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Axenfeld-Rieger syndrome diagnosed in adulthood: A case report

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Abstract
Axenfeld-Rieger Syndrome is a rare congenital disorder that affects the anterior segment of the eye and is often accompanied by systemic anomalies. Although it is typically diagnosed in childhood, some cases go undetected until adulthood, particularly when the ocular phenotype is subtle and glaucoma develops later. We report a case of a 40-year-old male diagnosed with Axenfeld-Rieger Syndrome, emphasizing the ocular and systemic findings, diagnostic challenges, and management strategies. This case also underscores the importance of genetic counseling, as it can provide crucial information and support to patients and their families, helping them understand the genetic basis of the syndrome and make informed decisions about their offspring's health.

Keywords: Axenfeld-Rieger syndrome, glaucoma, offspring's health, case report

Introduction
Axenfeld-Rieger Syndrome (ARS) is a developmental disorder of the anterior segment that is inherited in an autosomal dominant manner and exhibits variable expressivity. The syndrome primarily results from mutations in the PITX2 and FOXC1 genes [1, 2] that are responsible for neural crest cell migration, a critical process for both anterior eye segment and systemic development. The disorder encompasses a broad spectrum of phenotypic variability, making diagnosis challenging, especially in cases that manifest during adulthood. The ocular manifestations include posterior embryotoxon (anteriorly displaced Schwalbe's line), iris abnormalities (corectopia, polycoria, and stromal hypoplasia), iris strands, and secondary glaucoma, which occur in 50-60% of cases and often lead to progressive vision loss.
Systemic features may include craniofacial abnormalities (hypertelorism, maxillary hypoplasia), dental anomalies (hypodontia, microdontia, and conical teeth), umbilical abnormalities (redundant periumbilical skin or hernias), and congenital heart defects [3].
While ARS is typically recognized in childhood, adult presentations can occur when glaucoma develops later in life or when anterior segment anomalies go undiagnosed. An accurate diagnosis is crucial to prevent progressive visual impairment and address systemic manifestations through multidisciplinary care.

Case Presentation
We present a case of a 40-year-old male patient who attended the eye clinic seeking a second opinion after being diagnosed with glaucoma and advised to start using antiglaucoma medications (Taflupost nightly in both eyes), which he has been using since. The patient denies any history of previous ocular or systemic disorders and is not taking any other eye or systemic medication. Upon his physical examination, the patient presented peculiar facial features (Figure 1). These included hypertelorism, a flattened mid-face with a broad, flat nasal bridge, and a prominent forehead. Additionally, he exhibited some dental abnormalities (Figure 2), including microdontia, hypoplasia, malocclusion, and impactions. The eye exam revealed myopic astigmatism of -8-1.25 x 10 in the right eye and -7.50-0.25 x 95 in the left eye, with a best-corrected visual acuity of 20/20 in both eyes. The slit lamp examination showed bilateral posterior embryotoxon (Figure 3) and intraocular pressure (IOP) of 14 mmHg in the right eye and 16 mmHg in the left eye, both treated with Taflupost. The gonioscopy examination (Figure 4) showed a low-pigmented open angle with 360-degree iris strands bilaterally. The fundus examination revealed bilateral cupping of the optic disc (Figure 5) with nasal vessel displacement in both eyes and bayoneting in the right eye. The peripheral examination revealed areas of lattice degeneration with associated vitreous traction but a flat retina.

