# Axenfeld-Rieger Syndrome: A Case Series

# Síndrome de Axenfeld-Rieger: Uma Série de Casos

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## ABSTRACT

Axenfeld-Rieger syndrome (ARS) is a genetic disorder characterized by two key components: anterior segment dysgenesis and systemic abnormalities.

Regarding ocular features, posterior embryotoxon (anterior displacement of Schwalbe's line) is a hallmark. Rieger anomaly comprehends congenital iris abnormalities. When accompanied by systemic findings such as facial bone defects, odontological, pituitary or umbilical abnormalities, the condition is referred to as Rieger syndrome. Axenfeld anomaly and Rieger syndrome present simultaneously make the diagnosis of ARS. In rare cases, hearing loss and cardiac defects may also appear.

Patients with ARS have an increased risk of developing glaucoma due to impaired drainage of aqueous humor.

ARS is typically inherited as autosomal dominant but can also occur sporadically. Mutations in *PITX2*, *FOXC1*, *PAX6*, *FOXO1A*, and *CYP1B1* genes underlie ARS's genetic diversity.

The objective is to present clinical manifestations, treatment approaches, and outcomes of ARS, contributing to its understanding and management.

We present a case series of patients with ARS from the ophthalmology department of Hospital de São João, Porto, Portugal.

Five patients with ARS with different variants involving *PITX2* and *FOXC1* genes, in heterozygosity, are presented: a two-year-old girl with a deletion of *PITX2* gene; a seven-year-old girl and her forty-six-year-old mother with a duplication of exon 1 of *FOXC1* gene; a eleven-year-old boy with deletion and substitution of *FOXC1* gene; and a fifty-seven-year-old male with a deletion of the exon 1 of *FOXC1* gene.

Posterior embryotoxon, corectopia and iris hypoplasia are prevalent among the majority of patients. One patient exhibits mild ocular abnormalities. Notably, three patients have developed glaucoma, with two requiring ocular surgery. The eldest patient, most probably attributable to a delayed diagnosis, is the only individual with a substantial degree of visual impairment.

Systemic involvement is variable among patients and includes mostly hypertelorism, sensorineural hearing loss and cardiac abnormalities.

To conclude, our series highlights the diverse clinical presentations and challenges faced by affected individuals. As glaucoma management plays a pivotal role in mitigating potential vision loss in these cases, our findings underscore the paramount importance of early diagnosis and meticulous glaucoma management.

**KEYWORDS:** Anterior Eye Segment/abnormalities; Eye Abnormalities; Eye Diseases, Hereditary; Forkhead Transcription Factors/genetics; Glaucoma/genetics; Homeobox Protein PITX2; Homeodomain Proteins/genetics.

## RESUMO

A síndrome de Axenfeld-Rieger (ARS) é uma doença genética caracterizada por dois componentes: disgenesia do segmento anterior e anomalias sistémicas. Relativamente às características oculares, o embriotoxon posterior (anteriorização da linha de Schwalbe) é chave. A anomalia de Rieger compreende anomalias congénitas da íris. Quando acompanhada por alterações sistémicas (defeitos ósseos faciais, anomalias odontológicas, hipofisárias ou umbilicais) a condição designa-se síndrome de Rieger. Quando a anomalia de Axenfeld acompanha a síndrome de Rieger, o diagnóstico é ARS. Perda auditiva e defeitos cardíacos podem ocorrer.

Doentes com ARS têm risco aumentado de glaucoma devido à drenagem comprometida do humor aquoso.

ARS é tipicamente herdada como autossómica dominante, mas também pode ocorrer esporadicamente. Mutações nos genes *PITX2*, *FOXC1*, *PAX6*, *FOXO1A* e *CYP1B1* fundamentam a diversidade genética da ARS.

O objetivo é apresentar manifestações clínicas, abordagens terapêuticas e desfechos da ARS, contribuindo para uma melhor compreensão.

Apresentamos uma série de casos de ARS provenientes da consulta de oftalmologia do Hospital de São João, Porto, Portugal.

Um total de cinco doentes com ARS com diferentes variantes envolvendo os genes *PITX2* e *FOXC1*, em heterozigotia: criança de dois anos com deleção do gene *PITX2*; criança de sete anos e sua mãe de quarenta e seis anos com duplicação do exão 1 do gene *FOXC1*; criança de 11 anos com deleção e substituição do gene *FOXC1*; e homem de cinquenta e sete com deleção do exão 1 do gene *FOXC1*. Embriotoxon posterior, corectopia e hipoplasia da íris são prevalentes na amostra. Apenas um doente apresenta alterações oculares leves. Notavelmente, três doentes desenvolveram glaucoma, dois necessitando de cirurgia. O doente mais idoso, provavelmente devido ao diagnóstico tardio, é o único com grau substancial de hipovisão. O envolvimento sistémico varia entre doentes e inclui principalmente hipertelorismo, perda auditiva neurossensorial e anomalias cardíacas.

