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Axenfeld–Rieger syndrome in the pediatric population: A review

Nikhila S. Khandwala[1], Muralidhar Ramappa[2], Deepak P. Edward[1], Mehmet C. Mocan[1]*

Abstract:

Axenfeld–Rieger syndrome (ARS) is a rare autosomal-dominant neurocristopathy that presents with a variety of classical ocular and systemic findings. The pathophysiology of the disease involves anterior segment dysgenesis, and patients may present with ophthalmic complications early in life, including secondary glaucoma, high refractive errors, amblyopia, and permanent visual damage. There are a limited number of studies in the literature that focus primarily on pediatric patients with ARS. The purpose of this article was to review the current literature on clinical presentation, genetic associations, diagnosis, secondary complications, and treatment of ARS in pediatric patients. Evaluating the essential clinical aspects of the disease in children may allow for earlier diagnosis and treatment and prevent visual morbidity from amblyopia and secondary glaucoma that may result in permanent visual damage.

Keywords:

Amblyopia, Axenfeld–Rieger syndrome, pediatric glaucoma, secondary glaucoma

Introduction

Axenfeld–Rieger syndrome (ARS) is a rare autosomal-dominant condition with complete penetrance that affects multiple organ systems.[1-4] The incidence of the disease is about 1 in 100,000 live births, and the disease does not demonstrate an ethnic predilection.[2] ARS was initially characterized as three distinct conditions, however, has since been recognized as a spectrum of overlapping ocular and nonocular defects.[1] The pathophysiology of ARS is thought to be related to the abnormal migration of neural crest cells during embryogenesis. Development of the anterior chamber structures, including the ciliary body, cornea, and iris stroma, depends on neural crest cell migration and is, therefore, implicated in ARS.[1,5] Ocular manifestations of the disease are commonly related to anterior segment dysgenesis, including posterior embryotoxon, iris atrophy, angle dysgenesis, and less commonly, corneal haze.[1] Patients often present in early childhood with the presence of secondary glaucoma, decreased visual acuity, strabismus, or amblyopia, and are described in detail later in this review.[6-8] While the disease is diagnosed often in childhood, few studies have evaluated ARS in pediatric populations. The purpose of this review was to describe the spectrum of clinical presentation, genetic evaluation, diagnosis, and outcomes of ARS in the pediatric patient population.

ARS was previously described as three overlapping conditions. Axenfeld anomaly describes patients who present with disorders associated with posterior embryotoxon, while Rieger anomaly describes patients with central iris defects. Rieger syndrome includes patients with Rieger syndrome in addition to systemic findings.[5]

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[1]Department of Ophthalmology and Visual Sciences, Illinois Eye and Ear Infirmary, University of Illinois at Chicago, Chicago, Illinois, USA, [2]Centre for Rare Eye Diseases and Ocular Genetics, The Cornea Institute, Jasti V Ramanamma Children's Eye Care Center, L.V. Prasad Eye Institute, Hyderabad, Telangana, India

***Address for correspondence:**
Mehmet C. Mocan, MD, MPH, 1855 W, Taylor Street, Chicago, IL 60612, USA.
E-mail: cmocan@uic.edu

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Clinical Presentation

ARS presents as a wide phenotypic spectrum, associated with various ocular and systemic findings. The variable ocular and systemic phenotype in ARS may be attributed to the genotype of the disease.[3,8,9] ARS is thought to occur from developmental arrest of neural crest cell-based tissues. The genes commonly associated with ARS, *FOXC1*, and *PITX2* are expressed in neural crest cells that have migrated into the craniofacial, cardiac, and the anterior chamber of the eye.[4,10] Ocular findings are dependent on the degree of abnormal neural crest cell migration and differentiation as well as the retention of abnormal tissue in the anterior chamber.[11] Therefore, the spectrum of clinical findings in ARS is thought to be related to the type of mutation and gene implicated in the disease.[8-10]

