Diagnosis and management of Axenfeld-Rieger Syndrome in a pediatric patient

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Abstract: Axenfeld-Rieger Syndrome (ARS) is a rare congenital disorder with a spectrum of ophthalmic and systemic manifestations. It was diagnosed in a developmentally delayed pediatric patient who will be monitored for development of glaucoma.

I. Case History

- Patient demographics: Six year old Bangladeshi male
- Chief complaint: referred by pediatrician for ocular health evaluation
- Ocular history: His first eye exam was one year ago at an outside location. The parents reported knowledge of a developmental anomaly of the left eye with an abnormal pupil, but no further information could be provided about the previous diagnosis. The patient was prescribed spectacles one year ago for the first time which he uses only part-time.
- Medical history:
  - moderate developmental delays, microcephaly, cleidocranial dystosis
  - expressive/receptive language disorder, verbally limited
  - currently followed in both neurology and developmental clinics
  - MRI from 2010 revealed hypoplasia of vermis
- Medications: Multivitamins
- Other salient information:
  - Birth History: Full-term pregnancy, no complications, no forceps use during delivery, birth weight 7 lbs 4 oz. Our patient remained in the hospital for 3-4 days after birth in an incubator receiving oxygen due to breathing problems. He was hospitalized at one week old for 21 days due to a cold. He was not treated with medication and there have been no recurrences. No history of ocular trauma.
  - Educational History: Patient is in special education kindergarten, and is receiving physical, occupational, and speech therapy.

II. Pertinent findings

Clinical:

- Bilateral refractive amblyopia
  - OD +1.50 -2.00 x180 BCVA 20/30+2
  - OS +4.00 -2.75 x180 BCVA 20/50+2
- Right eye pupil round and reactive to light. Corectopia of left pupil, peaked nasally, reactive to light in all areas except for where pupil is irregular nasally. No APD.
- Bilateral posterior embryotoxin, more prominent in the left eye
- Additional corneal findings left eye: pigmented PPM fibers adhering to posterior cornea inferior-temporally, small round endothelial scar inferior-temporal to visual axis
- Bilateral SPK with instantaneous TBUT
- Approximate corneal diameter 10mm in each eye
- Iris flat and intact right eye. Left iris: corectopia with pupil peaked nasally, focal atrophy inferiorly, multiple PPM fibers nasally
- IOP 16/16 Goldmann Applanation Tonometry
- Gonioscopy deferred due to extremely poor patient cooperation/fixation
- Lens: likely epicapsular star left lens in area of irregular pupil
- Optic nerve head assessment
  - C/D: OD 0.5Vx0.45H OS 0.6Vx0.55H
  - Disc: pink, distinct, healthy rim tissue OD+OS. No signs of glaucomatous damage.
Physical: mild hypertelorism, flattened nasal bridge, ambulatory, makes good eye contact, only uses 8-10 single words to communicate, can follow simple one-step directions. No dental abnormalities.

III. Differential diagnosis
Primary/leading
- Axenfeld-Rieger Syndrome

Others
- Iridocorneal endothelial (ICE) Syndrome
- Complications secondary to trauma