Concluindo, esta série de casos sobre ARS oferece informações valiosas sobre apresentações clínicas e desafios em indivíduos afetados. Como o tratamento do glaucoma desempenha um papel fundamental na mitigação da perda visual nesses casos, os achados destacam a importância do diagnóstico precoce e tratamento meticuloso do glaucoma.

**PALAVRAS-CHAVE:** Anomalias Congénitas do Olho; Fatores de Transcrição Forkhead/genética; Glaucoma/genética; Oftalmopatias Hereditárias; Proteína Homeobox PITX2; Proteínas de Homeodomínio/genética; Segmento Anterior do Olho/anomalias congénitas.

## INTRODUCTION

Axenfeld-Rieger syndrome (ARS) is a rare genetic disorder that has drawn the interest of researchers, clinicians, and geneticists due to its complex combination of ocular and systemic features. It is a rare disorder, with prevalence estimated at 1 in 50 000 to 100 000 newborns. ARS has been described in different ethnic groups, including individuals from Europe, Africa, North and South America, the Middle East, and Asian populations.[1]

ARS is an entity marked by its dual identity comprising two principal components: anterior segment dysgenesis and systemic anomalies. The ocular facet of ARS is characterized by the presence of posterior embryotoxon, or Axenfeld anomaly, an aberration in corneal architecture defined by the anterior displacement of Schwalbe's line. Simultaneously, individuals with ARS often exhibit Rieger anomaly, a constellation of congenital iris malformations that may include iris hypoplasia, corectopia, and pseudopolycoria.[1,2]

However, when anterior segment dysgenesis is accompanied by systemic findings such as dental problems, facial bone defects (including maxillary hypoplasia), umbilical abnormalities, or pituitary gland involvement, it is referred to as Rieger syndrome. When both Axenfeld anomaly and

Rieger syndrome are present simultaneously in an individual, the diagnosis is ARS. In rare cases, ARS may also include hearing impairment and cardiac anomalies, highlighting its clinical diversity.[1,3,4] Congenital anomalies of the kidney and urinary tract (CAKUT) have also been detected in patients with ARS.[5]

ARS is classified into three types, each characterized by distinct systemic manifestations. In ARS type 1, common systemic features include dental irregularities, craniofacial dysmorphism and umbilical disorders. In ARS type 2, patients often exhibit oligodontia and microdontia, although craniofacial dysmorphism and umbilical disorders are less prevalent. Patients with ARS type 3 generally do not exhibit dental or facial abnormalities, but they may experience hearing loss and cardiac defects.[1,6]

Underlying these clinical manifestations is a complex genetic basis. ARS is primarily inherited through an autosomal dominant pattern, although it can also occur sporadically. Family-based investigations, conventional genetic methodologies employing linkage analysis, and the latest advancements in molecular genetics have successfully identified two primary genes associated with ARS in 40% of patients, namely pituitary homeobox 2 gene (*PITX2*, located on 4q25) and forkhead-box C1 gene (*FOXC1*, situated on 6p25), genes that regulate embryonic development and gene expression. Mutations in genes like *PAX6*, *FOXO1A* and *CYP1B1* also contribute to the genetic diversity of ARS.[1,6]

ARS is primarily caused by abnormal migration of neural crest cells during early embryogenesis, impacting crucial ocular structures such as the ciliary body, cornea, and iris stroma. Later in gestation, the primordial endothelium that covers the cornea should undergo resorption; disruption of this process may result in posterior embryotoxon and abnormal insertion of the iris causing pupillary changes such as pseudopolycoria or ectropion uveae. Additionally, abnormalities in the development of the anterior chamber can hinder the development of Schlemm's canal, potentially leading to increased risk of glaucoma. Abnormal neural crest cell migration can also affect extraocular tissues, such as vestibuloacoustic ganglion tissue, potentially justifying hearing loss in some individuals with ARS.[4]

A significant concern in ARS patients is the heightened susceptibility to glaucoma. This elevated risk arises from the anterior segment dysgenesis, namely the displacement of Schwalbe's line which leads to abnormalities in the iridocorneal angle, obstructing the outflow of aqueous humor, resulting in elevated intraocular pressure (IOP).[7]

Managing ARS requires a comprehensive approach. Collaboration among specialists, including ophthalmologists, pediatricians, geneticists, dentists, and orthodontists, among others, is crucial. This multidisciplinary cooperation goes beyond addressing ocular aspects and encompasses managing systemic abnormalities and associated health issues.