An OCT of the optic disc was performed (Figure 6), showing retinal nerve fiber layer thinning in both eyes, more so in the right eye, affecting all quadrants except the temporal one, with less pronounced thinning in the left eye where only the superior fiber layers were decreased. A visual field 24/2 was performed (Figure 7), showing an incipient inferior arcuate scotoma in the right eye and normal limits in the left eye. With all these findings, the patient was diagnosed with secondary glaucoma (pre-perimetric stage in the right eye) associated with Axenfeld-Rieger Syndrome and was advised to continue with the same antiglaucoma medication. Prophylactic peripheral retinal photocoagulation was performed. Due to the systemic condition of the disease, the patient was referred to cardiology and endocrinology for evaluation and to the genetic clinic to identify any anomalies. All results were negative. The first genetic test report was unable to identify a gene mutation. A second genetic test using a different technique was recommended, but the patient did not undergo it. The patient is currently being followed in the glaucoma clinic, and his IOP remains stable with antiglaucoma medications, with no progression in either the visual field or OCT detected.

Discussion

Axenfeld-Rieger Syndrome (ARS) is a rare congenital disorder affecting the anterior segment of the eye, often causing secondary glaucoma and systemic manifestations. It combines Axenfeld anomaly (involving posterior embryotoxon and iris strands attached to an anterior Schwalbe's line) and Rieger anomaly (including iris defects like hypoplasia, corectopia, and polycoria). Rieger anomaly is also linked to systemic abnormalities such as dental issues, facial bone defects, and sometimes cardiac or pituitary involvement. Together, these are known as Axenfeld-Rieger Syndrome.

When evaluating a patient with anterior segment abnormalities, it is important to consider several conditions alongside Axenfeld-Rieger Syndrome (ARS). For instance, primary congenital glaucoma (PCG) may initially appear similar due to the presence of elevated intraocular pressure and optic nerve changes; however, PCG generally does not present with the systemic craniofacial or dental anomalies characteristic of ARS. Peters anomaly is another consideration, as it involves central corneal opacities and adhesions, but it tends to exhibit central rather than peripheral corneal changes such as a prominent posterior embryotoxon. Additionally, Iridocorneal Endothelial (ICE) syndrome, which typically affects adult females and presents unilaterally, shows distinct corneal endothelial alterations that help differentiate it from the bilateral manifestations seen in ARS. Thus, a thorough clinical evaluation encompassing detailed ocular examinations, assessment of systemic features, and, when available, genetic testing is essential for accurately distinguishing ARS from these other conditions.

The inheritance pattern of most cases of ARS is autosomal dominant, although sporadic cases also arise. ARS is typically characterized by high penetrance but exhibits variable expressivity, with mutations commonly found in the PITX2 and FOXC1 genes. These genes are vital for the development of neural crest-derived tissues, and their disruption leads to the syndrome's multisystem involvement. While typically identified in childhood, ARS can remain undiagnosed until adulthood [5], particularly when ocular features are subtle and glaucoma presents later in life.

In addition to eye abnormalities, Axenfeld-Rieger Syndrome (ARS) presents with several systemic features. Common craniofacial abnormalities include midface hypoplasia, widely spaced eyes (hypertelorism), telecanthus, frontal bossing, a thin upper lip, and occasionally a cleft palate, contributing to a distinctive facial appearance. Dental anomalies are also frequent, with many patients having missing teeth (hypodontia or oligodontia), small or peg-shaped teeth (microdontia), and enamel defects (enamel hypoplasia), increasing the risk of cavities and requiring specialized dental care. A characteristic feature is periumbilical skin redundancy excess, wrinkled skin around the belly button, sometimes linked to an umbilical hernia, which can help in diagnosis, especially in infants. Less commonly, ARS can involve congenital heart defects, such as atrial septal defects and valve abnormalities, and there have been rare reports of aortic root dilation, suggesting possible connective tissue involvement.

In this case, the patient, a 40-year-old male, presented with systemic manifestations including facial and dental abnormalities, angle abnormalities, and secondary glaucoma. The diagnosis of ARS was confirmed based on these findings, highlighting the importance of a comprehensive approach to diagnosis and management.

