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REVIEW

Ophthalmological Manifestations of Axenfeld-Rieger Syndrome: Current Perspectives

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Abstract: Axenfeld-Rieger syndrome (ARS) is a rare congenital disease that is primarily characterized by ocular anterior segment anomalies but is also associated with craniofacial, dental, cardiac, and neurologic abnormalities. Over half of cases are linked with autosomal dominant mutations in either *FOXC1* or *PITX2*, which reflects the molecular role of these genes in regulating neural crest cell contributions to the eye, face, and heart. Within the eye, ARS is classically defined as the combination of posterior embryotoxon with iris bridging strands (Axenfeld anomaly) and iris hypoplasia causing corectopia and pseudopolycoria (Rieger anomaly). Glaucoma due to iridogoniodysgenesis is the main source of morbidity and is typically diagnosed during infancy or childhood in over half of affected individuals. Angle bypass surgery, such as glaucoma drainage devices and trabeculectomies, is often needed to obtain intraocular pressure control. A multi-disciplinary approach including glaucoma specialists and pediatric ophthalmologists produces optimal outcomes as vision is dependent on many factors including glaucoma, refractive error, amblyopia and strabismus. Further, since ophthalmologists often make the diagnosis, it is important to refer patients with ARS to other specialists including dentistry, cardiology, and neurology.

Keywords: Axenfeld-Rieger syndrome, Axenfeld anomaly, Rieger anomaly, glaucoma, posterior embryotoxon, iris hypoplasia

Introduction

Axenfeld Rieger syndrome (ARS) is a clinically and genetically heterogenous group of conditions characterized by anterior segment dysgenesis of the eye and varying degrees of systemic congenital abnormalities.[1–4] The disease was first recognized by Axenfeld in 1920 who reported a patient with anterior displacement of Schwalbe's line (posterior embryotoxon) in combination with corectopia.[5] In 1934, Rieger described two patients with "mesodermal dysgenesis" consisting of iris hypoplasia, pseudopolycoria, and posterior embryotoxon.[6] Due to phenotypic similarities, the cases described by Axenfeld and Rieger were considered as part of the same group of disorders known today as ARS.

ARS occurs in 1 of 100,000–200,000 live births.[4] Further, there is no gender or racial predilection and has been reported in ethnic groups in Europe, Africa, North and South America, Middle East, and Asia.[4] Mutations in the *PITX2* and *FOXC1* genes, which are crucial for normal embryologic development of the anterior segment and other organs affected in ARS, account for 40–60% of cases.[7–9] Vision loss is most commonly due to glaucoma, which affects more than 50% of individuals with ARS.[10] Thus, although rare, it is important for eye specialists to recognize ARS in order to monitor for glaucoma and potentially arrange care with other specialists.

ARS Genetics and Pathogenesis

ARS is inherited in an autosomal dominant pattern with eye and systemic findings showing complete and incomplete penetrance, respectively.[3,7,8,11] Family-based studies and linkage analysis identified that mutations in two genes, Paired-like Homeodomain 2 (*PITX2*) and Forehead Box C1 (*FOXC1*), are causative in approximately half of ARS cases.[9,12–16] The *PITX2* gene is located on 4q25, while the *FOXC1* gene is localized to 6p25, and both genes encode for transcription factors predominantly expressed during embryogenesis.[12,17] Disease causing mutations in *PITX2* and *FOXC1* are

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classified as type I and type III ARS. Type II ARS has been localized to 13q14, and a separate isolated case was associated with 16q24 deletion; however, the specific genes involved have yet to be identified.[3,7,18,19] Further, anterior segment dysgenesis, and in some cases specifically referenced as ARS, has also been associated with mutations in *CYP1B1, COL4A1, PAX6, FOXE3, CPAMD8*, and *PXDN*.[20–23] In addition, genetic testing utilizing targeted gene panels for anterior segment dysgenesis fails to identify gene mutations in many ARS patients indicating that much knowledge is still to be gained regarding the genetics of this disease.