Ocular Findings

Ocular findings in ARS are classically related to anterior segment dysgenesis, with most cases being bilateral, however, with an asymmetric presentation.[4,5] The most common anterior segment findings include anterior displacement of Schwalbe's line (posterior embryotoxon), iris bridging strands, iris aberrations, malformation of the angle, and corneal abnormalities [Table 1 and Figure 1].[11,12] Iris changes such as iris atrophy and iris hypoplasia may result in abnormal pupil appearance, including

Table 1: Common ocular findings in Axenfeld–Rieger syndrome

	Ocular findings
Cornea	Microcornea
	Sclerocornea
	Iridocorneal adhesions*
	Corneal opacification*
	Megalocornea
	Corneal edema
Angle	Posterior embryotoxon*
	Iridogoniodysgenesis*
	Peripheral anterior synechiae*
Iris	Iris atrophy*
	Iris hypoplasia*
	Corectopia*
	Polycoria*
	Iris adhesions
	Aniridia
	Iris processes*
Lens	Congenital cataract
	Early-onset cataract
Optic nerve	Optic nerve coloboma
	Optic nerve hypoplasia
	Optic atrophy
Retina	Foveal hypoplasia/pit
	Peripapillary chorioretinal atrophy
	Persistent hyperplastic primary vitreous
	Retinal detachment

*More common ocular findings associated with ARS. Description of ocular findings associated with ARS that have been previously noted in the literature. ARS: Axenfeld–Rieger syndrome

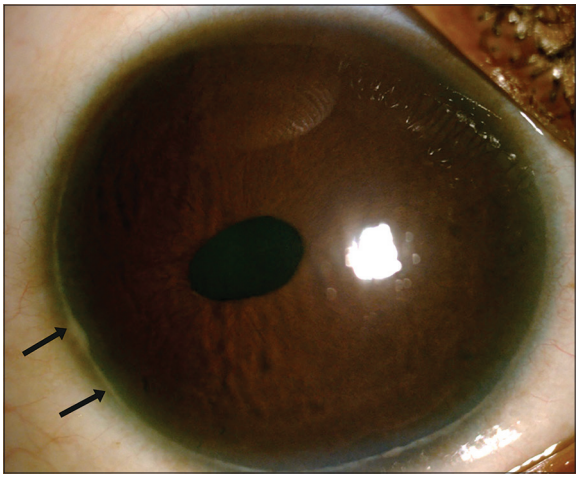

Figure 1: Posterior embryotoxon (black arrows)

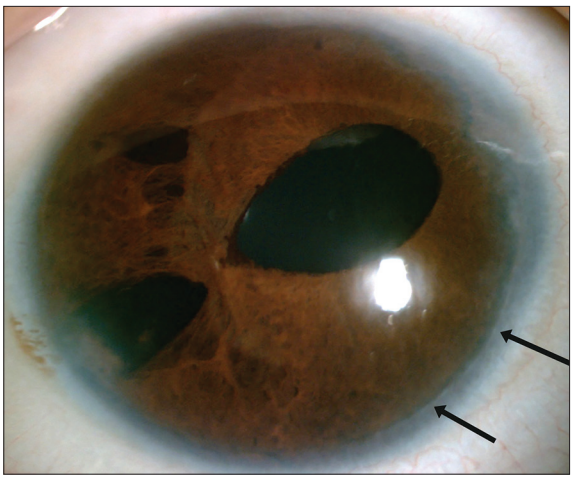

Figure 2: Iris atrophy, corectopia, and posterior embryotoxon (black arrows)