Glaucoma is the most serious ocular complication in ARS, affecting up to 50% of patients. The underlying mechanisms involve trabecular dysgenesis and developmental anomalies of the anterior chamber angle, leading to impaired aqueous humor outflow and elevated intraocular pressure. A scientific theory regarding the ocular features of A-R syndrome is proposed, suggesting a developmental arrest occurring late in gestation [4] within tissues derived from neural crest cells. This developmental halt results in the persistence of primordial endothelial tissue on the iris and across the anterior chamber angle, leading to observed iridic alterations and the formation of peripheral tissue strands. Continued contraction of these membranes postnatally accounts for the progressive changes seen in some patients. This primordial endothelium is also responsible for the production of excessive and atypical basement membrane, particularly near the corneolimbal junction, which explains the prominence of Schwalbe's line. Secondary glaucoma arises from the interrupted development of anterior chamber angle structures, evidenced by the incomplete maturation of the trabecular meshwork and Schlemm's canal, along with a high insertion of the iris.

Glaucoma management typically begins with standard topical ocular anti-hypertensive medications [1]. However, neonates with buphthalmos and corneal edema may be misdiagnosed with primary congenital glaucoma (PCG) instead of Axenfeld-Rieger syndrome (ARS). Differentiating between the two is important, as angle surgeries like goniotomy and trabeculotomy are generally ineffective in ARS and do not provide long-term intraocular pressure (IOP) control. Approximately two-thirds of ARS patients require surgical intervention beyond medications. [7] Most patients with ARS-associated glaucoma need angle-bypass procedures, typically trabeculectomy with anti-fibrotic agents such as mitomycin C or implantation of a glaucoma drainage device (GDD). While trabeculectomy avoids hardware, it poses challenges such as bleb leaks, over- or under-filtration, and a lifelong risk of bleb-related infections, resulting in endophthalmitis and vision loss if not

properly managed. Careful patient selection and education about these risks are essential. GDDs are often preferred for children with ARS due to their ability to provide immediate IOP reduction with a lower risk of hypotony. However, implanting GDDs in ARS cases can be complicated by thick iris strands and anatomical abnormalities, increasing the risk of bleeding and tube obstruction. In severe cases with shallow anterior chambers, lens removal and pars plana placement of the tube may be necessary. Ciliary body ablation (transscleral or endoscopic) can lower IOP but is more effective after establishing aqueous outflow with a GDD. In instances of severe anterior segment dysgenesis, cycloablation is sometimes considered, though it has a narrow margin between lowering pressure and causing hypotony or phthisis. Multiple ablation sessions often yield limited success, making angle-bypass surgery the primary option in many cases.

This case emphasizes several critical considerations:

- **Recognition of ARS in Adults:** Although often diagnosed in childhood, ARS can present in adulthood with glaucoma as the initial significant symptom. Comprehensive slit-lamp examinations, gonioscopy, systemic examinations, and genetic testing are essential for accurate diagnosis.
- **Challenges in Glaucoma Management:** Standard medical therapies may be insufficient, requiring early surgical interventions. However, procedures like trabeculectomy and glaucoma drainage implants have higher failure rates due to fibrosis and anatomical abnormalities inherent in ARS. [7]
- **Lifelong Monitoring:** Given the progressive nature of ARS-associated glaucoma, continuous follow-up with intraocular pressure monitoring, optic nerve assessments, and systemic evaluations are crucial to prevent both ocular and systemic complications.
- **Genetic Counseling:** As an autosomal dominant disorder with variable expressivity, genetic counseling is vital for patients and their families to understand inheritance patterns, recurrence risks, and potential systemic associations.