As *PITX2* and *FOXC1* mutations are most common, the phenotypes associated with these genes are best described.[3,15,24–31] Reports in the literature have suggested that *FOXC1* mutations are more likely to cause isolated ocular findings such that craniofacial and dental anomalies are rare.[3,32] This is in contrast to *PITX2* mutations, which in addition to anterior segment dysgenesis have been reported to be commonly associated with craniofacial abnormalities.[3,32–34] Further, a more recent study showed that *FOXC1* mutations had more corneal involvement and higher incidence of glaucoma in contrast to *PITX2* mutations which showed more iris abnormalities.[35] However, personal experience with numerous multi-generation families with ARS and either *FOXC1* or *PITX2* mutations challenges this division of gene function. Further, there is phenotypic variation in eye and systemic findings amongst affected family members that carry the same genetic mutation.[25,33,36]

Nevertheless, the association between ARS and mutations in *PITX2* and *FOXC1* yields important insight into disease pathogenesis. Mouse, chick and zebrafish animal models have demonstrated that *Pitx2* and *Foxc1* are expressed in neural crest cells during embryogenesis.[32,37–45] The neural crest is a transient stem cell population that originates at the edge of the neural tube, migrates throughout the embryo, and gives rise to a diverse set of tissues.[46–48] *Pitx2* and *Foxc1* are expressed in the cranial and cardiac neural crest subpopulations. The cranial neural crest arises from the edge of the mesencephalon and rhombencephalon and migrates into the craniofacial region to populate the 1st and 2nd pharyngeal arches, frontonasal process, and periocular mesenchyme.[49–51] In the mid- and lower face region, the cranial neural crest cells from the 1st and 2nd pharyngeal arches give rise to the odontoblasts and cementoblasts required for tooth formation, connective tissue, and the maxillary and mandibular bones.[51–57] The cranial neural crest cells within the periocular mesenchyme migrate into the anterior segment of the eye via the ocular fissure and between the surface ectoderm-derived corneal epithelium and neural epithelial-derived optic cup to contribute to the corneal stroma and endothelium, iris stroma and muscles, ciliary body stroma, trabecular meshwork and aqueous outflow tracts, and sclera.[49,51,55] The cardiac neural crest cells originate at the level of the third somite and migrate through the 3rd, 4th, and 5th pharyngeal arches on their way to the cardiac outflow region where they regulate tract septation and aortic arch formation.[58,59]

Genetic manipulation of *Pitx2* and *Foxc1* expression in animal models shows that absence of these genes halts cranial neural crest cell migration from the edge of the neural tube, which induces cell apoptosis.[42,60] Thus, few neural crest cells reach the pharyngeal arches and periocular mesenchyme resulting in absence of jaw and mid-face bone formation and disruption of cornea, iris, and iridocorneal angle development. Further, *Pitx2* and *Foxc1* expressed in the periocular mesenchyme regulate closure of the optic fissure on the inferonasal edge of the optic cup such that loss of these genes in neural crest cells also causes microphthalmia and colobomas.[41,42,60] Complete knockout or knockdown of *Pitx2* or *Foxc1* in mice and zebrafish results in embryonic lethality due to cardiac malformations; however, heterozygous *Pitx2* mice show anterior segment anomalies similar to human ARS.[43]

As ARS is inherited in an autosomal dominant fashion, gene dosage likely plays a role in disease pathogenesis.[61] In the heterozygous state, early craniofacial and cardiac neural crest development may proceed thereby preventing embryonic lethality; however, the phenotypes may reflect later roles of these genes. *Pitx2* and *Foxc1* continue to be expressed in neural crest-derived cells in the developing anterior segment. These neural crest cells form a continuous layer that separates the trabecular meshwork from the anterior chamber, preventing aqueous humor drainage.[1,20] This cell layer eventually retracts to expose the trabecular meshwork and allow for aqueous outflow. Inhibition of this retraction along with contraction of the layer is hypothesized to result in iridogoniodysgenesis. While there is interaction between the Pitx2 and Foxc1 proteins within neural crest cells, specific downstream targets are not well defined.[61] It is likely that additional genes associated with ARS that have yet to be identified interact within the *PITX2* and *FOXC1* pathways in neural crest cells and will yield further insight into disease pathogenesis.

