in OHTN patients by more than 50% at 5 years
  - 9.5% in observation group
  - 4.4% in medication group
- Implications
  - Decreasing IOP by 20% from Tmax decreases progression of OHTN into POAG by 50%

OHTS Phase 2

- OHTS phase 1: proof that medication reduces incidence of POAG in patients with OHTN
  - No indication *when* to begin treatment
  - No indication whether *all* OHTN patients should receive early medication
  - No indication whether there is a penalty for delaying medication



OHTS Phase 2

- After 7.5 years of observation, participants originally randomized to observation group start medication
- Compare incidence of POAG at 13 years
  - Delayed treatment group
  - Early treatment group

Phase 2 Summary

- Increased cumulative incidence of POAG at 13 years (delayed vs early treatment)
  - 22% vs 16%
- More eyes with structural and functional damage
  - 8% vs 5%
- More participants with bilateral disease
  - 6% vs 4%

OHTS Summary

- Early medical treatment reduces cumulative incidence of POAG
- Absolute effect is greatest in high-risk individuals
- Little absolute benefit of early treatment in low risk individuals
- Individualized assessment of risk is useful to patients and clinicians
- Do not adjust IOP based on CCT

OHTS: pachymetry – 3 outcomes

- Thin: < 555 HIGH RISK
- Average: 555-588 No changes in risk
- Thick: > 588 Low risk

Applied to patients with ocular hypertension

Corneal Hysteresis (CH)

- CH: difference in inward and outward pressure values obtained during the dynamic bi-directional applanation process employed in the Ocular Response Analyzer as a result of viscous damping in the cornea
- Glaucoma subjects have lower CH than normals
  - CCT is an independent risk factor for glaucoma risk
  - CH is even more powerful estimator of glaucoma risk

Independent risk factors for development of POAG

- Age
- IOP
  - IOP > 22 mmHg is a positive predictive factor for development of POAG
- CCT < 555 µ
  - Relative risk of POAG increased by 81% for every 40 µ decrease in CCT
- Vertical C/D ratio (> 0.6)
  - Increase in CDR by 0.1 leads to 32% increase in relative risk
- PSD
  - 0.2 dB increase in PSD led to 22% increase in relative risk of development of POAG

Clinical pearls

- Most OHTN patients are at low risk for developing POAG
- Most low risk OHTN patients can be followed without treatment
- Delaying treatment by 7.5 years resulted in only a small absolute increase in POAG in low risk patients

Clinical pearls

- Lowering IOP by 20% from Tmax delays or prevents conversion into POAG in high-risk patients
- High-risk OHTN patients may benefit from more frequent examinations and early treatment, taking into consideration:
  - Patient age
  - Health status
  - Life expectancy
  - Personal preference

Clinical pearls

- Consider burden of long-term treatment
- Consider patient's risk of developing POAG
- Consider patient's likelihood of being helped by medication
- Consider patient's health status and life expectancy
- Consider patient's risk factors

Indications for treatment

- High risk patients: multiple risk factors
- Monocular patients
- Unreliable VF or ONH assessment
- OHTN patient who desires treatment
- OHTN patient who has developed a vascular occlusion in either eye

THANK YOU!