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CASE REPORT

# Posterior embryotoxon and Axenfeld-Rieger syndrome: a case report

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## Abstract

**Introduction:** We report the case of a 14-month-old girl with ocular and craniofacial malformations that prompted a comprehensive evaluation and subsequent diagnosis of Axenfeld-Rieger syndrome (ARS). This case emphasizes the importance of thoroughness and a multidisciplinary approach in patient evaluation. **Case report:** A 14-month-old girl exhibited abnormal craniofacial and ocular features, including marked posterior embryotoxon with iris strands attached to the Schwalbe's line and patchy iris due to stroma hypoplasia. Systemic testing revealed only minimal mitral regurgitation as the only other finding. Genetic testing later confirmed the diagnosis of ARS and a familial study identified the same variant in the proband's mother. **Discussion:** ARS is a rare genetic disorder characterized by developmental abnormalities, including anterior segment malformations of the eye, along with classic systemic findings, notably craniofacial dysmorphisms, dental anomalies and periumbilical redundant skin. Diagnosis primarily relies on clinical assessment, particularly the ocular findings. Upon considering this hypothesis, further investigation for systemic malformations should occur, with genetic testing confirming the diagnosis.

***Keywords:*** Axenfeld-Rieger syndrome. Ocular abnormalities. Craniofacial dysmorphisms.

## *Embriotoxon posterior e síndrome de Axenfeld-Rieger: um caso clínico*

## Resumo

**Introdução:** Relato do caso de uma criança de 14 meses, sexo feminino, com malformações oculares e craniofaciais que motivaram uma avaliação completa com diagnóstico *a posteriori* de Síndrome de Axenfeld-Rieger (ARS). Este caso enfatiza a importância da avaliação clínica minuciosa e multidisciplinar. **Caso clínico:** Criança de 14 meses, sexo feminino, com anomalias craniofaciais e oculares, incluindo embriotoxon posterior evidente e hipoplasia da íris. O estudo sistémico revelou insuficiência mitral ligeira, sem outras alterações. O diagnóstico de ARS foi confirmado geneticamente e o estudo familiar identificou a mesma variante genética na mãe da doente. **Discussão:** A ARS é uma doença genética rara caracterizada por anomalias do desenvolvimento, incluindo malformações do segmento anterior do olho e achados sistémicos clássicos, nomeadamente dismorfias faciais, anomalias dentárias e pele periumbilical redundante. O diagnóstico é clínico e baseado nas alterações ao exame oftalmológico. Após considerar esta hipótese, outras malformações sistémicas associadas devem ser pesquisadas e o diagnóstico deve ser confirmado geneticamente.

***Palavras-chave:*** Síndrome de Axenfeld-Rieger. Anomalias oculares. Dismorfias craniofaciais.

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## Keypoints

**What is known**

– Axenfeld-Rieger syndrome is a rare genetic disease characterized by anterior segment malformations of the eye and craniofacial dysmorphisms, along with various other multisystemic findings, requiring a comprehensive approach.

**What is added**

– We report a rare case of ARS, aiming to review suggestive findings and illustrate the ocular abnormalities that should prompt further investigation by pediatricians during routine care.

## Introduction

Axenfeld-Rieger syndrome (ARS) is a rare, genetically and clinically heterogeneous syndrome with an autosomal dominant inheritance pattern and high penetrance. It comprises a spectrum of conditions with variable severity, characterized by developmental abnormalities of both ocular and extraocular structures[1-3].

We report the case of a 14-month-old girl with classic ocular and craniofacial malformations, indicative of this diagnosis. Pediatricians should be aware of this syndrome, which is primarily suggested by the ocular findings. The multisystemic manifestations make it essential to prompt a systemic clinical evaluation.

## Case report

A 14-month-old girl was observed at a general pediatrics clinic due to ocular and facial dysmorphisms after being examined by a pediatric ophthalmologist for suspected strabismus. The gestation progressed without complications, and fetal ultrasounds were normal. The infant was delivered by cesarean section at 38 weeks' gestation, weighing 2000 g, with a body length of 47 cm and an occipitofrontal circumference of 33 cm. Apgar scores at one minute, five minutes, and 10 minutes were 9/9/10, respectively. Psychomotor development and staturo-ponderal growth were appropriate for the child's age and gender. The personal history was uneventful, with a normal neonatal auditory screening. The family history included familial short stature and maternal sensorineural hypoacusia, hypertelorism, mild retrognathia, and two previous abortions. The infant has one healthy sibling. During the physical examination, abnormal craniofacial features were observed, including hypertelorism without telecanthus, a broad nasal bridge, and microretrognathia, with no dental defects. The ocular features included a marked posterior embryotoxon with iris strands attached to the Schwalbe's line, patchy iris due to stroma hypoplasia, left eye corectopia, and an oval pupil (Fig. 1).