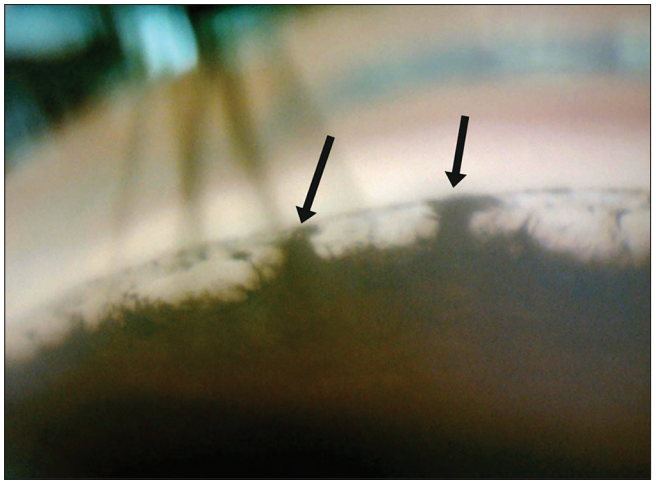

Figure 3: Gonioscopy showing iris processes (black arrows)

corectopia and polycoria [Figures 2 and 3].[4,5] Corneal abnormalities include the absence of the corneal endothelium and Descemet's membrane, resulting in stromal opacification.[13] These findings may be attributed to decreased endothelial cell density and mean cell area in ARS patients compared to the general population.[14] ARS often presents in early childhood when family members or primary care physicians note abnormal iris appearance or signs of secondary glaucoma, including buphthalmos, photophobia, tearing, and corneal clouding.[3] Early diagnosis of ARS is imperative in children to ensure prompt treatment and prevent the development of amblyopia and permanent visual impairment.[4]

While ocular features related to ARS are classically related to anterior segment dysgenesis, other ocular findings have been reported in the literature. Congenital and early-onset cataracts may be seen in patients with ARS.[4] Cataract extraction in this patient population may be more challenging due to iris malformation, including aniridia or iris atrophy, leading to poor pupil dilation. Corneal haze in pediatric patients with secondary glaucoma may also prove a challenge in lensectomy.[15] Retinal findings seen in rare cases of ARS include retinal detachments and persistent fetal vasculature.[16-18] There are a few case reports of foveal hypoplasia in families with ARS diagnosed with *PITX2* mutation.[19] Few case reports in the literature describe optic nerve coloboma, optic nerve hypoplasia, and peripapillary chorioretinal atrophy in ARS.[20-23] Glaucomatous optic nerve damage may be seen in patients with ARS–glaucoma.[24]

Systemic Findings

There is a wide variety of systemic findings associated with ARS in pediatric patients that represent manifestations of abnormal neural crest cell differentiation. Dysmorphic facial features include maxillary hypoplasia, hypertelorism, telecanthus, thin upper lip, and prominent forehead. Dental abnormalities are a common presenting characteristic related to maxillary and malar hypoplasia, resulting in hypodontia, oligodontia, and microdontia [Figure 4].[25-28] With regard to gastrointestinal abnormalities, redundant umbilical skin, Meckel diverticulum, and feeding difficulties may be seen with ARS.[8] Skeletal abnormalities include joint hypermobility or degeneration, scoliosis, and hip anomalies.[27] Cranial abnormalities shown in children with ARS include pituitary dysfunction that manifests as short stature or abnormal thyroid function, cerebrovascular disease, and neuropsychiatric symptoms.[29,30] Cardiac abnormalities have also been seen in patients with ARS, including atrial septal defects, mitral valve defects, and left-sided obstructive lesions. Cardiac anomalies may be more prevalent in patients with *FOXC1* mutations given the association of *FOXC1* in the development of the cardiac valves and atrial septum seen in mouse studies, which may be life-threatening in a pediatric patient.[31,32]

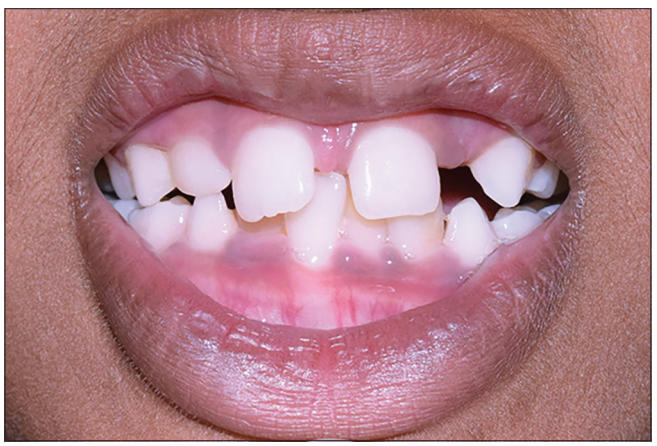

Figure 4: Dental abnormalities in Axenfeld–Rieger syndrome. Example of patient with Axenfeld–Rieger syndrome presenting with oligodontia and microdontia