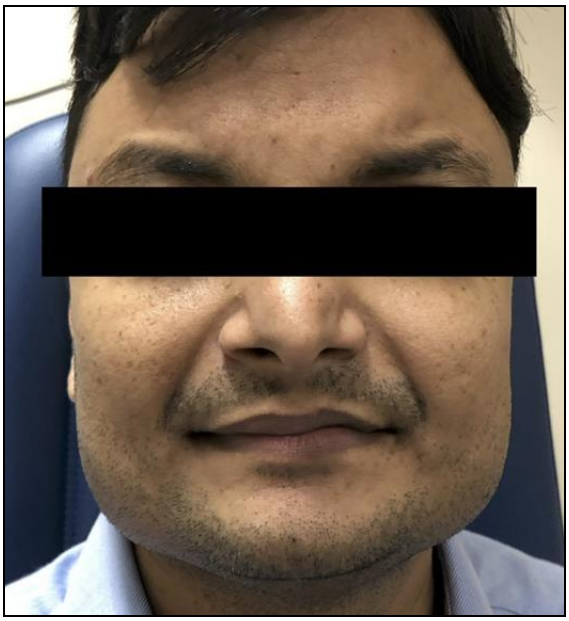

Fig 1: Facial characteristics of Axenfeld Rieger Syndrome: Hypertelorism, flattened mid-face with a broad flat nasal bridge and maxillary hypoplasia.

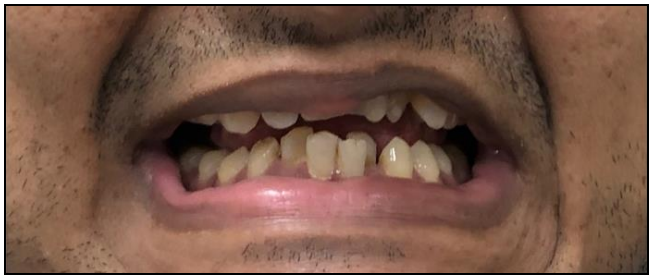

Fig 2: Dental abnormalities in Axenfeld Rieger Syndrome: Microdontia, hypoplasia, malocclusion and impactions.

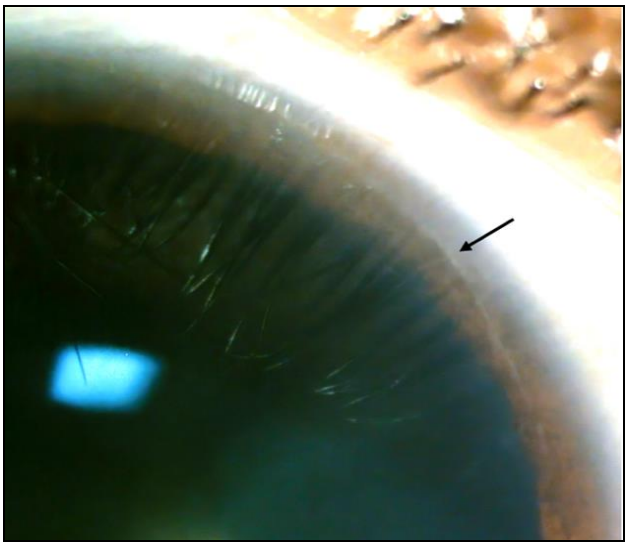

Fig 3: Posterior embryotoxon (arrow)