Given the ophthalmological findings and facial dysmorphisms, the diagnostic hypotheses were either Alagille Syndrome or ARS. The laboratory workup showed normal liver function. The abdominal and renal ultrasounds were normal. The spinal radiograph revealed no abnormal vertebrae. The cardiac ultrasound showed minimal mitral regurgitation with no hemodynamic significance. The ocular malformations, which are very specific to ARS, along with the absence of findings on the spinal radiograph and cardiac and abdominal ultrasound, made the diagnosis of Alagille Syndrome less likely. The genetic study revealed heterozygosity for duplication of segments 93 to 111 at exon 1 of the *FOXC1* gene - variant c.93_111dup(p.(Thr38Glyfs*51)), which has been associated with ARS type 3. This confirmed the final diagnosis at the age of 27 months. The familial genetic study demonstrated that the proband's mother had the same genetic variant with no ophthalmological abnormalities. Multidisciplinary follow-up was warranted with pediatric cardiology, otorhinolaryngology (ORL), ophthalmology, clinical genetics, and general pediatrics. During the pediatric cardiology consultation at three years of age, mild mitral insufficiency was still present, along with a persistent oval foramen. The ocular anatomic dysgenesis remained stable. The patient also presented high bilateral hyperopia (glasses were prescribed) and intermittent exotropia of the left eye. At three years of age, she began to develop ocular hypertension, which has been controlled with timolol plus dorzolamide eye drops with no visible damage to the optic nerve. Follow-up by ORL revealed mild hearing impairment after performing auditory evoked potentials at four years of age. The spinal radiograph was normal, and statural growth has been adequate (50$^{th}$ percentile), as has neurological development. Currently, the proband is five years old and has adequate growth and neurological development, nearly normal vision (visual acuity recorded as 10/10 in the right eye and 8/10 in the left eye, using the Snellen scale), mild hearing deficit, mild mitral insufficiency, and some classic dysmorphic features and eye abnormalities.

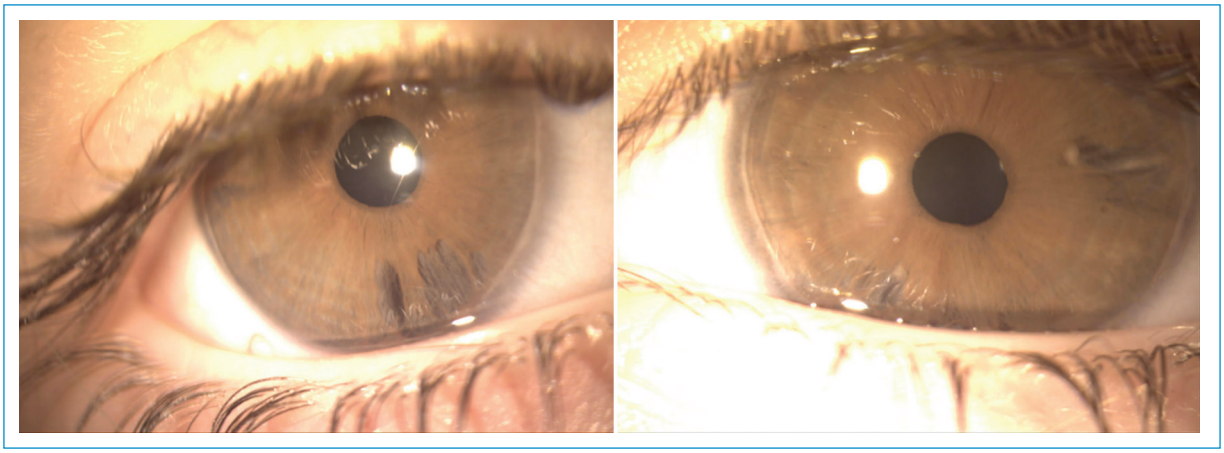

**Figure 1.** Posterior embryotoxon and iris atrophy.

## Discussion

ARS was originally divided into Rieger and Axenfeld anomalies (ocular features with and without pupillary anomalies, respectively) and Rieger and Axenfeld syndromes (ocular and extraocular abnormalities). However, the realization that these were all part of the same spectrum of conditions with overlapping phenotypes made the term ARS increasingly popular[2,4].

The ocular malformations affect the iris (stromal hypoplasia, pseudopolycoria, corectopia, and ectropion uvea), the cornea (posterior embryotoxon with iris strands attached to the Schwalbe's line), and the anterior chamber angle (usually open, although there may be a high insertion of the iris). A posterior embryotoxon is characterized by a prominent and anteriorly displaced Schwalbe's line and presents as a visible ring around the cornea. These malformations are often bilateral, although they may be asymmetric or unilateral. Extraocular muscle insertions may also be altered, leading to strabismus. These features can result in increased intraocular pressure (IOP) and later, the development of glaucoma, which is eventually diagnosed in at least half of patients. Iris abnormalities and posterior embryotoxon are important and common findings that suggest the diagnosis of ARS but may not be present in every patient[1,3-6].

Classic systemic findings include craniofacial dysmorphism (hypertelorism, telecanthus, maxillofacial hypoplasia, an abroad forehead, flat nasal bridge, thin upper lip, and prominent lower lip), dental anomalies (microdontia, oligodontia, and root, crown, or enamel abnormalities), and periumbilical redundant skin. Less frequent features are cardiac outflow tract defects, omphalocele, hypospadias, anal stenosis or atresia, sensorineural hearing loss, and pituitary and skeletal abnormalities (affecting the limbs and vertebrae), resulting in short stature[1,3-5].