The goal of this case series on ARS is to present clinical manifestations, treatment approaches, and outcomes in a cohort of patients, aiming to contribute to the understanding and management of this rare genetic condition.

## CASE REPORTS

The pre-birth history of the patients is characterized by normal supervised pregnancies, followed by eutocic or cesarian deliveries, without complications. A total of five patients of four different families with ARS with different

**Table 1. Summary characterization of the patients – description of PITX2/FOXC1 genotype and associated systemic and ocular phenotype of the five patients.**

| Patient | Mutation | Systemic features | Ocular features |
|---|---|---|---|
| **1** | Delection (c.427_428del) of the *PITX2* gene | Brachycephaly<br>Low set and posteriorly rotated ears<br>Umbilical hernia and omphalitis | Posterior embryotoxon<br>Iris hypoplasia<br>Corectopia<br>Iridocorneal tissue adhesions |
| **2** | Duplication (c93_111dup) of the exon 1 of the *FOXC1* gene | Hypertelorism<br>Retrognathia<br>Wide and tall nose bridge<br>Cardiac abnormalities (mitral insufficiency and patent foramen ovale) | Posterior embryotoxon<br>Iris hypoplasia<br>Corectopia<br>Glaucoma |
| **3** | Duplication (c93_111dup) of the exon 1 of the *FOXC1* gene | Hypertelorism<br>Retrognathia<br>Wide and tall nose bridge<br>Neurosensorial hypoacusis | Corectopia |
| **4** | Deletion (c.1476_1481del) and a substitution (c246C>G) of the *FOXC1* gene | Hypertelorism<br>Microdontia<br>Urinary tract anomaly (renal pelvis dilation)<br>Cardiac abnormalities (pulmonary valve stenosis, mitral insufficiency and patent foramen ovale)<br>Neurosensorial hypoacusis | Posterior embryotoxon<br>Iris hypoplasia<br>Corectopia<br>Glaucoma<br>Exotropia |
| **5** | Delection (c.724_742del) of the exon 1 of the *FOXC1* gene | Low set ears<br>Dental misalignment<br>Neurosensorial hypoacusis | Posterior embryotoxon<br>Iris hypoplasia<br>Megalocornea<br>Glaucoma |

variants involving *PITX2* and *FOXC1* genes, in heterozygosity, are currently in follow-up at the ophthalmology department in Centro Hospitalar Universitário de São João, Porto, Portugal. Genotype and phenotype descriptions of the patients are summarized in Table 1.

## CASE 1

The first case refers to a two-year-old girl who presented with several congenital anomalies. She was born with brachycephaly, low set and posteriorly rotated ears, and an exuberant umbilical hernia (Fig. 1). During the first days of life, she developed omphalitis with the isolation of *Escherichia coli*, requiring antibiotic treatment with ampicillin and gentamicin.


Figure 1. Facial characteristics and exuberant umbilical hernia with redness from the infectious process (omphalitis).

During her neonatal period, she was exclusively bottle-fed with infant formula, yet encountered difficulties in gaining weight. An ophthalmological evaluation was promptly requested, revealing significant ocular abnormalities: extensive posterior embryotoxon, iris hypoplasia, and corectopia. Additionally, iridocorneal tissue adhesions were observed (Fig. 2).

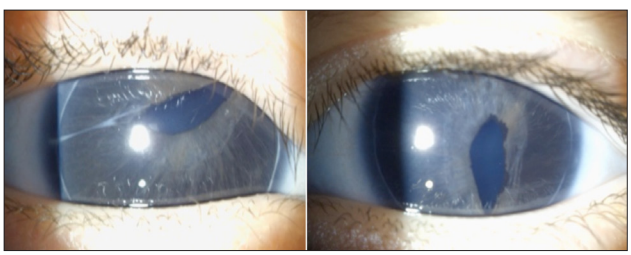

Figure 2. RE (left) and LE (right) with extensive posterior embryotoxon, a white line anterior to the limbus in the cornea, several areas of iris hypoplasia, and corectopia. In the RE, the visible white strand corresponds to an iridocorneal adhesion.

The combination of these ocular findings, along with the pre-existing umbilical abnormalities and distinctive facial characteristics led to the hypothesis of ARS. Subsequently, a genetic study was conducted, which unveiled a deletion (c.427_428del) of the *PITX2* gene as the underlying genetic mutation in this case, supporting the diagnosis.

The child appears to possess good visual acuity, as she demonstrates the ability to track movements, focus on and identify objects, recognize familiar faces, and navigate her surroundings with confidence.