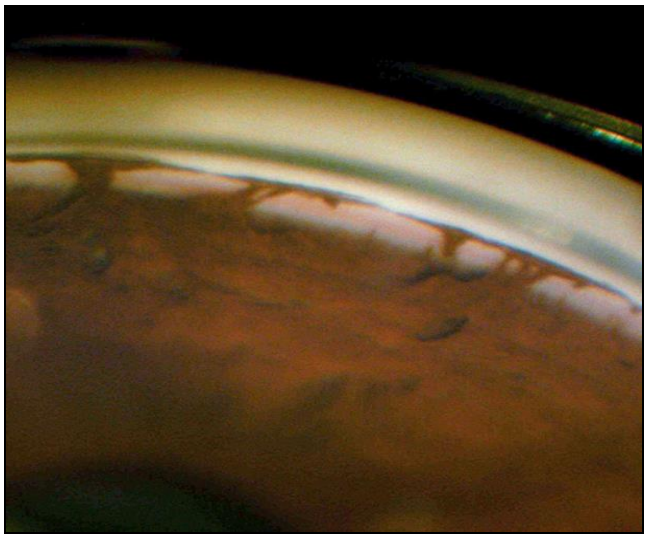

Fig 4: Iris Strands

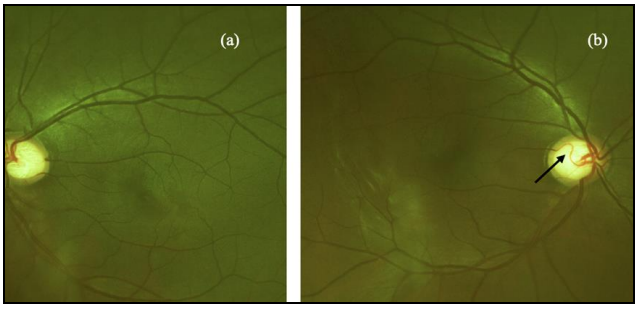

Fig 5: Optic disc nerve of the left (a) and right eye (b). Bilateral disc cupping and bayoneting change in the right eye (arrow).