Genetic Association

ARS has been characterized as a disease with complete penetrance but variable expressivity.[33] Approximately 40%–70% of ARS cases may be attributable to *PITX2* and *FOXC1* mutations which code for transcription factors that are expressed during embryogenesis.[8,16] Gene dosage as well as the interaction between these two transcription factors may explain the phenotypic variability of ARS.[10,16] While ARS is a genetic disorder with complete penetrance, it may have variable clinical manifestations depending on the associated mutation of *FOXC1* versus *PITX2* [Table 2]. *FOXC1* mutations are more commonly associated with isolated ocular findings compared to *PITX2* mutations that are associated with defects in other organ systems. However, rates of secondary glaucoma are similar between both mutations.[8,9,34] *FOXC1* mutations are also associated with a more variable ocular presentation.[8] *PITX2*

Table 2: Phenotypic differences between *PITX2* and *FOXC1* mutation

Ocular manifestations	Systemic manifestations
PITX2 defects	
Posterior embryotoxon	Dental findings: Hypodontia, oligodontia, and microdontia
Corectopia	Umbilical abnormalities
	Meckel diverticulum
FOXC1 defects	
Iris hypoplasia	Isolated atrial septal defect
Corectopia	Congenital heart disease
Peripheral anterior synechiae	Hearing loss
Posterior embryotoxon	Hip abnormalities
Iridogoniodysgenesis	Feeding difficulties
	Joint/skeletal abnormalities

Comparison of phenotypic differences between the two common genetic mutations associated with ARS. ARS: Axenfeld–Rieger syndrome

mutations have been shown to be more closely related to the development of ARS compared to *FOXC1*.[33] Rates of glaucoma within the first 2 years of diagnosis are more frequent for *FOXC1* mutations compared to *PITX2*, where secondary glaucoma may present in later childhood, adolescence, or adulthood.[8] However, not all patients with the clinical phenotype of ARS have mutations in these two genes, suggesting that other genes or mechanisms may be involved in the pathogenesis of the disease.[4]

Systemic manifestations are more commonly associated with *PITX2* mutations compared to *FOXC1*.[8,9] Odontogenic disease, umbilical abnormalities, and Meckel diverticulum are more common in *PITX2* mutations, whereas congenital heart disease, feeding difficulties, hearing loss, and skeletal abnormalities are more common in *FOXC1* mutations.[8] Therefore, the use of genetic testing is helpful in confirming the diagnosis of ARS and predicting the extent of systemic involvement in patients with ARS phenotypical features.

Diagnosis

Diagnosis of ARS in pediatric patients depends on meticulous ocular and systemic examination. Such a detailed clinical assessment may be difficult in pediatric patients due to poor cooperation with examination, and therefore, ophthalmologists should be mindful of changes in visual acuity, ocular fixation preference, development of strabismus, and corneal opacifications as manifestations of ARS.[4] Frequent assessments with examination under anesthesia are required to undertake glaucoma work-up, including intraocular pressure (IOP) measurements, determine amblyogenic refractive errors, and detect corneal alterations in size and clarity. However, some patients with ARS-associated craniofacial abnormalities may be at high risk for anesthetic complications.[35] Important parameters to note during the initial examination include visual acuity, fixation behavior, anterior segment alterations, IOP, and optic nerve evaluation.[2,4,36] It is also important to perform or initiate a thorough physical examination to identify the associated systemic findings, including craniofacial abnormalities, cardiac defects, and skeletal deformities, followed by referral to pediatricians for further management of the systemic aspects of ARS.