Regarding IOP, it has consistently remained within the normal range since birth, with initial measurements of 10 mmHg in each eye during the first appointment. However, in the most recent evaluation, at two years of age, IOP readings were 21 mmHg in the right eye (RE) and 20 mmHg in the left eye (LE). During fundus examinations, a normal optic disc has consistently been observed. This recent increase in IOP raises potential concerns and deserves our close attention.

## CASES 2 AND 3

The second and third cases involve a seven-year-old girl and her forty-six-year-old mother.

The girl was initially evaluated at 14 months due to suspected exotropia. Before this, her development had been entirely normal. During the ophthalmological examination, a slightly increased distance between her eyes (hypertelorism) was noted (Fig. 3). However, her ocular alignment was found to be good, with normal results on the cover test and normal ocular movements. Slit lamp ex-

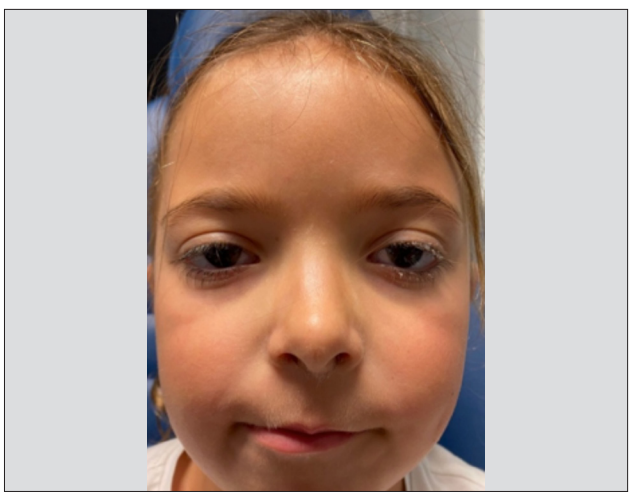

Figure 3. Facial characteristics of the seven-year-old girl showing a slightly increased distance between the globes (hypertelorism)

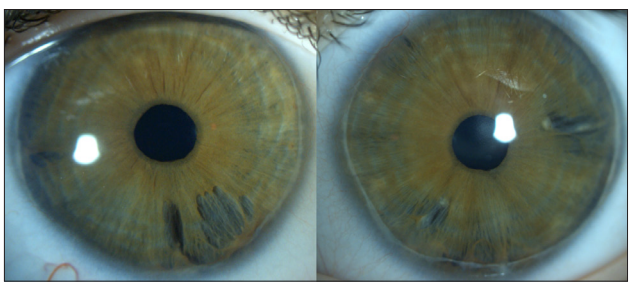

Figure 4. RE (left) and LE (right) with extensive posterior embryotoxon and few areas of iris hypoplasia.

amination revealed posterior embryotoxon and areas of iris hypoplasia (Fig. 4). Initially, IOP was 13 mmHg in the RE and 14 mmHg in the LE. Fundus examination at this point showed a normal optic disc, with no excavation. A genetic study was conducted, unveiling a duplication (c93_111dup (p.(Thr38Glyfs*51)) of the exon 1 of the *FOXC1* gene that introduces a premature stop codon and thus confirms the ARS diagnosis.

A systemic evaluation revealed a minor mitral insufficiency and the presence of a patent foramen ovale. Aside from these findings, the evaluation was unremarkable, including normal dental development, no umbilical abnormalities, and normal hearing.

Subsequent ophthalmology follow-up appointments showed consistently rising IOP, accompanied by a simultaneous increase in optic disc excavation, despite ongoing treatment with hypotensive eye drops.

In the most recent appointment, at seven years of age, the best corrected visual acuity (BCVA) was of 20/25 in both eyes, IOP readings were 21 mmHg in the RE and 22 mmHg in the LE, and the cup-to-disc ratio was of 0.4 in the RE and of 0.5 in the LE, despite combined treatment with drops of timolol 5 mg/mL and dorzolamide 20 mg/mL in both eyes. Given this progression of the disease, the next step in the treatment plan will involve surgical intervention in the form of a trabeculotomy to better manage the condition.

Given the diagnosis, the girl's family members were examined, which lead to the observation of some disease features in her forty-six-year-old mother: BCVA was of 20/20 in the RE and 20/20 in the LE, slit lamp examination showed minimal corectopia of the RE and LE, IOP was 12 mmHg in both eyes, gonioscopy was normal and fundus examination was unremarkable, with a cup-to-disc ratio of 0.2 in both eyes (Fig. 5). Facial features included hypertelorism, retrognathia and a wide and tall nose bridge. Otorhinolaryngology examination revealed a neurosensorial hypoacusis of both ears, compatible with type 3 ARS. A genetic study revealed the same mutation as in the index case.