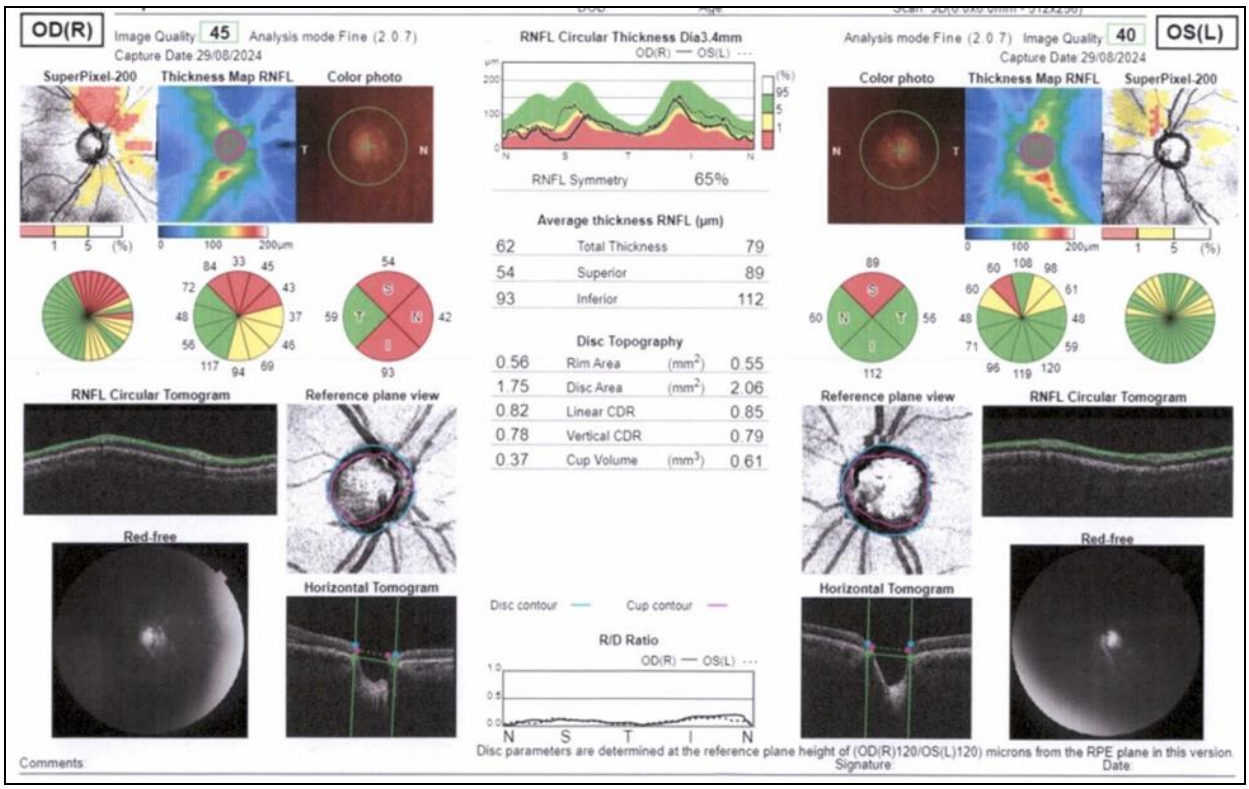

Fig 6: OCT RNFL of the right and left eye

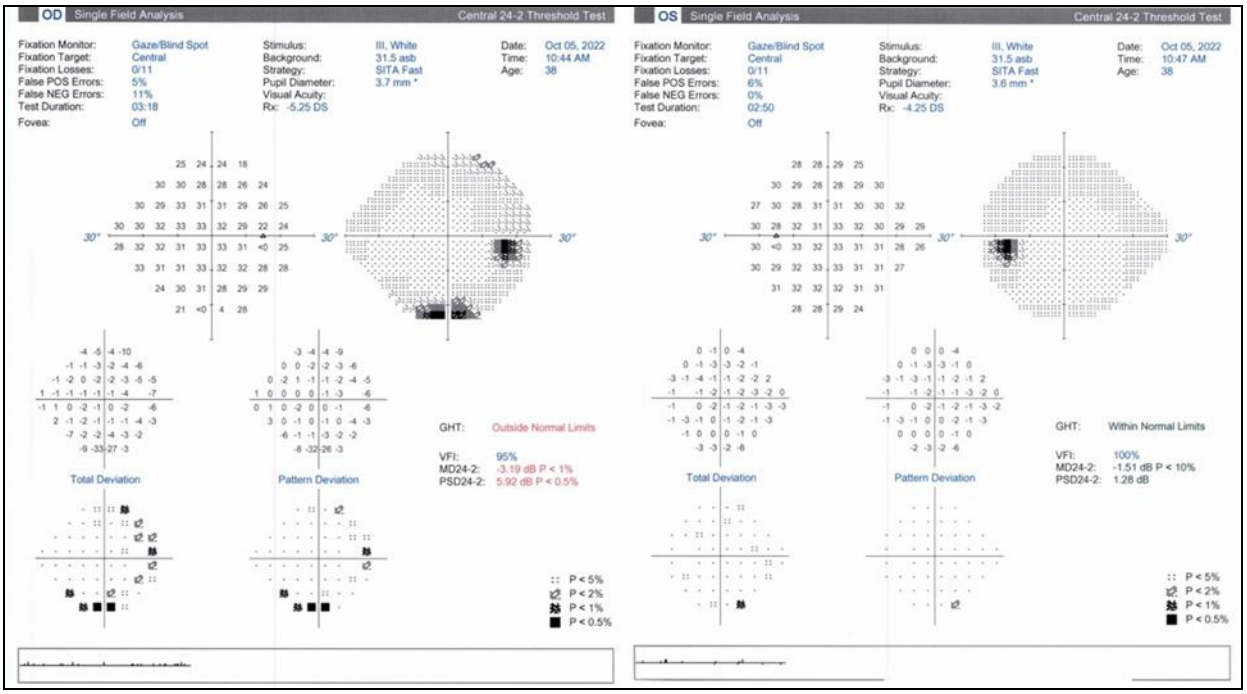

Fig 7: Visual field of the right and left eye

Conclusion

In conclusion, ARS in adults is an under recognized entity, often diagnosed only when glaucoma develops. A high index of suspicion is necessary when encountering unexplained anterior segment anomalies and secondary glaucoma. Early identification and management are essential to preserve visual function, while a multidisciplinary approach ensures optimal systemic care. Future advancements in gene therapy and targeted glaucoma treatments may improve long-term outcomes [6] for patients with this challenging disorder

Conflict of Interest

Not available

Financial Support

Not available

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