IV. Diagnosis and discussion
- There was no reported history of trauma to the patient as reported by the parents, so trauma was ruled out as an etiology for his clinical appearance.
- ICE Syndrome usually presents unilateral, manifests in young adults, and is more common in women. This does not relate to our patient. In addition, it does not usually have associated systemic findings, whereas our patient was being followed for various systemic conditions which could relate to ARS.
- ARS is a genetic condition that encompasses a wide range of ocular and systemic findings as part of a continuum. It is usually autosomal dominant in its inheritance pattern, but sporadic cases do occur.
- Several gene mutations have been identified that cause the manifestations of ARS. Two genes that have been researched most are PITX2 and FOXC1. These genes code for transcription factors and have variable expressivity, which explains the limited genotype-phenotype correlation and the spectrum of the condition’s presentation.
- The mechanism of ARS is that there is an arrest of tissue development in the anterior segment. In embryologic development of the eye, neural crest cells differentiate into several of the ocular tissues, and this process is abnormal in patients with ARS. The neural crest cells line the anterior chamber until late in gestation. In ARS, the cells do not migrate properly, leaving primordial tissue retained on the anterior iris and in the angle. In addition, the trabecular meshwork can be poorly developed and compressed with reduced spaces. Together this can lead to impaired aqueous outflow. Contraction of the primordial tissue over the anterior iris can contribute to corectopia, polycoria, and iris atrophy seen in ARS. This contracture may be progressive. Our patient presented with several of these anterior segment abnormalities consistent with ARS.
- Patients with ARS typically present with posterior embryotoxin, an anteriorly displaced Schwalbe’s line. This is very common, although not required for diagnosis. Up to 15% of the normal population without ARS may present with posterior embryotoxin. Additional clinical features include iris strands which can bridge to the trabecular meshwork, iridocorneal adhesions, iris stromal hypoplasia, corectopia, and polycoria. The ocular signs alone (without glaucoma) may be benign and not sight threatening. They may be, however, what prompts parents or caregivers to bring the child in for an exam.
- Glaucoma development is the most serious concern in patients with ARS. It is a result of incomplete and malformed angles and secondary IOP increase. Research has shown that there is a 50% chance of developing glaucoma in these patients. It is usually diagnosed early in childhood. The severity does not usually correlate with the amount of abnormal tissue in the angle but instead with the level of iris insertion into the angle. At the present time, our patient did not display any signs of glaucomatous damage but he will be monitored.
- Various other organ systems are affected in patients with ARS. There may be cardiovascular outflow tract abnormalities. Craniofacial abnormalities including maxillary hypoplasia, telecanthus, hypertelorism, and a broad and flat nasal bridge can also be present. Patients may have dental abnormalities such as hypodontia and microdontia and redundant periumbilical skin.

V. Treatment, management
- Our patient with ARS syndrome fortunately does not have any signs of glaucoma, so he will be monitored with IOP checks every four months. He has a concurrent superficial punctate keratitis
secondary to dry eye syndrome, for which artificial tears QID OU and artificial tear ointment qhs OU was prescribed. A full-time spectacle Rx was prescribed given his refractive amblyopia. He is returning in two months for an anterior segment and visual acuity evaluation.

- The treatment of patients with ARS would involve managing glaucoma, should it develop. Because the risk is high and it often is diagnosed in childhood, it is important to follow patients with ARS frequently to monitor IOP and the optic nerve appearance. Any changes in the anterior segment should be noted. Gonioscopy should be performed, although it was deferred due to lack of cooperation in our patient until he is more mature in the future. In infants and other uncooperative patients, it may be necessary to consider anesthetizing the patient for examination if there are serious concerns about elevated IOP and optic nerve damage. Often the glaucoma is difficult to manage with topical medications and frequently surgical options are be considered.
- Clinicians should be careful managing the glaucoma with medications due to their systemic side effects and how they may affect systems in the body that are abnormal due to ARS. In particular, alpha agonists can complicate cardiac outflow further in a poorly developed system.
- Interdisciplinary communication is important in patients with ARS with the goal of collaborative care. It is important that these patients have evaluations by other physicians to define and monitor any systemic associations.

VI. Conclusion
- It is important to keep in mind that ARS constitutes a spectrum of developmental anomalies, both ocular and systemic. It may present with one or more of the typical phenotypic characteristics in varying degrees, some of which may be subtle.
- Multidisciplinary approach to management is necessary. Consider referrals to dentists, cardiologists, and primary care physicians.
- Recommend dental evaluations, routine physicals to rule out other systemic manifestations of ARS.
- Recommend optometric examinations to any siblings, given congenital nature of syndrome.
- These patients will need to be monitored for life with a systemic surveillance approach.

References