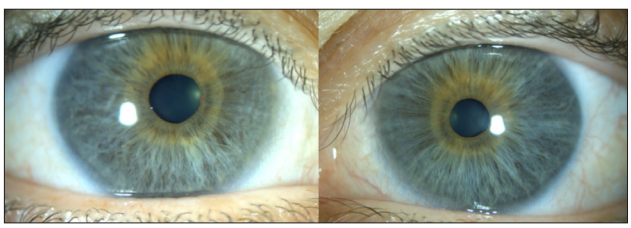

Figure 5. RE (left) and LE (right) with minimal corectopia.

## CASE 4

The fourth case concerns an eleven-year-old boy who, during his initial ophthalmological examination under general anesthesia at 13 months of age, exhibited IOP measurements ranging between 20 and 25 mmHg in both eyes while receiving medical treatment with timolol 5 mg/mL drops.

A posterior embryotoxon and Haab's striae were observed in both eyes and inferior corectopia was observed in the LE (Fig. 6). The corneal horizontal diameter was 14 mm and the vertical diameter was 13.5 mm in both eyes. Fundus examination at this point showed a cup-to-disc ratio of 0.6 in both eyes, leading to the child being submitted to trabeculotomy of the RE and LE at this age.

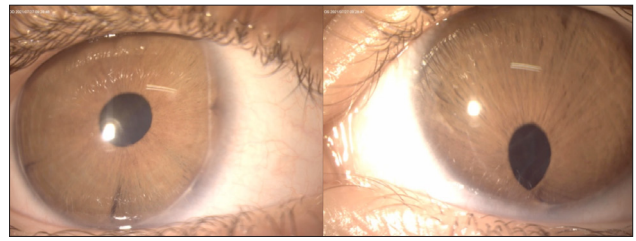

Figure 6. RE (left) and LE (right) with extensive posterior embryotoxon and few areas of iris hypoplasia. A marked corectopia is evident in the LE.

A renal pelvis dilation was detected on prenatal ultrasound and subsequently confirmed after birth, requiring the administration of prophylactic antibiotics to prevent urinary tract infections until the age of 15 months. Due to a murmur detected at birth, a cardiac evaluation revealed a minor pulmonary valve stenosis, a moderate mitral insufficiency and a patent foramen ovale.

Given the ocular, urinary tract and cardiac abnormalities, a posterior dental evaluation was requested and revealed microdontia, with abnormally small teeth. A discrete hypertelorism was noticeable and an audiogram revealed neurosensorial hypoacusis.

A genetic study was conducted, unveiling a deletion (c.1476_1481del) and a substitution (c246C>G) of the *FOXC1* gene and thus confirming the ARS diagnosis.

The patient developed a significant exotropia which required surgery at the age of seven, involving the recession of the lateral rectus muscles in both eyes, which successfully corrected the issue.

In the most recent appointment, at eleven years of age, BCVA was of 20/32 in the RE and 20/50 in the LE, IOP readings were 15 mmHg in the RE and 13 mmHg in the LE under treatment with timolol 5 mg/mL, dorzolamide 20 mg/mL and latanoprost 0.05 mg/mL. The cup-to-disc ratio was 0.8 in the RE and 0.7 in the LE.

Given the diagnosis, the boy's family members were examined and it was brought to the attention that his forty-three-year-old father underwent cardiac surgery during childhood for pulmonary valvulotomy to alleviate congenital pulmonary stenosis, as well as suture closure of a patent foramen ovale.

At the first ophthalmological examination, BCVA was 20/20 in the RE and 20/20 in the LE, slit lamp examination showed a discrete posterior embryotoxon in the RE and LE, a Krukenberg's spindle in both eyes, several areas of iris transillumination defects and *ectropion uvea* (Fig. 7). IOP was 19 mmHg in both eyes, gonioscopy was normal and optic nerve examinations showed bilateral glaucomatous cupping with a cup-to-disc ratio of 0.7. Optical coherence

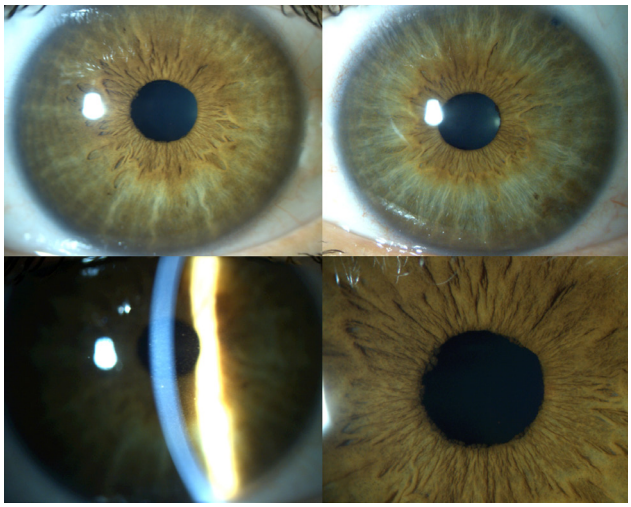

Figure 7. RE (left) and LE (right) with discrete posterior embryotoxon. A Krukenberg's spindle and ectropion uvea are evident in both eyes.