Ocular Manifestations

ARS presents with characteristic anterior segment findings that are typically bilateral but can be asymmetric or, rarely, unilateral (Supplemental Table 1).[4,15,16,25–27,31,35,62] By convention, ARS is the combination of posterior embryotoxon with iris bridging strands (Axenfeld anomaly) and iris hypoplasia (Rieger anomaly) (Figure 1A–D).[2–4,8,24] Posterior embryotoxon is classically described as premature termination of Descemet's membrane (Schwalbe's line); however, a more recent histological study has shown that the line itself is a peripheral corneal stroma nub that is present due to an attenuated Descemet's membrane.[63] Clinically, posterior embryotoxon varies in presentation from a discontinuous subtle line in the peripheral cornea that runs parallel to the limbus to a prominent continuous white line (Figure 1E, arrowheads). Findings are more evident on gonioscopy, especially if iris strands that traverse the angle structures are present.[3,64] These bridging strands may be thin or thick, but unlike peripheral anterior synechiae do not typically cause angle closure or restrict aqueous outflow.[3] Although posterior embryotoxon is found in the majority of patients with ARS, it is not necessary for the diagnosis. Additionally, 15% of the normal population may have some degree of posterior embryotoxon, but it is less pronounced and not associated with iris bridging strands.[64] Rieger anomaly refers to iris hypoplasia and can be associated with corectopia and pseudopolycoria (Figure 1A–D).[2–4,8,24] Absence or malformation of the iris stroma and muscles (sphincter and dilator) in conjunction with iris bridging strands leads to pupil distortion and iris tears. The corectopia and pseudopolycoria are rarely visually significant but may cause cosmetic concerns. However, not all patients with ARS have corectopia or pseudopolycoria, and the hypoplasia may manifest as a gray, featureless (lack of crypts, furrows, and rings) iris (Figure 1F).[35]

In addition to these classic findings, other ocular structures can show abnormalities. Congenital and early-onset cataracts are common; however, lensectomy can be challenging due to corneal abnormalities, poor pupil dilation and iris floppiness.[65,66] In rare cases, congenital cataracts in ARS can be associated with persistent fetal vasculature and microphthalmia, which further complicates surgical removal.[17,24] Corneal involvement can be more extensive as eyes can also show Peters anomaly and sclerocornea.[16,24,31,35,62,67–69] These congenital corneal abnormalities especially when coupled with glaucoma (discussed in next section) can predispose for corneal edema and scarring due to decompensation.[35,62] Although traditionally considered an anterior segment dysgenesis, optic nerve and retinal abnormalities have also been reported in ARS.[70] Optic nerve colobomas, hypoplasia, and dysplasia (Figure 2A), foveal hypoplasia (Figure 2B) and atrophy, and chorioretinal colobomas have all been reported in patients with ARS.[16,25,71,72] The importance of recognizing these other abnormalities as part of the disease spectrum is emphasized by phenotypic variations causing delayed diagnosis in individuals belonging to families with genetically confirmed ARS.

Glaucoma in ARS

Glaucoma secondary to the anterior segment dysgenesis is the main source of morbidity in ARS and affects more than 50% of patients.[10,35] Although it is tempting to attribute elevated intraocular pressure (IOP) to the iris strands that bridge the iridocorneal angle, the pathogenesis of glaucoma is more likely due to congenital malformation of the iridocorneal angle structures as severing of the iris bridging strands is ineffective in obtaining pressure control.[10]

Elevated IOP may be present at birth or not manifest until adulthood; however, most individuals with glaucoma secondary to ARS will be diagnosed during childhood. Further, glaucoma is typically bilateral, but may asymmetrically