Genetic testing in concert with physical examination is instrumental in confirming the diagnosis of ARS, regardless of family history due to the implication on family members and potential future offspring.[2] In patients with both ocular and systemic manifestations, the sensitivity of genetic testing has been shown to be around 35%–40%, with a specificity of around 95%.[37-39] A child born to a person with ARS has a 50% chance of inheriting the trait; however, the mutation is *de novo* in 50%–70% of patients.[2] While ARS is mainly diagnosed based on clinical presentation, genetic testing may help differentiate the diagnosis between other disorders associated with anterior segment dysgenesis such as Peters anomaly and primary congenital glaucoma (PCG).[39]

Imaging modalities have the potential to assist in diagnosis and monitoring of ARS, especially ARS-related glaucoma, in children. Optical coherence tomography (OCT) of the optic nerve, portable OCT, and anterior segment OCT are some imaging modalities that may assist in identifying various components of ARS, including angle anatomy and glaucomatous damage to the optic nerve. Portable OCT has shown effectiveness in aiding in optic nerve evaluation in pediatric patients, especially when corrected for age-related optical parameters.[40] Handheld disc photos and fundus examination may be difficult to obtain in ARS due to the presence of corneal haze. Anterior segment OCT may help visualize anterior segment anomalies of ARS, including iris atrophy, posterior embryotoxon, peripheral bridging tissue bands, trabecular meshwork elongation, and high insertion of iris root into the posterior trabecular meshwork.[41] Visual field assessment may be difficult to perform in pediatric patients given the difficulty of fixating on a target, poor attention span, and cooperation, leading to increased variability among this cohort. Reliable visual field testing is also unlikely in children until they reach 9–10 years of age.[42] Efforts have been made to develop pediatric-friendly visual field assessments; however, variability remains high and, therefore, may not be helpful in clinical practice.[43]

When establishing the diagnosis of ARS, it is crucial to differentiate it from other diseases associated with childhood glaucoma, primarily from conditions such as PCG, Peters anomaly, and other diseases of anterior segment dysgenesis. PCG represents an isolated developmental abnormality of the anterior chamber angle, whereas secondary glaucoma is associated with aqueous outflow obstruction due to either congenital or acquired ocular disease.[44] Clinical features of PCG include an enlarged globe, cloudy cornea, presence of Haab striae, and optic nerve cupping. Even though a component of isolated iris hypoplasia may be present, findings such as corectopia, broad iridocorneal adhesions, or prominent Schwalbe's line are not observed.[45] On the other hand, the highlighting feature of Peters anomaly includes the presence of central corneal opacity and adhesions between the corneal and iris surrounding the central corneal opacity. Peters plus syndrome has additional systemic findings of cleft lip or palate, short stature, abnormal ear anatomy, and intellectual disability.[46] While clinical presentation may

help distinguish ARS from other diseases associated with childhood glaucoma, genetic analysis may be extremely helpful to differentiate between ARS and other causes of early childhood glaucoma. PCG has been associated with CYP1B1, LTBP2, and TEK genetic mutations, while Peters anomaly has multiple genetic associations, including PAX6, PITX2, PITX3, FOXC1, FOXE3, CYP1B1, B3GLCT and COL4A1.[47,48] Therefore, the use of clinical presentation, examination findings, and genetic analysis may help distinguish ARS-related glaucoma from PCG and Peters anomaly.

Secondary Glaucoma

Glaucoma has been reported as a secondary complication in about 50%–70% of ARS cases and is the main cause of long-term vision loss for these patients.[7,11,12] Elevated IOP occurs due to congenital malformation of the angle structures.[4,11] Childhood glaucoma has an incidence of 1 in 10,000–18,000 births.[49] Studies evaluating secondary glaucoma in pediatric patients have found ARS as one of the more common etiologies of secondary glaucoma.[36,44,50] ARS-related glaucoma typically presents either during adolescence or early adulthood or within the 1st few years of life. Most patients with secondary glaucoma related to ARS present with elevated IOP in childhood.[4,50] The pathophysiology for early-onset glaucoma in ARS is associated with halted development of the anterior chamber structures, dysgenesis of the trabecular meshwork, and Schlemm's canal.[7,11]

Presenting clinical features of children with secondary glaucoma include globe enlargement (buphthalmos), increased corneal diameters, Haab striae, corneal edema elevated IOP, optic nerve cupping, and axial length elongation.[4] In older children, progressive myopia, failed vision exam tests, and sensory strabismus can bring glaucoma to attention.