tomography (OCT) disc assessment showed a normal mean peripapillary retinal nerve fiber layer (RNFL) thickness with a borderline reduced thickness in the nasal superior and temporal inferior sectors of the right optic disc, with a normal mean peripapillary RNFL thickness and a borderline reduced thickness in the temporal inferior sector in the LE. A 24-2 Humphrey visual field test showed discrete alterations in the RE and was normal in the LE.

Regular follow-up for the last ten years has been showing controlled IOP without any medical treatment, with no decrease in peripapillary RNFL thickness and no visual field alterations. In the most recent appointment, BCVA was 20/20 in the RE and 20/20 in the LE, IOP was 15 mmHg in both eyes (without IOP-lowering drops) and OCT disc assessment was very similar to the baseline.

However, despite conducting the genetic study twice, contrary to expectations, the mutation was not detected on both occasions. For that reason, it is not possible to confirm an ARS diagnosis on this patient.

## CASE 5

The fifth case concerns a fifty-seven-year-old male, with low-set ears and dental misalignment, who sought consultation in the ophthalmology department for progressing glaucoma with difficult IOP control (Fig. 8). The patient reported a family history of blindness in both his father and brother, and has endured persistent visual impairment throughout his entire life, yet unaware of the underlying cause.

BCVA was of counting-fingers (CF) in the RE and light-perception (LP) in the LE. Slit lamp examination revealed posterior embryotoxon, several areas of iris hypoplasia, and a megalocornea in the LE. Additionally, it was noticeable diffuse ocular hyperemia due to long-term use of IOP-lowering drops and an inferior leukoma with corneal neovascularization in the LE (Fig. 9). IOP was 14 mmHg in the RE and 55 mmHg in the LE despite maximal medical therapy, previously prescribed in an ophthalmological consultation in another institution. Fundus examination revealed a cup-to-disc ratio of 0.9 in the RE (Fig. 10) and 1 in the LE (deficient fixation and miosis precluded fundus photography of the LE).

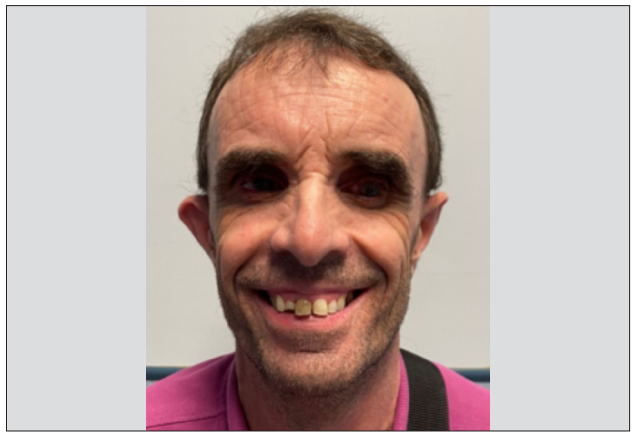

Figure 8. Facial characteristics of the fifty-seven-year-old male evidencing low set ears and dental misalignment.

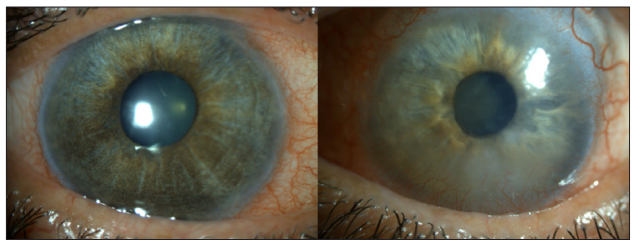

Figure 9. RE (left) and LE (right) with extensive posterior embryotoxon and several areas of iris hypoplasia. There is diffuse ocular hyperemia due to long-term use of IOP-lowering drops and an inferior leukoma with corneal neovascularization in the LE.

