GLAUCOMA'S GRAY AREA

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This case based presentation examines two areas that fall into the "gray area" of clinical glaucoma understanding. The first is the diagnosis and management of children who either have glaucoma or are suspected of having glaucoma. The second examines patients with glaucoma who follow a more ominous course with greater risk and likelihood of visual disability. Discussion will focus on features that may portend a poorer prognosis and alert practitioners to be mindful in follow up and aggressive in medical management and care.

Pediatric and Congenital Glaucoma

- Pediatric glaucoma is a term that includes any form of glaucoma that presents between birth and age 18 years. Pediatric glaucoma can be either primary or secondary and the angle may be open or closed. However, there is confusing and overlapping terminology. Primary congenital and primary infantile glaucoma (terms often used synonymously) occur secondary to trabeculodysgenesis, a developmental angle anomaly, and can manifest any time between birth and early childhood. Pediatric developmental glaucomas are also classified by the time that they appear in a patient; primary congenital glaucoma occurring between birth and 1 month of age, primary infantile glaucoma occurring between 1 month and 2 years of age, and late onset primary infantile glaucoma (also known as late-onset primary congenital glaucoma) occurring after 2 years of age. Primary infantile glaucoma overlaps with juvenile-onset open angle glaucoma (JOAG), a non-developmental glaucoma similar to primary open angle glaucoma in adults, which develops late in childhood in the absence of angle anomalies. It is most commonly accepted that the term primary congenital glaucoma refers to patients in all three age groups in the presence of developmental anterior chamber angle abnormalities.

Primary congenital glaucoma

- Known as buphthalmos
- IOP elevated during intrauterine life
- Birth through 1 month of life
- Developmental anomaly of the trabecular meshwork – trabeculodysgenesis
  - Aqueous outflow is impaired by an isolated trabeculodysgenesis
  - Maldevelopment of the trabecular meshwork, including the iridotrabecular junction, with no other major ocular abnormalities
  - TM become exposed to the AC as the angle recess deepens and move posteriorly
    - Posterior sliding of iris, ciliary muscle, and ciliary processes
  - In the newborn eye, the iris and ciliary body usually have recessed to at least the level of the scleral spur

    - Posterior sliding of the uveal tissues continues during the first 6 to 12 months
    - Glaucoma: The iris and ciliary body have failed to recede posteriorly, and thus the iris insertion and anterior ciliary body overlap the posterior portion of the TM
- Characterized by absence of the angle recess with the iris inserted directly into the trabecular meshwork. This insertion can be either flat or concave
    - Flat iris insertion manifests with the iris inserting flat and flush at or anterior to the scleral spur.
    - Concave insertion is one where superficial iris tissue sweeps over the iridotrabecular junction. The scleral spur and ciliary body are obscured by the overlying iris tissue which is either sheet like or consists of a dense arborizing meshwork
- 75% bilaterality
- Surgical
- 90% cure rate

Primary infantile glaucoma

- Trabeculodysgenesis
- Manifests between 1 month and 2 yrs
- Late-onset primary infantile – after 2 years of age
    - Overlaps with juvenile open angle glaucoma (JOAG)
        - Difference is trabeculodysgenesis, which is not present in JOAG
        - Thus, categorizing childhood glaucomas based upon time of onset is not as exact as by mechanism of glaucoma development

Juvenile open angle glaucoma (JOAG)

- POAG diagnosed during childhood
- Occurring between age 3 years and early adulthood
- Pressure rise occurs after 3rd birthday, but before 16th birthday
- Upper age debatable
- Often the cause when advanced and end stage glaucoma diagnosed in late 30s or early 40s
- Very strong hereditary component- autosomal dominant
    - Check all family members

Other Pediatric Glaucomas

- Glaucoma associated with congenital cataract surgery
    - In aphakic or pseudophakic children following congenital cataract surgery.
    - Mechanism in aphakic glaucoma is unclear, but gonioscopy may reveal a blockage of the trabecular meshwork secondary to an acquired repositioning of the iris against the posterior trabecular meshwork. Also, prolapsed vitreous may block meshwork
    - There is often associated abnormal pigmentation and synechiae formation within the meshwork.
- Glaucoma associated with non-acquired systemic disease or syndrome
    - Sturge-Weber

