Title: It’s All About the Angle: Anterior Segment Dysgenesis and Secondary Glaucoma in a Juvenile Patient

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Abstract: Glaucoma in young patients is difficult to manage due to the progressive nature of the disease over an increasing average life span. Careful examination of ocular structures is essential in diagnoses and management of patients.

Case History
- Patient demographics
  - 23 year old black male

Chief Complaint
- Referred to University Eye Center as glaucoma suspect for consultation and treatment in January 2014
- Ocular History
  - Correspondence from previous visit at referring doctor:
    - Goldmann Applanation Tonometry: 28/30
    - (+) Family history of glaucoma, half-sister
    - Compound Myopic Astigmatism in both eyes
    - No history of ocular trauma or surgeries
- Medical history
  - Unremarkable
  - No medications

Pertinent Findings
Clinical
- Entering visual acuity with spectacles
  - OD: 20/20
  - OS: 20/20
- Pupils: ERL (-) APD R/L

Physical
- Slit Lamp Examination: unremarkable OU
- Goldmann Tonometry (i gtt Fluorescein Sodium 0.25% and Benoxinate Hydrochloride 0.4% Ophthalmic Solution)
  - OD: 28 mm Hg
  - OS: 30mm Hg
  - 9:20am
- Gonioscopy 4 Mirror
  - OU: dysgenic angles, open to ciliary body 360*, grade 1 pigment, flat approach, scattered iris pigment atrophy at iris root 360*
- Pachymetry:
  - OD: 514
- OS: 509
- Dilated Fundus Examination (1 gtt 1% Tropicamide, 1 gtt 2.5% Phenylephrine)
  - OD: C/D 0.65 round, deep cup, pink and distinct neuro-retinal rim tissue (-) drance hemes
  - OS: C/D 0.75 round, deep cup, pink and distinct neuro-retinal rim, rim thinning superior and inferior temporal with corresponding RNFL defects, bayonetting of vessel at 6 o’clock, (-) drance hemes

**Imaging Studies:**
- Zeiss OCT 1/2014
  - Average RNFL thickness: OD 94um, OS 87um
  - Clock hours: OD: No quadrants flagged, OS: 1-2 o’clock and 5 o’clock flagged <5%
- Humphrey Visual Field 24-2 SITA Standard 1/2014:
  - OD: reliable, generalized depression; mild superior defects
  - OS: reliable, generalized depression; mild superior defects

**Differential diagnosis**
- Juvenile Open Angle Glaucoma (JOAG) secondary to angle dysgenesis
- Congenital Glaucoma
- Primary Open Angle Glaucoma
- Ocular Hypertension

**Diagnosis and discussion**

**Juvenile Onset Open Angle Glaucoma Secondary to Anterior Segment Dysgenesis (ASD)**

- Glaucoma encompasses a broad spectrum of ocular diseases with different causes that clinically exhibit retinal ganglion cell death, optic nerve damage and subsequent visual field deficits corresponding with nerve fiber layer damage. In some types of glaucoma, an impediment or resistance to aqueous outflow will put the patient at risk for elevated intraocular pressures. As a result, damage to the retinal nerve fiber layer occurs. (1)
- Dysgenesis or malformation of the anterior segment occurs during development of the ocular structures during gestation, primarily during the differentiation and development of the mesenchymal cells. (2) Anterior Segment Dysgenesis can affect the cornea, lens, iris, trabecular meshwork and Schlemm’s Canal. There is a broad spectrum of phenotypes that are classified within the category of anterior segment dysgenesis including Peter’s Anomaly, Axenfeld-Rieger syndrome, posterior embryotoxin and iridogoniodyssgenesis. Presentation can range from severe ocular deformities to very subtle gonioscopy findings. (3) Due to the abnormal draining structures and changes in the extracellular matrix, 50% of patients with any form of anterior segment dysgenesis will develop glaucoma. (4) Patients with dysgenic angles are more likely to have earlier onset glaucoma than those with normal angles. (5)
- Angle dysgenesis can have many variations in phenotypic presentation, but some features to be aware of are high insertion of the iris anterior to the ciliary body, a
featureless angle with compact trabecular meshwork and poor differentiation between the trabecular meshwork and scleral spur, and prominent iris processes. (5)