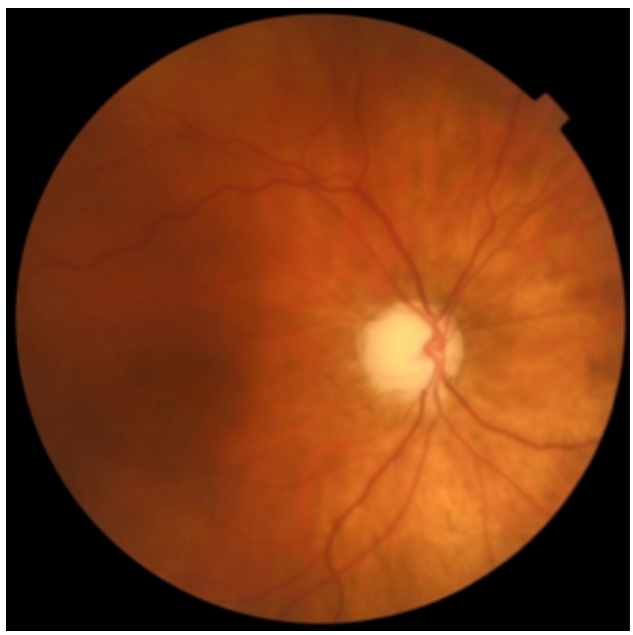

Figure 10. RE fundus photography at the last follow-up visit, showing an enlarged cup-to-disc ratio.

Upon inquiry, the patient reported experiencing hearing difficulties, subsequently diagnosed as neurosensory hypoacusis affecting both ears, as confirmed through an otolaryngological examination.

ARS was suspected and a genetic study was conducted, revealing a delection (c.724_742del) of the exon 1 of the *FOXC1* gene that introduces a premature stop codon.

In the most recent appointment, BCVA was of CF in the RE and no LP in the LE. IOP readings were 14 mmHg in the RE and 8 mmHg in the LE, with maximum medical treatment in both eyes, and the cup-to-disc ratio did not aggravate. This IOP control, despite not having altered the treatment, seems to be due to improved therapeutic compliance. A conservative approach involving the maintenance of medical treatment was preferred due to the advanced disease stage, with the patient's clear understanding of the grim prognosis.

## DISCUSSION

Our case series on Axenfeld-Rieger syndrome offers valuable insights into the diverse clinical presentations and the challenges faced by affected individuals. Firstly, it is noteworthy that one individual with the mutation exhibits minimal clinical characteristics of the disease, while, conversely, another individual with pronounced clinical features and familial history of the condition has an unconfirmed genetic diagnosis, underscoring the complexity of diagnosing ARS. Based on the type of mutation, affected individuals exhibit variable expressivity with some limited genotype-phenotype correlations, contributing to the variety of clinical presentations.

In the present case series, regarding the ocular phenotypes, there is variability among patients, but for the most part, they exhibit posterior embryotoxon, with only one of the patients lacking this feature, aligning with the current literature.[1] Iris hypoplasia and corectopia are among the most frequent features as well. Glaucoma has been diagnosed in three of the patients, while in the patient with the *PITX2* mutation, an intraocular pressure ascending profile is evident, raising concerns about the imminent development of glaucoma. One of the patients also exhibits megalocornea. While it is not a defining feature of ARS, there can be an overlap between these two conditions. In some individuals with ARS, megalocornea may be among the observed ocular abnormalities.[8]

In terms of the systemic manifestations of the disease, hypertelorism and neurosensory hypoacusis are the prevailing alterations seen in these patients. Notably, two of the patients with *FOXC1* mutations also exhibit cardiac abnormalities, and a patient with a *FOXC1* mutation displays renal pelvis dilation, which is associated in the literature with CAKUT. Furthermore, the first case is marked by a history of umbilical hernia and omphalitis.

Regarding the genetic study, we report four cases of ARS with identified *FOXC1* mutation (two cases with duplication, one case with a deletion inducing a nonsense mutation and one case with a combination of a deletion and a substitution that produces a nonsense mutation) and one case with *PITX2* mutation (deletion).

Research has characterized *FOXC1* mutations as frameshift, nonsense, missense, deletions, and duplications. *PITX2* has associations with splice-site mutations, deletions and chromosomal translocations in patients with ARS, which goes in line with our series.[1,2,5,8 9]

In addition to small point mutations, several patients with chromosomal deletions at 6p25, including the *FOXC1* locus, have been also documented in the literature.[10] Likewise, deletions within 4q, involving the *PITX2* gene, have been observed in individuals affected by ARS. Furthermore, studies have suggested that ARS type 2 can be caused by a deletion of 13q14, supported by linkage analyses, although the specific causative gene mutations have yet to be identified.[11] In rare instances, ARS has been associated with the deletion of the *PAX6* gene at 11p13 and deletions within the 16q23-q24 region.12 Mutations in genes like *FOXO1A* and *CYP1B1* also contribute to the genetic diversity of ARS.[1,2,5,8,9]