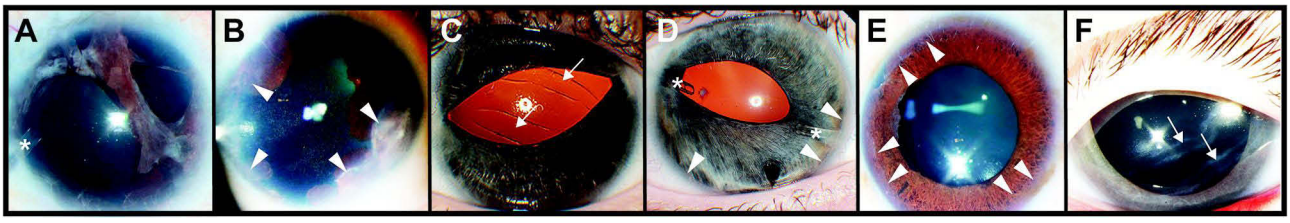

Figure 1 Anterior segment findings in ARS. Six eyes of patients with ARS display characteristic anterior segment findings including pseudopolycoria (**A**), corectopia (**B**–**D**), and posterior embryotoxon with varying degrees of iris bridging strands (arrowheads, **B**–**E**). Iris hypoplasia can appear as loss of pigment (**A**), gray-brown appearance (**C** and **D**), and featureless with loss of crypts, furrows, and rings (**F**). Glaucoma affects over 50% of individuals with ARS and elevated IOP in infants and young children can cause Haab's striae (arrows, **C** and **F**). Glaucoma drainage devices (stars, **A** and **D**) have been implanted in two of the eyes.

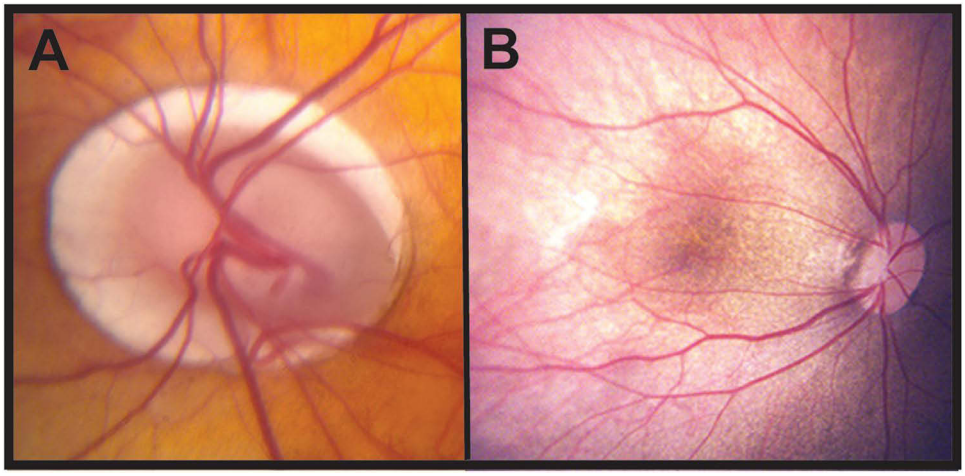

Figure 2 Posterior segment findings in ARS. Two eyes of patients with ARS show optic nerve dysplasia with significant peripapillary chorioretinal atrophy (**A**) and foveal hypoplasia (**B**).

affect one eye greater than the other.[10] Thus, individuals with ARS need to be routinely and carefully monitored for signs and symptoms of glaucoma. In addition to increased IOP and optic nerve cupping, children under 5–7 years of age may also show the classic signs and symptoms usually associated with primary congenital glaucoma (PCG). These include buphthalmos with increased corneal diameter and axial length, Haab's striae (breaks in Descemet's membrane), and corneal edema, which results in photophobia, blepharospasm, and epiphora.[73,74] Especially in toddlers where IOP readings obtained in clinic may not be accurate due to poor cooperation, attention should be paid to changes in visual function, ocular preference, strabismus measurements, corneal clarity, cycloplegic refraction, and optic nerve appearance.

Glaucoma management typically starts with standard topical ocular anti-hypertensive medications.[10] The exception can be neonates presenting at birth with buphthalmos and corneal edema who, unless there is a known family history of ARS, are often initially misdiagnosed with PCG. Careful slit-lamp examination and gonioscopy, if not obscured by corneal edema, can help distinguish between classic ARS and PCG. It is important to note that iridogoniodysgenesis, which should be classified as a variant of ARS due to its genetic association with *PITX2* and *FOXC1* mutations, shares more clinical similarity with PCG as posterior embryotoxon, iris bridging strands, corectopia and pseudopolycoria are often absent.[75–78] Examination for craniofacial abnormalities (discussed below) as well as careful assessment of past medical history, review of systems, and family history often helps to differentiate between these two entities. This is relevant as unlike PCG, angle surgery (goniotomy and trabeculotomy) does not usually yield long-term IOP control in iridogoniodysgenesis or ARS.[10]