- Clinical observation alone of dysgenic angles on gonioscopy does not always correlate with the presence or severity of the glaucoma. Histological examination of the trabecular meshwork and Schlemm’s canal reveals cellular and metabolic abnormalities that cause a disregulation of aqueous humor drainage, resulting in increased intraocular pressure. (7) Not only are malformations seen in the trabecular meshwork, but genetic mutations causing abnormalities in the extracellular matrix in the juxtacanalicular region and the endothelial lining of Schlemm’s Canal may play an even larger role than the trabecular meshwork in increased resistance of outflow. (6)

- A large array of phenotypic presentations make ASD difficulty to classify, but recently genetic studies with mouse models have isolated several genes that appear to impact the formation of the anterior segment and it’s structures, allowing researchers to better classify these cases. (7)

Treatment and Management
The patient was given a prescription for Latanoprost 0.005% ophthalmic solution to use at bedtime in both eyes and scheduled for regular follow up every 3 months.

- Follow Up:
  - February 2014 through February 2015: IOPs remained stable in the high teens with good medication compliance in both eyes. No reported changes in medical or ocular health.
  - February 2015: Both Visual Field show repeatable mild superior defects, OCT indicates structural progression
  - April 2015: Visual Fields re-tested and show repeatable mild superior defects in both eyes
  - July 2015: IOPs have remained stable in high teens. The patient expressed interest in surgical management of glaucoma over topical drops
  - August 2015: Visual fields were repeated and have improved, but repeatable points remain flagged superiorly. Anterior segment photos taken with gonioscopy documented dysgenic angles. Anterior segment OCT of angle taken.

Conclusion and Clinical Pearls
- Anterior Segment Dysgenesis can lead to glaucoma in 50% of patients. Obvious phenotypic presentations such as those with Peter’s Anomaly and Axenfeld-Rieger syndrome are easier to detect while more subtle forms may only be detectable upon careful gonioscopic examination. It is important to perform a careful gonioscopy examination on all patients with newly diagnosed glaucoma. (3)

- In a study that evaluated gonioscopic features found in eyes diagnosed with JOAG, 66% had anomalous angles. The eyes with anomalous angles were more likely to have earlier onset glaucoma compared to those with normal angles. (5)

- It is likely that there are more cases of anterior segment dysgenesis leading to glaucoma than there is documented in the literature. Some developmental abnormalities of the draining structures are not always clinically detectable.
histological and metabolic deformities may be affecting the aqueous drainage, without affecting clinical appearance. Theoretically, this could result in many patients who do in fact have glaucoma secondary to clinically undetectable ASD being diagnosed with primary open angle glaucoma. (2)

- Treatment and management of glaucoma secondary to anterior segment dysgenesis is best achieved through the use of topical glaucoma medications to control intraocular pressure. (3) Due to the abnormal histological characteristics of the trabecular meshwork, Schlemm’s canal and extracellular matrix, conventional laser surgery (selective laser trabeculoplasty, argon laser trabeculoplasty) does not prove effective in control of intraocular pressure. (8) The most successful surgeries for ASD glaucoma are those that provide an alternate drainage route, such as sclerotomy, trabeculectomy and glaucoma drainage device implantation. (3)

- Careful follow up, along with setting and achieving a low target pressures are essential with these patients.

- In newly diagnosed glaucoma patients or those which anterior segment dysgenesis is suspected, gonioscopy with a 3 mirror lens and methylcellulose solution is recommended for optimal views of the structures within the angle

- Mutations in PITX2 and FOXC1 account for 40% of cases of ASD. (3) Advancements in mouse model genetics are providing greater insight into the pathogenesis of these conditions, and creating a better classification of clinical presentations taking into account phenotypic and genotypic presentations. (7) This will lead to more accurate and specific diagnosis and treatment plans for patients.

References:

6. Vranka Janice A, Kelley Mary J, Acott Ted S, Keller Kate E; Extracellular matrix in the trabecular meshwork: Intraocular pressure regulation and dysregulation in glaucoma; Experimental Eye Research. 2015; 133: 112-125
7. Gould Douglas B, John Simon W M; Anterior segment dysgenesis and the developmental glaucomas are complex traits; Human Molecular Genetics. 2002; 11: 1185-1193