Notably, ARS patients bearing mutations in *PITX2* or *FOXC1* genes consistently manifest the characteristic ocular phenotype with complete penetrance. Nevertheless, the variability in the expression of this phenotype is contingent on the nature of the mutation, leading to limited genotype-phenotype correlations among affected individuals.[1,7,8]

Regarding the father in the fourth case, despite the absence of a confirmed genetic diagnosis, there are notable clinical findings consistent with ARS, including posterior embryotoxon, *ectropion uvea*, and glaucomatous damage. Additionally, he has a history of cardiac surgery for congenital pulmonary stenosis and closure of a patent foramen ovale. Given the high clinical suspicion, genetic testing was performed twice and is currently being considered for repetition to further investigate the potential diagnosis. These cases must remain documented and monitored, even when genetic confirmation is elusive. Although rare, pigment dispersion syndrome may occasionally occur as a secondary feature in individuals with ARS as reported by Li *et al*.[13]

Currently, the primary focus of treating patients with ARS is the management of glaucoma. Due to the high risk of glaucoma, which can be detected in childhood, it is essential to regularly monitor these patients for IOP and optic nerve changes.[1]

Treatment strategies for glaucoma in ARS have not yet been definitively established, which is largely due to the rarity of the condition. Consequently, there is a lack of studies that statistically compare different therapeutic approaches in the existing literature. As a result, it is imperative to assess therapeutic recommendations on an individual basis. These treatment options do not significantly deviate from standard approaches for open-angle glaucoma. However, it is crucial to note that the failure rate is notably higher in ARS, often requiring repeated interventions and carrying a heightened risk of complications.[14,15]

The existing medical therapy options aim to reduce the accumulation of aqueous humor and include various classes of medications such as alpha-adrenergic agonists, beta-blockers, carbonic anhydrase inhibitors, osmotic

agents, parasympathomimetic agonists, and prostaglandin analogs.[1,16] For instance, alpha agonists pass through the blood-brain barrier, potentially causing central nervous system toxicity. There are reports of bradycardia, hypotension, hypothermia, hypotonia, and apnea in infants, which is the reason that justifies its contraindication in children.[1,15]

The primary surgical approaches for glaucoma in ARS patients encompass angle surgery, drainage surgery, and cyclophotocoagulation. The corneal diameter serves as a general guideline for selecting the appropriate surgical intervention, mainly in children. Specifically, a corneal diameter of less than 13 mm typically signifies mild glaucoma, leading to surgical choices such as goniotomy or trabeculotomy. For corneal diameters ranging from 13 to 16 mm, indicating moderate severity, angle surgeries have a heightened risk of failure but may still be considered. Additional options include combined trabeculotomy-trabeculectomy, conventional trabeculectomy, or the use of a glaucoma drainage implant. In cases where the corneal diameter exceeds 16 mm, denoting severity of the disease, cyclophotocoagulation may be considered as a last-resort treatment option.[15] In cases 2 and 4, the surgical approach chosen was angle surgery. Circumferential trabeculotomy *ab interno* with upper-180° incision was specifically preferred due to the experience of our center in performing this procedure for pediatric glaucomas.

Genetic counseling for ARS involves assessing the risk of passing the condition to descendants. If a person with ARS has children, there is a 50% chance of inheritance. In some cases, the genetic mutation causing ARS is new (de novo). Family members should be checked for ARS if there's a suggestive family history. If ARS is suspected, patients should see a medical geneticist for examination and specialized tests. Testing parents is recommended when probands have detectable *FOXC1* or *PITX2* pathogenic variants.[1]

If one parent has ARS, there's a 50% risk of passing it on. If the genetic change cannot be found in either parent, the recurrence risk is lower but still elevated due to potential genetic changes in the parent's reproductive cells (germline mosaicism).[1]

Nevertheless, it is important to acknowledge that, although approximately 40% of patients have a mutation in either *FOXC1* or *PITX2*, in the remaining 60% of the cases the underlying genetic defect remains unknown. Therefore, further studies to identify additional genes involved in ARS are necessary and may provide new opportunities for management of patients with ARS.[7]

Finally, despite not being an experimental study, it is essential to acknowledge the limitations of this research, specifically its retrospective and observational nature, which may introduce potential information biases.

## CONCLUSION

This case series provides a valuable and insightful perspective on the diverse clinical presentations of Axenfeld-Rieger syndrome, aligning with the current literature.

Collaborative care through interdisciplinary communication is crucial for ARS patients. Comprehensive examinations should be conducted to identify and monitor any systemic associations. The ocular prognosis of ARS largely depends on the timely diagnosis of glaucoma since optic nerve damage is irreversible, and previously damaged nerves are more susceptible to further harm.

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