The management of ARS-associated glaucoma is difficult, especially in pediatric patients as the disease progresses rapidly.[9] The management of ARS-related glaucoma is through medical or surgical means. While surgical management is usually the definitive step in the treatment of pediatric glaucoma, medical therapy is often the first step in IOP control, unless patients present with neonatal onset glaucoma with very high IOPs. In the past, beta-blockers were the first choice in the treatment of pediatric glaucoma, however, were associated with apnea in neonates and tachyphylaxis after long-term use. Prostaglandin analogs are often used as a first-line therapy in secondary pediatric glaucoma as studies have shown significant IOP reduction over long-term use; however, side effects include orbitopathy.[51] Other medications, including carbonic anhydrase inhibitors (topical and systemic), and newer medications like netarsudil have also been shown to have IOP-lowering effect in pediatric glaucoma.[11,50,52] However, medical therapy in pediatric cases often fails to control IOP in over 67% of patients in the long run, and surgical management is required for definitive IOP control.[4,6,7,44]

Surgical management of ARS-associated glaucoma has been frequently debated as there is no consensus as to which procedure has the greatest success. Furthermore, there is limited literature on surgical management of ARS-related glaucoma in pediatric patients. Therefore, most patients require an average of two glaucoma surgeries for adequate IOP control.[7] When determining which surgical technique to pursue, a comparison of the risks and benefits of each procedure should be considered [Table 3]. While goniotomy is often the first step in the surgical management of PCG, studies have shown that goniotomy has poor success in ARS-associated glaucoma.[7,38,41,42] The pathophysiology of ARS may lead to poor results with goniotomy due to the presence of iridocorneal attachments, and some authors describe goniotomy as contraindicated in diseases of anterior segment dysgenesis.[11,53] Trabeculectomy has been shown to have poor success in ARS patients; however, trabeculectomy with antifibrotics like mitomycin-C has been shown to have more favorable outcomes with reports of up to 57% success over 18 years.[7,10,36,41] However, trabeculectomy has certain limitations in younger pediatric patients due to the thick and active Tenon's capsule and rapid wound healing, thereby necessitating the use of antimetabolites for long-term success.[6] Complications associated with trabeculectomy, including bleb-related infections, have also limited the use of this procedure in pediatric patients due to difficulty in the postoperative examination.[53] The combination of trabeculectomy and trabeculotomy in infant patients has been shown to have a high long-term success rate of IOP control under experienced hands in ARS–glaucoma patients with success in 68.2% at a 5-year follow-up.[6,7] Glaucoma drainage implants are being used with increasing frequency in pediatric secondary glaucomas.[54,55] The Baerveldt glaucoma implant has been shown to have better IOP control compared to the Ahmed glaucoma valve in cases of ARS-associated glaucoma, with 70% success rate with Baerveldt versus 25% success rate with Ahmed valve at 2 years.[7] One case report describes the successful use of minimally invasive glaucoma surgery with placement of XEN45 in a patient with ARS who had undergone prior surgeries with failed IOP control; however, this technique has not been described in children with ARS–glaucoma.[56] Transscleral cyclophotocoagulation has been used to treat ARS-related glaucoma, however,

Table 3: Comparison of various surgical approaches in patients diagnosed with Axenfeld–Rieger syndrome-associated glaucoma