Three types of ARS have been described: type 1, with both ocular and systemic findings; type 2, more frequently associated with dental abnormalities and, to a lesser extent, maxillary hypoplasia and umbilical defects; and type 3, which usually only exhibits ocular features, despite hearing loss and cardiac malformations being more common in this type[1].

The genetic defect is unknown in approximately 60% of cases. However, different mutations have been associated with this syndrome, and two major genes have been identified: *PITX2* (usually associated with systemic features and related to ARS type 1) and *FOXC1* (mainly detected in patients with exclusively ocular findings, associated with ARS type 3). In both genes, the same mutation can lead to variable expressivity and result in different phenotypes, with a wide range of clinical manifestations and severity. A *6p25* microdeletion syndrome, with a distinctive autosomal recessive phenotype, has also been described. Different phenotypes have been reported within the same and different families[1,3,4,7,8]. *De novo* mutations have been described in up to 70% of patients who underwent molecular diagnosis. Some studies suggest that intrauterine viral infections may be responsible for the genetic mutations associated with abnormal ocular development, as well as certain forms of ARS. Moreover, the asymmetric phenotypes often observed in the eyes of the same patient might be explained by varying viral loads[6].

Diagnosis is primarily clinical and is mainly suggested by the ocular findings, especially the iris abnormalities, as described in this case. Once this hypothesis is considered, further systemic malformations should be searched for, and the diagnosis should be confirmed

by genetic testing[3,5]. The differential diagnosis of ARS includes other disorders that also present with anterior segment dysgenesis, such as Iris Hypoplasia Syndrome, Peters anomaly, and Primary Congenital Glaucoma. Alagille Syndrome should also be considered in patients who present with posterior embryotoxon[3,5].

Once the diagnosis is confirmed, a cardiac and pituitary axis evaluation should be conducted, along with routine examination by an ophthalmologist to assess the need for glaucoma treatment, and an otorhinolaryngologist to promptly diagnose progressive sensorineural hearing loss through serial audiometry[3-5].

This case illustrates the importance of thoroughness and a holistic approach when dealing with patients, as many syndromes present with multi-organ or progressive symptoms. ARS is a rare genetic condition that should always be considered when iris abnormalities and/or posterior embryotoxon are present. The presence of classic craniofacial features and other malformations may also suggest the diagnosis. Although mutations are not inherited in most cases, early referral and genetic testing should be considered for individuals with a family history of ARS, as it follows an autosomal dominant inheritance pattern. Once the diagnosis is confirmed, a multidisciplinary approach should be pursued, including evaluation by ophthalmology, otorhinolaryngology, and cardiology.

### Authors' contribution

For all: All authors intervened in the conception and design of the case report, as well as acquiring data from the patient. BPN reviewed research studies and literature and analysed and interpreted its data. BPN and TM drafted the article. PFC and AM participated with the critical review of the article for intellectual content.

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### Conflicts of interest

None.

### Ethical disclosures

**Protection of human and animal subjects.** The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

**Confidentiality of data.** The authors declare that they have followed the protocols of their work center on the publication of patient data.

**Right to privacy and informed consent.** The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

**Use of artificial intelligence for generating text.** The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

## References

1. Seifi M, Walter MA. Axenfeld-Rieger syndrome. Clinical Genetics. 2018;93(6):1123-30.
2. Shields MB, Buckley E, Klintworth GK, Thresher R. Axenfeld-Rieger syndrome. A spectrum of developmental disorders. Surv Ophthalmol. 1985;29(6):387-409.
3. Tümer Z, Bach-Holm D. Axenfeld–Rieger syndrome and spectrum of PITX2 and FOXC1 mutations. European Journal of Human Genetics. 2009;17(12):1527-39.
4. Maclean K, Smith J, Heaps LS, Chia N, Williams R, Peters GB, et al. Axenfeld–Rieger malformation and distinctive facial features: Clues to a recognizable 6p25 microdeletion syndrome. American Journal of Medical Genetics Part A. 2005;132A(4):381-5.
5. Chang TC, Summers CG, Schimmenti LA, Grajewski AL. Axenfeld-Rieger syndrome: new perspectives. Br J Ophthalmol. 2012;96(3):318-22.
6. Rao A, Padhy D, Sarangi S, Das G. Unclassified Axenfeld-Rieger Syndrome: A CASE SERIES and Review of Literature. Seminars in Ophthalmology. 2018;33(3):300-7.
7. Alward WL. Axenfeld-Rieger syndrome in the age of molecular genetics. Am J Ophthalmol. 2000;130(1):107-15.
8. Gripp KW, Hopkins E, Jenny K, Thacker D, Salvin J. Cardiac anomalies in Axenfeld-Rieger syndrome due to a novel FOXC1 mutation. Am J Med Genet A. 2013;161A(1):114-9.