- Glaucoma associated with non-acquired ocular anomalies
    - Axenfeld syndrome
- Glaucoma associated with acquired conditions
    - Glaucoma can occur in a pediatric patient from a number of other causes including but not limited to trauma, inflammation, episcleral venous pressure elevation as seen in Sturge-Weber syndrome, tumor, pupil block from subluxation, retinopathy of prematurity and infectious disease

Clinical Pearl: Any glaucoma occurring before age 18 years is considered pediatric glaucoma. The terms congenital, developmental, and infantile are overlapping and confusing. Any childhood glaucoma caused by trabeculodysgenesis is considered primary congenital glaucoma. A child with glaucoma but without angle abnormalities has JOAG.

Clinical Pearl: Aphakic and pseudophakic children must be followed lifelong for the development of glaucoma. However, the presence of an intraocular lens seems to reduce the incidence of glaucoma development, though the reasons are unclear.

Signs and Symptoms of Primary Congenital Glaucoma

- The classic triad of congenital glaucoma is epiphora, photophobia, and blepharospasm
- Corneal clouding from edema
- Megalocornea-corneal enlargement (> 12mm)
- Myopia
- Amblyopia
- IOP > 20 mm hg
- Globe enlargement
- Descemet's tears-horizontal or vertical (Haab's striae)
- Scleral ring enlargement
- Rapid cupping
- Cupping reversible if caught in time
- In infants, C/D ratio greater than 0.3 or asymmetrical cupping, myopic refractive error, or enlarged axial length lead to suspicion of glaucoma

Management of Suspected Pediatric Glaucoma

- Descemet's tears, megalocornea, classic triad, corneal edema
    - Obvious referral to pediatric glaucoma surgeon:
- Large c/d ratio w/o IOP rise:
    - Photos and imaging
- Elevated IOP with normal angle and disc
    - Photos and imaging; close observation

Surgical options for congenital glaucoma

- Goniotomy
- A knife is passed through the cornea through the anterior chamber, and cuts the trabecular meshwork for 180º.
- Trabeculotomy

- A probe is introduced into the lumen of Schlemm's canal and rotated into the anterior chamber, thus rupturing the trabecular meshwork.
- Viscocanalostomy
- Filtering surgery
- Cyclocryotherapy
- YAG cyclophotocoagulation
- Diode laser photoablation

Medical therapy

- Medicines only adjunctively with surgery for congenital glaucoma
  - Primary medical therapy for congenital glaucoma inappropriate
  - Medical and surgical therapy for JOAG and other forms of childhood glaucoma are case-by-case
- Topical beta blockers are a safe and effective class when used in children.
- Prostaglandin analogs are safe and well tolerated, but unfortunately not very effective in the pediatric glaucoma population. The children where efficacy is best demonstrated are older children (>15yrs) with JOAG.
- Topical carbonic anhydrase inhibitors (CAIs) are a safe and effective means by which to lower IOP. The best option.
- Brimonidine, though effective in lowering IOP in children, crosses the blood-brain barrier and can potentially affect the central nervous system (CNS). This medication has demonstrated an unacceptable level of adverse events in children and should not be used

Clinical Pearl: Juvenile open angle glaucoma typically presents with significantly elevated IOP. There are no pediatric 'normal tension' glaucoma patients.

Summary

Congenital/ Infantile	Juvenile Open Angle Glaucoma/ Secondary
Abnormal angle	Normal angle
Globe enlargement	Normal axial length
Corneal edema	Clear cornea
Onset near birth	Onset later
Megalocornea	Normal corneal size
Symptomatic: Blepharospasm, photophobia, lacrimation	Asymptomatic

What Patient's Do We Most Worry About?