Glaucoma in ARS is often refractory to medications such that two-thirds of affected patients require at least one IOP-lowering surgery. As mentioned above, goniotomy and trabeculotomy are less effective in obtaining and maintaining IOP control.[10] This suggests that the restriction of aqueous humor outflow does not solely reside within the trabecular meshwork, but also involves downstream and alternative tracts. However, this has not been confirmed histologically or via aqueous humor outflow imaging. As a result, the majority of patients with glaucoma secondary to ARS require angle-bypass surgery, typically trabeculectomy with anti-fibrotics or placement of a glaucoma drainage device (GDD) to achieve long-term IOP control.[10] Trabeculectomy surgery in children and young adults requires adjunctive anti-fibrotics, usually mitomycin C, to prevent bleb scarring. While trabeculectomies avoid the use of hardware, this surgery presents post-operative challenges such as over- or under-filtration and bleb leaks that can be difficult to manage in infants and children. In addition, trabeculectomies carry a life-long risk of bleb-related infections that if not diagnosed and managed appropriately can result in vision loss due to endophthalmitis.[79–81] Careful patient selection based on the ability to monitor and manipulate the bleb in clinic as well as patient and parent understanding of the risks associated with trabeculectomies is critical. Thus, despite the fact that trabeculectomies are generally able to achieve lower eye pressures, GDDs have become the mainstay of angle-bypass surgery in children.[82–90]

GDDs are divided into two main categories, valved and non-valved. Valved GDDs, such as the Ahmed FP7 and FP8, afford immediate IOP lowering effect and less risk of hypotony. While the post-operative management is more straightforward, early outflow of aqueous humor, which is hypothesized to carry pro-inflammatory cytokines, can lead to bleb encapsulation and the hypertensive phase by 4 to 8 weeks after surgery.[91–94] This hypertensive phase is a poor prognostic indicator for overall success and survival of the Ahmed GDD. Non-valved GDDs, such as Baerveldt and Molteno implants, require either a dissolvable ligature suture or implantation in two steps as the resistance to aqueous outflow is dependent on the formation of a capsule around the GDD plate.[88] The pressure lowering effect should be delayed for at least 3 weeks, but hypotony can still be a challenge.[88,95] However, the absence of early aqueous humor outflow in non-valved implants is thought to limit plate encapsulation and ultimately increase success and survival time compared to valved GDDs.

Implantation of GDDs in ARS presents unique challenges. The iris bridging strands, especially when thick, can bleed and prevent ideal placement of the tube. In addition, the intraocular portion of the tube should be placed as far from the cornea as possible to decrease the risk of exacerbating the endothelial layer. However, this needs to be balanced with iris floppiness that can lead to tube obstruction. In cases of severe anterior segment dysgenesis with shallow anterior chambers, the lens may need to be removed such that the tube can be placed in the pars plana.[96–98]

Ciliary body ablation, either transscleral or endoscopic, can help control IOP, but is most effective after aqueous outflow has been established with a GDD.[10,88,99] In severe anterior segment dysgenesis, transscleral cycloablation can seem like an attractive option given the challenges and potential complications of intraocular surgery in these complex eyes. However, the window between glaucoma and hypotony is slim if there is no adequate outflow. Multiple sessions of ciliary body ablation often yield minimal effect on IOP, and ultimately angle-bypass surgery may be required.[88] However, the outflow may then be greater than aqueous production resulting in hypotony and phthisis.

When managing glaucoma secondary to ARS, it is important to develop a well thought out strategy since most eyes will require more than one IOP-lowering surgery.[10] GDDs tend to be favored in children but may need to be combined with cycloablation for optimal pressure control.[82–90] Trabeculectomy with anti-fibrotics is also highly effective but is typically reserved for adolescents and adults. Further, in children, there is a great need for maximizing surgical options for the future given the life-long need for treatment.