Surgical technique	Benefits	Disadvantages
Angle procedures		
Goniotomy	Access several clock hours of the anterior chamber angle	Presence of iridocorneal adhesions may prevent an approach to the angle
	Conjunctiva sparing allows for future glaucoma procedures	Not possible in cases with corneal edema or opacification
	No foreign body inserted	
	May be repeated	
Trabeculotomy ab externo	Allows ab externo approach in eyes with or without corneal involvement	Extensive iridocorneal attachments in the setting of ARS may hinder the creation of a patent passage into the anterior chamber
	May be repeated	
Trabeculectomy (± mitomycin C)	Standard technique that may be performed by ophthalmologists	Risk of failure due to thick, Tenon's capsule and robust wound healing in pediatric patients
	No foreign body within the eye	Lifelong risk of bleb-related infections with the use of mitomycin C
		Difficult to monitor in the pediatric population
Combined trabeculectomy and trabeculotomy	Higher rate of IOP control after a single surgery	Risk of hypotony, choroidal detachment, and anterior chamber hyphema and those seen with trabeculectomy with mitomycin C
	Addresses angle anomaly and provides alternate outflow pathway simultaneously	
	Familiar surgical landmarks for surgeons	Risk of early bleb failure
Glaucoma drainage devices		
Ahmed valve implant	Valvular design prevents postoperative hypotony	High risk of bleb encapsulation
		Increased risk of shunt exposure and tube retraction in children
Baerveldt implant	Easier implantation	Placement of a large shunt plate could be difficult in a child's eye
	Large surface area to allow for increased diffusion of aqueous humor	Risk of hypotony and increased risk of shunt exposure and tube retraction in children
Refractory IOP		
Transscleral cyclophotocoagulation	Minimally invasive procedure	Reserved for refractory cases
		Risk of hypotony and phthisis bulbi
		May cause scleral thinning in children
		IOP lowering unpredictable and not long term

Description of benefits and disadvantages of various surgical techniques pursued in the management of ARS-associated glaucoma. ARS=Axenfeld–Rieger syndrome, IOP=Intraocular pressure

is reserved as a last resort in pediatric patients.[7,11] Despite successful surgical management of ARS-related glaucoma in children, most patients need more than one surgical procedure as well as adjuvant topical therapy for long-term IOP control and require lifelong monitoring.[4,6,7,57]

Outcomes

A variety of factors associated with ARS may lead to permanent vision loss and the development of amblyopia in children, therefore necessitating close follow-up with an ophthalmologist during childhood. One study reported that the average best-corrected visual acuity in children with ARS averaged 20/60; however, there is a wide range from 20/20 to light perception depending on a multitude of factors.[7] Clinical characteristics associated with anterior segment dysgenesis, including corneal clouding, iris anomalies, congenital cataracts, optic nerve hypoplasia, retinal abnormalities, as well as refractive errors, may lead to the development of amblyopia and visual impairment.[21,58,59]

Risk factors for visual impairment in children with glaucoma include deprivation amblyopia, uncontrolled secondary glaucoma, strabismus, uncorrected refractive error, age at glaucoma diagnosis of <3 months, and interval to surgery >3 months.[60,61] Therefore, a multi-subspecialist approach by glaucoma, pediatric ophthalmology, and cornea specialists that includes close glaucoma monitoring, regular refractive assessments, and corneal assessments should be undertaken in children with ARS to prevent permanent vision loss.

Conclusion

ARS is a rare autosomal-dominant disease defined by a spectrum of ocular and clinical manifestations. ARS is often diagnosed in childhood, especially in cases of secondary glaucoma. However, few studies have defined the prevalence, clinical presentation, management, and outcomes of ARS in the pediatric population. Given the high risk of permanent visual loss in pediatric patients with the disease, it is imperative for ophthalmologists to be able to accurately diagnose and treat ARS and

its related complications. Perhaps, more importantly, ophthalmologists are posited in a uniquely central role in initiating the work-up for systemic organ involvement by recognizing the various clinical findings of this neural crest cell disorder and facilitating the early identification of systemic involvement in ARS.

Declaration of patient consent

The authors certify that they have obtained all appropriate consent forms from the legal guardians of the patients. In the form, the guardians have given the consents for the images and other clinical information of the patients to be reported in the journal. The guardians understand that the names and initials of the patients will not be published and due efforts will be made to conceal the identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests in this article.

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