Natural History of Primary Open Angle Glaucoma

- POAG is a progressive disease
- Elevated IOP is the greatest risk factor for disease development and progression
- Patients with lower levels of IOP baseline have been shown to be very slowly progressive in many cases and progression may not occur over several years of study

- Patients with very high baseline IOP often present with advanced disease and if IOP levels remain unaltered, progression and visual disability are likely to occur.
- Magnitude of initial IOP reduction has been shown to have a significant impact on disease progression
    - Patients with very high initial IOP reduced to upper teens or low 20s may do well
    - Patients with lower levels of baseline IOP (low to mid 20s) who have IOP lowered to mid-teens tend to fare poorly.
- The majority of patients with POAG follow a predictable course and, with therapy, have a low risk of visual disability. However, some patients will follow an unpredictable course, often without explanation
    - Some patients who should fare well do rather poorly on occasion
    - Some patients who should de poorly actually fare well on occasion
- The challenge is to identify quickly which patients are expected to have a poor outcome and be more aggressive in management.

Risk Factors for Progression:

- IOP level
    - The most significant modifiable risk factor for glaucoma development and progression
- IOP fluctuation
    - Possibly indicates changing perfusion pressure and decreased autoregulatory ability
    - This was identified in the AGIS study, but faulty reasoning has led the glaucoma community to reject this as an independent risk factor
- Exfoliation
    - Higher IOP, worse disease, more difficult to control, noted in numerous studies in association with progression
- Central Corneal Thickness (CCT)
    - OHTS and many others point out that thin cornea a risk factor
- Disc hemorrhages
    - Patients with normal tension glaucoma, primary open angle glaucoma, ocular hypertension
        - Anemia, posterior vitreous detachment, vascular occlusion can cause hemorrhages of the disc that are mistaken for glaucomatous disc hemorrhages
    - Ischemic or mechanical
        - Possible infarction of the blood supply to the ONH and/or mini-occlusion and shearing of blood vessels from mechanical displacement of tissue
    - Inferior, inferior temporal, superior, superior temporal regions of the disc most susceptible and account for virtually all true disc hemorrhages
        - Hemorrhages at other areas of the disc (nasal and temporal) tend to not be associated with glaucoma
        - Typically occurs where notches occur
        - Resides in the retinal nerve fiber layer
            - Not in the cup
        - Small and contiguous with the neuroretinal rim
        - Can be recurrent and, if it recurs, it typically is in the same place on the disc

each time
        - Disc hemorrhages do not constitute a diagnosis of glaucoma nor a progression or conversion to glaucoma or an endpoint for any major glaucoma
- Time
    - Glaucoma is by nature a progressive disease and treatment likely only slows the progression
    - Given enough time, most will demonstrate progression and this is not a sign of treatment failure
- Ocular Perfusion Pressure (OPP)
        - The difference between systemic blood pressure and intraocular pressure.
            - A measure of retinal and optic nerve perfusion
        - Systolic Perfusion Pressure (SPP)
            - SPP = Systolic Blood Pressure – IOP
        - Diastolic Perfusion Pressure (DPP)
            - DPP = Diastolic Blood Pressure – IOP
        - Mean Perfusion Pressure (MPP)
            - MPP = Mean arterial pressure – IOP
                - Mean Arterial Pressure = 2/3 DBP + 1/3 SBP
    - Lower OPP strongly associated with prevalence of POAG
    - Six-fold excess risk of having glaucomatous optic nerve damage in persons with lowest category of OPP

Patient Compliance

- Nearly 50% of patients show non-continuous use by 6 months after start of therapy
- Communication Skills and Information Exchange
    - How well the Doctor communicates the importance of compliance
- Choice of Medications and the treatment regimen
    - Managing side effects
    - Impact the diagnosis and medication has on one's quality of life
- Situational and Environmental factors
    - Other diseases
    - Life events
    - Social support
- Assorted other factors
    - Cost
    - Insurance and formulary issues
    - Physical barriers
        - Drop instillation difficulties due to arthritis

Risk Factors for Progression: Summarizing What the Major Studies Tell Us

- Disc hemorrhage (NTGS, OHTS, EMGT)
    - NTGS, EMGT saw no difference with IOP reduction
- Fluctuation of IOP (AGIS)
    - Technically reported, but not accurate or accepted
- Thin cornea (EMGT, OHTS)
- Higher baseline IOP (EMGT, OHTS, AGIS)

    - Not CNTGS
- Exfoliation (EMGT)
- Cardiovascular disease (EMGT, NTGS)
- Lower OPP (EMGT)
- Older age (EMGT, AGIS)
    - *not* CNTGS