Visual Outcomes in ARS

Few studies have assessed visual outcomes in ARS due to the rarity of the disease. In one of the largest case series of ARS patients, the average best corrected visual acuity was approximately 20/60 in thirty-two affected individuals, but vision ranged from 20/20 to light perception.[10] Visual outcomes in ARS are dependent on numerous factors. While glaucomatous optic neuropathy first affects the visual field and at late stages central visual acuity, other consequences of elevated IOP in children with ARS can impact visual outcomes.[73,74] Haab's striae directly impair vision if present in the central visual axis but also indirectly affect vision by inducing high amounts of irregular astigmatism. Further, increased axial length associated with buphthalmos can lead to significant myopia.[100,101] However, in the previously referenced study, there was no significant difference in average best corrected visual acuity between eyes with ARS that did or did not have glaucoma.[10] Although more rare, involvement of other ocular structures including cataracts, Peters Anomaly, sclerocornea, optic nerve and retinal colobomas worsens visual prognosis.[10,99] Since ARS is a congenital disease and glaucoma is typically diagnosed during childhood, it is also critical to address refractive error, amblyopia, and strabismus.[101,102] Both high myopia and astigmatism can cause bilateral amblyopia if the refractive error is left uncorrected. Furthermore, asymmetry of refraction (anisometropia) or ocular findings affecting the cornea, lens, retinal or optic nerve can lead to unilateral amblyopia. This can be further exacerbated by strabismus, which due to asymmetry of vision and lack of fusion, is common.[100] As a result, correction of refractive error with glasses or contact lenses, part-time occlusion and strabismus surgery may be needed to optimize visual outcomes. Thus, coordinated management between glaucoma specialists and pediatric ophthalmology is critical in patients with ARS.

Systemic Manifestations in ARS

While the ocular findings in ARS draw the most attention, there are systemic manifestations that are important to recognize as they may help solidify the clinical diagnosis and potentially require other subspecialty care (Supplemental Table 1).[15,17–19,21,24,25,27,31,35,62] Due to the common origin of craniofacial and ocular neural crest cells, there is a characteristic craniofacial appearance associated with ARS which consists of maxillary hypoplasia with mid-face flattening, mandibular hypoplasia, hypertelorism, micrognathia, cleft palate, and telecanthus.[3,4,17–19,25,30,31,33,34,62,103] Dental anomalies due to decreased odontoblast and cementoblasts are very common in ARS and are classically microdontia (small teeth) and oligodontia (too few teeth).[2,15,19,21,24,25,27,31,35,62,68,104] Further, tooth enamel is often abnormal leading to a high rate of dental caries.[62,105] As a result of these teeth abnormalities, children with ARS need evaluation and close monitoring by pediatric dentistry.[106] Although less common than the craniofacial and dental abnormalities, congenital heart defects such as aortic and mitral valve stenosis and hypoplasia of the cardiovascular outflow tracts have been found in almost one-quarter of ARS patients.[15,19,35,62,67,68,107–109] Additional systemic findings, including redundant periumbilical skin, hypospadias, anal stenosis, hearing loss, skeletal anomalies, and growth retardation have all been reported with ARS.[10,17–19,25,27,31,33–35,62,68,110–113] Further, neurologic involvement including white matter hyperintensities, hydrocephalus, Dandy Walker malformations, and arachnoid cysts with developmental delays and learning disabilities have all been described in individuals with ARS.[17,19,25,31,35,62,106,114] More recently, *FOXC1* and *PITX2* mutations have been associated with small cerebral vessel abnormalities that increase stroke risk such that all individuals diagnosed with ARS should undergo brain imaging.[42] With the rarity of ARS, there is often under-recognition of the constellation of systemic and ocular manifestations. Greater knowledge of this disease amongst specialists including ophthalmologists, dentists, and cardiologists is needed.

Conclusions

As ARS is often diagnosed by ophthalmologists, it is important to recognize both the eye and systemic manifestations and coordinate appropriate care with other specialties.[62] Glaucoma is the main source of morbidity and often requires angle-bypass surgery to obtain IOP control.[10] However, in children affected with ARS, it is critical to also simultaneously address refractive error, amblyopia, and strabismus to optimize visual outcomes.[101,102] Since ARS is inherited in an autosomal dominant pattern, biological parents of affected children should be examined as there can be phenotypic variation and eye findings may be subtle. Genetic testing can help confirm the diagnosis, but lack of identification of a gene mutation does not rule out this clinical diagnosis. The discovery of additional genes associated with ARS will improve our understanding of molecular pathways involved in craniofacial and ocular neural crest cell development.

Disclosure

The authors report no conflicts of interest in this work.

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